Clinical trial results:
A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma

Summary

EudraCT number	2015-005731-41
Trial protocol	DE HU IE ES GB BE NL
Global end of trial date	15 September 2022

Results information

Result version number	v1 (current)
This version publication date	08 September 2023
First version publication date	08 September 2023

Trial information

Trial identification

Sponsor protocol code	3475-361

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02853305
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 163458, Merck Protocol Number: MK-3475-361, Merck: KEYNOTE-361

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States Minor Outlying Islands, 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	15 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2020
Global end of trial reached?	Yes
Global end of trial date	15 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the efficacy and safety of pembrolizumab (pembro, MK-3475) with or without chemotherapy versus chemotherapy alone in participants with advanced or metastatic urothelial carcinoma (bladder cancer). The primary hypotheses are that pembrolizumab plus chemotherapy is superior to chemotherapy alone with respect to Progression-free Survival (PFS) and Overall Survival (OS) in all participants, and that pembrolizumab alone is superior to chemotherapy alone with respect to OS in all participants and in participants with programmed cell death ligand 1 (PD-L1) positive tumors (Combined Positive Score [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	15 September 2016
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: 19
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	Chile: 19
Country: Number of subjects enrolled	France: 115
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 62
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Israel: 58
Country: Number of subjects enrolled	Japan: 104
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Spain: 107
Country: Number of subjects enrolled	Taiwan: 34

Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	Turkey: 73
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	United States: 105
Worldwide total number of subjects	1010
EEA total number of subjects	381

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)	346
From 65 to 84 years	645
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Participants with advanced or metastatic urothelial carcinoma were recruited to examine the efficacy and safety of pembrolizumab plus chemotherapy (pembro combo) versus pembrolizumab alone (pembro) or chemotherapy alone (chemo).

Pre-assignment

Screening details:

1,010 participants were randomized 1:1:1 to receive pembrolizumab plus chemotherapy, pembrolizumab alone, and chemotherapy alone. Per protocol, response/progression or adverse events (AEs) that occurred during the second course were 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	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + ST Chemotherapy (Pembro Combo)

Arm description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for a maximum of 35 doses PLUS standard therapy (ST) chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR carboplatin at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle. Eligible participants who stopped 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	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered 200 mg IV on Day 1 of each 3-week cycle for a maximum of 35 doses

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

Dosage and administration details:

Administered 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

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

Dosage and administration details:

Administered at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle 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:

Administered 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle

Arm title	Pembrolizumab (Pembro)

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 35 doses. Eligible participants who stopped pembrolizumab with 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	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered 200 mg IV on Day 1 of each 3-week cycle for a maximum of 35 doses

Arm title	ST Chemotherapy (Chemo)

Arm description:

Participants received ST chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle OR carboplatin at AUC 5 (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

Arm type	Active comparator
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:

Administered 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle

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

Dosage and administration details:

Administered 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

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

Dosage and administration details:

Administered at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle 3-week cycle

Number of subjects in period 1	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)
Started	351	307	352
Received First Course of Pembrolizumab	349	302	342
Received Second Course of Pembrolizumab	14	15	0
Completed	0	0	0
Not completed	351	307	352
Adverse event, serious fatal	287	249	300
Consent withdrawn by subject	2	8	3
Transferred to Extension Study	46	30	25
Did Not Continue on Extension Study	16	20	24

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab + ST Chemotherapy (Pembro Combo)

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for a maximum of 35 doses PLUS standard therapy (ST) chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR carboplatin at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle. Eligible participants who stopped 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 (Pembro)

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 35 doses. Eligible participants who stopped pembrolizumab with 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	ST Chemotherapy (Chemo)

Reporting group description:

Participants received ST chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle OR carboplatin at AUC 5 (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

Reporting group values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)
Number of subjects	351	307	352
Age categorical Units: Subjects			
Adults (18-64 years)	118	109	119
From 65-84 years	228	189	228
85 years and over	5	9	5
Age Continuous Units: years			
arithmetic mean	68.3	67.0	68.0
standard deviation	± 9.2	± 10.1	± 9.6
Sex: Female, Male Units:			
Female	79	79	90
Male	272	228	262
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	64	47	70
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	3	4
White	243	212	235
More than one race	1	2	1

Unknown or Not Reported	42	42	42
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	26	25	32
Not Hispanic or Latino	269	231	261
Unknown or Not Reported	56	51	59
PD-L1 CPS Status-IVRS			
The Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by immunohistochemistry (IHC). Higher percentages of PD-L1 CPS staining corresponded to higher positivity of PD-L1 on a tumor. The number of participants with CPS <10% and CPS ≥10% at baseline randomization by Interactive Voice Response System (IVRS) is presented			
Units: Subjects			
PD-L1 CPS<10	192	148	193
PD-L1 CPS≥10	159	159	159
Investigator Choice of Cisplatin or Carboplatin - IVRS			
The Investigator’s choice of chemotherapy drug (cisplatin or carboplatin) at baseline randomization by IVRS is presented.			
Units: Subjects			
Cisplatin	160	138	160
Carboplatin	191	169	192

Reporting group values	Total		
Number of subjects	1010		
Age categorical Units: Subjects			
Adults (18-64 years)	346		
From 65-84 years	645		
85 years and over	19		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units:			
Female	248		
Male	762		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	181		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	690		
More than one race	4		
Unknown or Not Reported	126		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	83		
Not Hispanic or Latino	761		
Unknown or Not Reported	166		

PD-L1 CPS Status-IVRS			
The Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) Status indicates tumor PD-L1 positivity using both tumor cells and inflammatory cells that are positive for PD-L1 by immunohistochemistry (IHC). Higher percentages of PD-L1 CPS staining corresponded to higher positivity of PD-L1 on a tumor. The number of participants with CPS <10% and CPS ≥10% at baseline randomization by Interactive Voice Response System (IVRS) is presented			
Units: Subjects			
PD-L1 CPS<10	533		
PD-L1 CPS≥10	477		
Investigator Choice of Cisplatin or Carboplatin - IVRS			
The Investigator’s choice of chemotherapy drug (cisplatin or carboplatin) at baseline randomization by IVRS is presented.			
Units: Subjects			
Cisplatin	458		
Carboplatin	552		

End points

End points reporting groups

Reporting group title	Pembrolizumab + ST Chemotherapy (Pembro Combo)

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle for a maximum of 35 doses PLUS standard therapy (ST) chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR carboplatin at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle. Eligible participants who stopped 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 (Pembro)

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 35 doses. Eligible participants who stopped pembrolizumab with 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	ST Chemotherapy (Chemo)

Reporting group description:

Participants received ST chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle OR carboplatin at AUC 5 (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

Primary: Pembro Combo vs Chemo: Progression-free Survival (PFS) Using Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Pembro Combo vs Chemo: Progression-free Survival (PFS) Using Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS in the pembro combo arm was compared to the chemo arm as a pre-specified primary analysis of the Intent-To-Treat (ITT) population (all randomized participants). PFS is reported here for all randomized participants in the pembro combo arm and chemo arm. Per protocol, PFS was compared separately between all participants of the pembro arm and chemo arm and is presented later in the record.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	0[1]	352	
Units: Months				
median (confidence interval 95%)	8.3 (7.5 to 8.5)	(to)	7.1 (6.4 to 7.9)	

Notes:

[1] - PFS was compared separately between all participants of the pembro arm and chemo arm

Statistical analyses

Statistical analysis title	PFS: Pembro Combo vs Chemo

Statistical analysis description:

PFS in all participants of the pembro combo arm was compared to PFS in all participants of the chemo arm to address the first primary hypothesis (superiority to chemo). The hazard ratio (HR) and its 95% confidence interval (CI) were estimated using a stratified Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator's choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0033
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.93

Primary: Pembro Combo vs Chemo: Overall Survival (OS)

End point title	Pembro Combo vs Chemo: Overall Survival (OS)

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 chemo arm as a pre-specified primary analysis of the ITT population (all randomized participants). OS is reported here for all randomized participants in the pembro combo arm and chemo arm. Per protocol, OS was compared separately between all participants of the pembro arm and chemo arm and is presented later in the record.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	0[2]	352	
Units: Months				
median (confidence interval 95%)	17.0 (14.5 to 19.5)	(to)	14.3 (12.3 to 16.7)	

Notes:

[2] - OS was compared separately between all participants of the pembro arm and chemo arm

Statistical analyses

Statistical analysis title	OS: Pembro Combo vs Chemo

Statistical analysis description:

OS in all participants of the pembro combo arm was compared to OS in all participants of the chemo arm to address the second primary hypothesis (superiority to chemo). The HR and its 95% CI were estimated using a stratified Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator's choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0407
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.02

Primary: Pembro vs Chemo: OS in Participants With Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (CPS) ≥10%

End point title	Pembro vs Chemo: OS in Participants With Programmed Cell Death Ligand 1 (PD-L1) Combined Positive Score (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 CPS ≥10% subset of the pembro arm was compared to OS in the CPS ≥10% subset of the chemo arm for this endpoint as a pre-specified primary analysis of the ITT population. OS is reported here for all randomized participants in the pembro arm and chemo arm who were PD-L1 CPS ≥10%. Per protocol, OS in the CPS ≥10% subset of the pembro combo arm was not a pre-specified analysis of the ITT population and is not presented.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	160	158	
Units: Months				
median (confidence interval 95%)	(to)	16.1 (13.6 to 19.9)	15.2 (11.6 to 23.3)	

Notes:

[3] - OS in the CPS ≥10% subset of the pembro combo arm was not a pre-specified analysis of ITT population

Statistical analyses

Statistical analysis title	OS: Pembro vs Chemo, CPS ≥10%

Statistical analysis description:

OS in CPS≥10 participants of the pembro arm was compared to OS in CPS≥10 participants of the chemo arm. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.32

Primary: Pembro vs Chemo: OS

End point title	Pembro vs Chemo: OS

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 arm was compared to the chemo arm as a pre-specified primary analysis of the ITT population (all randomized participants). OS is reported here for all randomized participants in the pembro arm and chemo arm. Per protocol, OS was compared separately between all participants of the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Primary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	307	352	
Units: Months				
median (confidence interval 95%)	(to)	15.6 (12.1 to 17.9)	14.3 (12.3 to 16.7)	

Notes:

[4] - OS was compared separately between all participants of the pembro combo arm and chemo arm

Statistical analyses

Statistical analysis title	OS: Pembro vs Chemo

Statistical analysis description:

OS in all participants of the pembro arm was compared to OS in all participants of the chemo arm. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.11

Secondary: Number of Participants Who Experience an Adverse Event (AE)

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

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The number of participants that experienced at least one AE was reported for each treatment arm. All randomized participants who received at least 1 dose of trial treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 55 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	349	302	342	
Units: Participants	348	289	341	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinue Study Drug Due to an AE

End point title	Number of Participants Who Discontinue Study Drug Due to an AE

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. The number of participants that discontinued any study drug due to an AE was reported for each treatment arm. All randomized participants who received at least 1 dose of trial treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 52 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	349	302	342	
Units: Participants	108	48	62	

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro vs Chemo: PFS Using RECIST 1.1 as Assessed by BICR

End point title	Pembro vs Chemo: PFS Using RECIST 1.1 as Assessed by BICR

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS in the pembro arm was compared to the chemo arm as a pre-specified analysis of the ITT population (all randomized participants). PFS is reported here for all randomized participants in the pembro arm and chemo arm. Per protocol, PFS was compared separately between all participants of the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	307	352	
Units: Months				
median (confidence interval 95%)	(to)	3.9 (2.3 to 5.1)	7.1 (6.4 to 7.9)	

Notes:

[5] - PFS was compared separately between all participants of the pembro combo arm and chemo arm

Statistical analyses

Statistical analysis title	PFS: Pembro vs Chemo

Statistical analysis description:

PFS in all participants of the pembro arm was compared to PFS in all participants of the chemo arm. The comparison was based on a Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.58

Secondary: Pembro Combo vs Chemo: Duration of Response (DOR) Using RECIST 1.1 as Assessed by BICR

End point title	Pembro Combo vs Chemo: Duration of Response (DOR) Using RECIST 1.1 as Assessed by BICR

End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 based upon BICR, 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. DOR is reported here for all randomized participants in the pembro combo arm and chemo arm who demonstrated a confirmed CR or PR. Per protocol, DOR was assessed separately in responders of the pembro arm and chemo arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	192	0[6]	158	
Units: Months				
median (confidence interval 95%)	8.5 (8.2 to 11.4)	(to)	6.2 (5.8 to 6.6)	

Notes:

[6] - DOR was assessed separately in responders of the pembro arm and chemo arm

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Chemo: Objective Response Rate (ORR) Using RECIST 1.1 as Assessed by BICR

End point title	Pembro Combo vs Chemo: Objective Response Rate (ORR) Using RECIST 1.1 as Assessed by BICR

End point description:

ORR was defined as the percentage of participants in the analysis population who had a Complete Response (CR: disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. based upon BICR. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, ORR in the pembro combo arm was compared to the chemo 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 randomized participants in the pembro combo arm and chemo arm. Per protocol, ORR was compared separately between participants of the pembro arm and chemo arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	0[7]	352	
Units: Percentage of Participants				
number (confidence interval 95%)	54.7 (49.3 to	(to)	44.9 (39.6 to	

	60.0)	50.2)

Notes:

[7] - ORR was compared separately between participants of the pembro arm and chemo arm

Statistical analyses

Statistical analysis title	ORR: Pembro Combo vs Chemo

Statistical analysis description:

ORR in participants of the pembro combo arm was compared to ORR in participants of the chemo arm. The comparison was based on the Miettinen & Nurminen method stratified by investigator's choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	17.1

Secondary: Pembro Combo vs Chemo: Disease Control Rate (DCR) Using RECIST 1.1 as Assessed by BICR

End point title	Pembro Combo vs Chemo: Disease Control Rate (DCR) Using RECIST 1.1 as Assessed by BICR

End point description:

DCR was defined as the percentage of participants who had a confirmed CR (disappearance of all target lesions), PR (at least a 30% decrease in the sum of diameters of target lesions), or Stable Disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD [at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD]). Per protocol, DCR in the pembro combo arm was compared to the chemo arm as a pre-specified secondary analysis of the ITT population. The percentage of participants who experienced a confirmed CR, PR, or SD according to RECIST 1.1 as assessed by BICR was reported as the DCR for all randomized participants in the pembro combo arm and chemo arm. Per protocol, DCR was compared separately between participants of the pembro arm and chemo arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	0[8]	352	
Units: Percentage of Participants				
number (confidence interval 95%)	80.3 (75.8 to 84.4)	(to)	75.9 (71.0 to 80.2)	

Notes:

[8] - DCR was compared separately between participants of the pembro arm and chemo arm

Statistical analyses

Statistical analysis title	DCR: Pembro Combo vs Chemo

Statistical analysis description:

DCR in participants of the pembro combo arm was compared to DCR in participants of the chemo arm based on the Miettinen & Nurminen method stratified by investigator's choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	703
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	10.6

Secondary: Pembro vs Chemo: ORR Using RECIST 1.1 as Assessed by BICR

End point title	Pembro vs Chemo: ORR Using RECIST 1.1 as Assessed by BICR

End point description:

ORR was defined as the percentage of participants in the analysis population who had a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. based upon BICR. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, ORR in the pembro arm was compared to the chemo 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 randomized participants in the pembro arm and chemo arm. Per protocol, ORR was compared separately between participants of the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	307	352	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	30.3 (25.2 to 35.8)	44.9 (39.6 to 50.2)	

Notes:

[9] - ORR was compared separately between participants of the pembro combo arm and chemo arm

Statistical analyses

Statistical analysis title	ORR: Pembro vs Chemo

Statistical analysis description:

ORR in participants of the pembro arm was compared to ORR in participants of the chemo arm. The comparison was based on the Miettinen & Nurminen method stratified by investigator's choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22
upper limit	-7.4

Secondary: PFS Using RECIST 1.1 as Assessed by BICR at 6 Months

End point title	PFS Using RECIST 1.1 as Assessed by BICR at 6 Months

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS was compared between arms as a pre-specified secondary analysis of the ITT population (all randomized participants). PFS is reported here for all randomized participants at 6 months based on the product-limit (Kaplan-Meier) method for censored data.

End point type	Secondary

End point timeframe:

6 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	307	352	
Units: Percentage of Participants				
number (confidence interval 95%)	73.7 (68.6 to 78.0)	43.6 (37.9 to 49.1)	70.3 (64.8 to 75.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro vs Chemo: DCR Using RECIST 1.1 as Assessed by BICR

End point title	Pembro vs Chemo: DCR Using RECIST 1.1 as Assessed by BICR

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS was compared between arms as a pre-specified secondary analysis of the ITT population (all randomized participants). PFS is reported here for all randomized participants at 6 months based on the product-limit (Kaplan-Meier) method for censored data.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	307	352	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	47.2 (41.5 to 53.0)	75.9 (71.0 to 80.2)	

Notes:

[10] - DCR was compared separately between participants of the pembro combo arm and chemo arm

Statistical analyses

Statistical analysis title	DCR: Pembro vs Chemo

Statistical analysis description:

DCR in participants of the pembro arm was compared to DCR in participants of the chemo arm based on the Miettinen & Nurminen method stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)

Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentage
Point estimate	-28.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.9
upper limit	-21.6

Secondary: Pembro vs Chemo: DOR Using RECIST 1.1 as Assessed by BICR

End point title	Pembro vs Chemo: DOR Using RECIST 1.1 as Assessed by BICR

End point description:

For participants with confirmed CR (disappearance of all target lesions) or PR (≥30% decrease in sum of diameters of target lesions) per RECIST 1.1 based upon BICR, DOR was defined as 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 date of last tumor assessment. Per RECIST 1.1, PD 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. Appearance of 1 or more new lesions also considered PD. DOR reported for all randomized participants in pembro arm and chemo arm who had CR or PR. Values of 9999 indicate undefined DOR upper 95% confidence limit (DOR rate not low enough at time of cut-off date). Per protocol, DOR was assessed separately in responders of the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	93	158	
Units: Months				
median (confidence interval 95%)	(to)	28.2 (13.5 to 9999)	6.2 (5.8 to 6.6)	

Notes:

[11] - DOR was assessed separately in responders of the pembro combo arm and chemo arm

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Chemo: 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 Combo vs Chemo: 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. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared between all treated participants of the pembro combo arm and the chemo arm with ≥1 EORTC-QLQ-C30 assessment completed. Per protocol, change from baseline (CFB) to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro arm and chemo arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	0[12]	337	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	2.54 (-0.08 to 5.16)	(to)	-0.14 (-2.91 to 2.63)	

Notes:

[12] - CFB to Week 18 in GHS/QoL combined score compared separately between the pembro arm and chemo arm

Statistical analyses

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

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 chemo arm. Comparison based on constrained longitudinal data analysis (cLDA) model with GHS/QoL score as response variable, and with treatment by study visit interactions and stratification factors (investigator's choice of chemotherapy [cisplatin or carboplatin] and PD-L1 status [CPS<10 vs. CPS≥10]) at baseline as covariates.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in LS Means
Point estimate	2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	6.12

Secondary: PFS Using RECIST 1.1 as Assessed by BICR at 18 Months

End point title	PFS Using RECIST 1.1 as Assessed by BICR at 18 Months

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS was compared between arms as a pre-specified secondary analysis of the ITT population (all randomized participants). PFS is reported here for all randomized participants at 18 months based on the product-limit (Kaplan-Meier) method for censored data.

End point type	Secondary

End point timeframe:

18 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	307	352	
Units: Percentage of Participants				
number (confidence interval 95%)	23.0 (18.4 to 27.8)	19.1 (14.7 to 24.0)	13.5 (9.3 to 18.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Using RECIST 1.1 as Assessed by BICR at 12 Months

End point title	PFS Using RECIST 1.1 as Assessed by BICR at 12 Months

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. The sponsor allowed a maximum of 10 target lesions in total and 5 per organ on this study. Per protocol, PFS was compared between arms as a pre-specified secondary analysis of the ITT population (all randomized participants). PFS is reported here for all randomized participants at 12 months based on the product-limit (Kaplan-Meier) method for censored data.

End point type	Secondary

End point timeframe:

12 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	307	352	
Units: Percentage of Participants				
number (confidence interval 95%)	33.7 (28.6 to 38.9)	26.6 (21.6 to 31.9)	20.9 (16.0 to 26.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pembro Combo vs Chemo: Time to Deterioration (TTD) in the EORTC-QLQ-C30 GHS/QoL (Items 29 and 30) Combined Score

End point title	Pembro Combo vs Chemo: Time to Deterioration (TTD) in the EORTC-QLQ-C30 GHS/QoL (Items 29 and 30) Combined Score

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the QoL 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). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. TTD in GHS/QoL was defined as the time from first dose date to the first onset of a ≥10 point decrease from baseline in GHS/QoL combined score without confirmation. Per protocol, TTD in GHS/QoL combined score was compared between all treated participants of the pembro combo arm and chemo arm with ≥1 EORTC-QLQ-C30 assessment at baseline. TTD in GHS/QoL combined score was compared separately between the pembro arm and chemo arm and is presented later in the record.

End point type	Secondary

End point timeframe:

Baseline up to approximately 25 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	314	0[13]	311	
Units: Months				
median (confidence interval 95%)	8.0 (5.9 to 10.3)	(to)	4.5 (2.8 to 8.2)	

Notes:

[13] - TTD in GHS/QoL combined score was compared separately between the pembro arm and chemo arm

Statistical analyses

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

Statistical analysis description:

TTD in GHS/QoL combined score was compared between all participants of the pembro combo arm and

the chemo arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab + ST Chemotherapy (Pembro Combo) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1

Secondary: Pembro vs Chemo: Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL Combined Score

End point title	Pembro vs Chemo: Change from Baseline To Week 18 in the EORTC QLQ-C30 GHS/QoL 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. Per protocol, change from baseline to Week 18 in the GHS/QoL combined score was compared between all treated participants of the pembro arm and the chemo arm with ≥1 EORTC-QLQ-C30 assessment completed. Per protocol, change from baseline (CFB) to Week 18 in the GHS/QoL combined score was compared separately between all participants of the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	301	337	
Units: Score on a Scale				
least squares mean (confidence interval 95%)	(to)	-1.89 (-5.04 to 1.26)	-0.95 (-3.95 to 2.06)	

Notes:

[14] - CFB to Week 18 in GHS/QoL combined score compared separately between pembro combo arm and chemo arm

Statistical analyses

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

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 arm and the chemo arm. Comparison based on cLDA model with GHS/QoL score as response variable, and with treatment by study visit interactions and stratification factors (investigator's choice of chemotherapy [cisplatin or carboplatin] and PD-L1 status [CPS<10 vs. CPS≥10]) at baseline as covariates.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in LS Means
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	3.18

Secondary: Pembro vs Chemo: TTD in the EORTC-QLQ-C30 GHS/QoL (Items 29 and 30) Combined Score

End point title	Pembro vs Chemo: TTD in the EORTC-QLQ-C30 GHS/QoL (Items 29 and 30) Combined Score

End point description:

EORTC-QLQ-C30 is a 30-item questionnaire developed to assess the QoL 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). Raw scores were standardized by linear transformation so that scores ranged from 0 to 100, with a higher score indicating a better overall outcome. TTD in GHS/QoL was defined as the time from first dose date to the first onset of a ≥10 point decrease from baseline in GHS/QoL combined score without confirmation. Per protocol, TTD in GHS/QoL combined score was compared between all treated participants of the pembro arm and chemo arm with ≥1 EORTC-QLQ-C30 assessment at baseline. TTD in GHS/QoL combined score was compared separately between the pembro combo arm and chemo arm and is presented earlier in the record.

End point type	Secondary

End point timeframe:

Baseline up to approximately 25 months

End point values	Pembrolizumab + ST Chemotherapy (Pembro Combo)	Pembrolizumab (Pembro)	ST Chemotherapy (Chemo)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[15]	275	311	
Units: Months				
median (confidence interval 95%)	(to)	3.6 (2.1 to 5.2)	4.5 (2.8 to 8.2)	

Notes:

[15] - TTD in GHS/QoL combined score was compared separately between the pembro combo arm and chemo arm

Statistical analyses

Statistical analysis title	EORTC QLQ-C30 GHS/QoL TTD: Pembro vs Chemo

Statistical analysis description:

TTD in GHS/QoL combined score was compared between all participants of the pembro arm and the chemo arm. Comparison based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by investigator’s choice of chemotherapy (cisplatin or carboplatin) and PD-L1 status (CPS<10 vs. CPS≥10) at baseline.

Comparison groups	Pembrolizumab (Pembro) v ST Chemotherapy (Chemo)
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.49

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 70 months

Adverse event reporting additional description:

All-Cause Mortality reported for all randomized participants. Serious and Other AEs include all treated participants according to treatment received. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to drug excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

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

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for a maximum of 35 doses PLUS ST chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle, OR carboplatin at an area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

Reporting group title	Pembrolizumab (Pembro) First Course

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for a maximum of 35 doses.

Reporting group title	Pembrolizumab (Pembro) 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 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 + ST Chemotherapy (Pembro Combo) 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 ST 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	ST Chemotherapy (Chemo) First Course

Reporting group description:

Participants received ST chemotherapy with EITHER cisplatin 70 mg/m^2 IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine IV infusion 1,000 mg/m^2 on Day 1 and Day 8 of each 3-week cycle OR carboplatin at AUC 5 (or AUC 4.5 if required per local guidelines) IV on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle plus gemcitabine 1,000 mg/m^2 IV on Day 1 and Day 8 of each 3-week cycle.

Serious adverse events	Pembrolizumab + ST Chemotherapy (Pembro Combo) First Course	Pembrolizumab (Pembro) First Course	Pembrolizumab (Pembro) Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	189 / 349 (54.15%)	145 / 302 (48.01%)	0 / 15 (0.00%)
number of deaths (all causes)	283	244	8
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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
Adenocarcinoma of colon			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 pain			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Lymphangiosis carcinomatosa			

subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Embolism			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Deep vein thrombosis			
subjects affected / exposed	4 / 349 (1.15%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial haemorrhage			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Lymphoedema			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Iliac artery occlusion			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypovolaemic shock			

subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Pelvic venous thrombosis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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 pain			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Asthenia			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	6 / 349 (1.72%)	3 / 302 (0.99%)	0 / 15 (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
Fatigue			

subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Influenza like illness			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
General physical health deterioration			
subjects affected / exposed	3 / 349 (0.86%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Inflammation			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Gait disturbance			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Medical device site laceration			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Mucosal inflammation			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pyrexia			
subjects affected / exposed	6 / 349 (1.72%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	3 / 7	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Oedema peripheral			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Sarcoidosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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

Pelvic pain			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Aspiration			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pharyngeal stenosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Haemoptysis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Pneumothorax			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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

Pneumonitis			
subjects affected / exposed	1 / 349 (0.29%)	4 / 302 (1.32%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Dyspnoea			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 embolism			
subjects affected / exposed	6 / 349 (1.72%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Productive cough			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Confusional state			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Delirium			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Mental status changes			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Product issues			
Device occlusion			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood potassium increased			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
International normalised ratio increased			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Liver function test increased			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Platelet count decreased			
subjects affected / exposed	11 / 349 (3.15%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	12 / 13	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Femur fracture			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Joint dislocation			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Joint injury			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Lower limb fracture			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Hip fracture			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Overdose			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Post procedural complication			

subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Post procedural discharge			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Skull fracture			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Post procedural haematoma			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Procedural pneumothorax			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Rib fracture			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Post procedural fever			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Urethral injury			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Urostomy complication			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Congenital, familial and genetic disorders			
Dolichocolon			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Odontogenic cyst			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Angina pectoris			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Aortic valve stenosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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

Arrhythmia			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Atrial fibrillation			
subjects affected / exposed	4 / 349 (1.15%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Cardiac failure			
subjects affected / exposed	0 / 349 (0.00%)	5 / 302 (1.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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 failure chronic			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 arrest			
subjects affected / exposed	3 / 349 (0.86%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 2	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Cardiomyopathy			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Coronary artery disease			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Myocarditis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Left ventricular failure			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Myocardial infarction			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Left ventricular dysfunction			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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 thrombosis			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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 haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 349 (0.57%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Dementia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Encephalitis autoimmune			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Myoclonus			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Ischaemic stroke			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Headache			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Polyneuropathy			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Seizure			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Spinal cord compression			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Uraemic encephalopathy			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Syncope			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	9 / 349 (2.58%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	8 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Anaemia			
subjects affected / exposed	15 / 349 (4.30%)	6 / 302 (1.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	11 / 15	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematotoxicity			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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	12 / 349 (3.44%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	13 / 15	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	10 / 349 (2.87%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	9 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Neutropenia			

subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Eye disorders			
Cataract			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Diplopia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Epiretinal membrane			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 disorders			
Autoimmune colitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Abdominal pain			
subjects affected / exposed	3 / 349 (0.86%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Ascites			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Colitis			

subjects affected / exposed	2 / 349 (0.57%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Constipation			
subjects affected / exposed	2 / 349 (0.57%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 349 (0.86%)	5 / 302 (1.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Enterocolonic fistula			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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 fistula			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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 haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Enterocolitis haemorrhagic			

subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Ileus			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Inguinal hernia			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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
Melaena			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Large intestinal obstruction			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Intestinal obstruction			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nausea			

subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal ulcer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Vomiting			
subjects affected / exposed	3 / 349 (0.86%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 349 (0.29%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Short-bowel syndrome			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Cholecystitis			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Cholecystitis acute			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Cirrhosis alcoholic			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Liver injury			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Hepatotoxicity			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 / 349 (0.29%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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			
Angioedema			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Dermatitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Dermatitis acneiform			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 ulcer			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Toxic skin eruption			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Purpura			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Pruritus			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Drug eruption			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	17 / 349 (4.87%)	13 / 302 (4.30%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	10 / 21	3 / 15	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Bladder perforation			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Bladder tamponade			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Chronic kidney disease			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Nephropathy			

subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Renal failure			
subjects affected / exposed	2 / 349 (0.57%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Pollakiuria			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	9 / 349 (2.58%)	14 / 302 (4.64%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	4 / 10	1 / 20	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Urinary tract obstruction			

subjects affected / exposed	1 / 349 (0.29%)	4 / 302 (1.32%)	0 / 15 (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
Urinary retention			
subjects affected / exposed	1 / 349 (0.29%)	5 / 302 (1.66%)	0 / 15 (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
Urethral fistula			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Ureteric obstruction			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Hypophysitis			
subjects affected / exposed	2 / 349 (0.57%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			

subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Thyroiditis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Back pain			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Chondrocalcinosis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Intervertebral disc protrusion			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Osteoporosis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Pain in extremity			
subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Polyarthritis			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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
Spinal stenosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Pathological fracture			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Bacteraemia			

subjects affected / exposed	2 / 349 (0.57%)	0 / 302 (0.00%)	0 / 15 (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
Abdominal sepsis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Acute hepatitis B			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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 infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Bacterial diarrhoea			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Bronchitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Catheter site infection			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Cellulitis			
subjects affected / exposed	3 / 349 (0.86%)	4 / 302 (1.32%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Cystitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Dengue fever			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Endocarditis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Diverticulitis			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Device related sepsis			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Gastroenteritis			
subjects affected / exposed	1 / 349 (0.29%)	2 / 302 (0.66%)	0 / 15 (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
Escherichia urinary tract infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Escherichia sepsis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Enterobacter bacteraemia			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Oral candidiasis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Neutropenic sepsis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Lung abscess			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Intervertebral discitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Influenza			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Pelvic abscess			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotid abscess			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Osteomyelitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Peritonitis			

subjects affected / exposed	1 / 349 (0.29%)	2 / 302 (0.66%)	0 / 15 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Periodontitis			
subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Pseudomembranous colitis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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 bacterial			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Pneumonia			
subjects affected / exposed	8 / 349 (2.29%)	6 / 302 (1.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Pyonephrosis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Pyelonephritis acute			
subjects affected / exposed	4 / 349 (1.15%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	5 / 349 (1.43%)	6 / 302 (1.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Rash pustular			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Respiratory tract infection			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Scrotal infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Septic arthritis staphylococcal			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Septic shock			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin bacterial infection			

subjects affected / exposed	0 / 349 (0.00%)	0 / 302 (0.00%)	0 / 15 (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
Skin infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Stoma site infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Urinary tract infection			
subjects affected / exposed	31 / 349 (8.88%)	19 / 302 (6.29%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	9 / 65	2 / 22	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Urosepsis			
subjects affected / exposed	13 / 349 (3.72%)	7 / 302 (2.32%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 15	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Viral infection			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Wound infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acidosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Decreased appetite			
subjects affected / exposed	0 / 349 (0.00%)	2 / 302 (0.66%)	0 / 15 (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
Dehydration			
subjects affected / exposed	3 / 349 (0.86%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 349 (0.29%)	1 / 302 (0.33%)	0 / 15 (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
Failure to thrive			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Fluid retention			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Hypokalaemia			
subjects affected / exposed	2 / 349 (0.57%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	3 / 349 (0.86%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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
Hyperkalaemia			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Hyponatraemia			
subjects affected / exposed	5 / 349 (1.43%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 349 (0.00%)	1 / 302 (0.33%)	0 / 15 (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
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 349 (0.29%)	0 / 302 (0.00%)	0 / 15 (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

Serious adverse events	Pembrolizumab + ST Chemotherapy (Pembro Combo) Second Course	ST Chemotherapy (Chemo) First Course	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	138 / 342 (40.35%)	
number of deaths (all causes)	4	300	
number of deaths resulting from adverse events	0	2	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Embolism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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			
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site laceration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal stenosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 14 (0.00%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 14 (0.00%)	15 / 342 (4.39%)	
occurrences causally related to treatment / all	0 / 0	22 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural discharge			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Dolichocolon			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odontogenic cyst			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis autoimmune			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	11 / 342 (3.22%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	19 / 342 (5.56%)	
occurrences causally related to treatment / all	0 / 0	15 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	10 / 342 (2.92%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Autoimmune colitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolonic fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Short-bowel syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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			
Angioedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	9 / 342 (2.63%)	
occurrences causally related to treatment / all	0 / 0	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	5 / 342 (1.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral fistula			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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			
Gouty arthritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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			
Abdominal abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	6 / 342 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyonephrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	4 / 342 (1.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic arthritis staphylococcal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin bacterial infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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	0 / 14 (0.00%)	22 / 342 (6.43%)	
occurrences causally related to treatment / all	0 / 0	7 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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			
Diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acidosis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 / 14 (0.00%)	5 / 342 (1.46%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 342 (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 + ST Chemotherapy (Pembro Combo) First Course	Pembrolizumab (Pembro) First Course	Pembrolizumab (Pembro) Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	345 / 349 (98.85%)	275 / 302 (91.06%)	1 / 15 (6.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 349 (6.59%)	13 / 302 (4.30%)	0 / 15 (0.00%)
occurrences (all)	26	17	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	84 / 349 (24.07%)	42 / 302 (13.91%)	0 / 15 (0.00%)
occurrences (all)	138	50	0
Fatigue			
subjects affected / exposed	147 / 349 (42.12%)	78 / 302 (25.83%)	0 / 15 (0.00%)
occurrences (all)	199	94	0
Malaise			
subjects affected / exposed	12 / 349 (3.44%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences (all)	13	3	0
Mucosal inflammation			
subjects affected / exposed	20 / 349 (5.73%)	4 / 302 (1.32%)	0 / 15 (0.00%)
occurrences (all)	23	4	0
Oedema peripheral			
subjects affected / exposed	47 / 349 (13.47%)	27 / 302 (8.94%)	0 / 15 (0.00%)
occurrences (all)	55	34	0
Pyrexia			
subjects affected / exposed	77 / 349 (22.06%)	43 / 302 (14.24%)	0 / 15 (0.00%)
occurrences (all)	112	58	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 349 (15.76%)	30 / 302 (9.93%)	0 / 15 (0.00%)
occurrences (all)	65	34	0
Dyspnoea			
subjects affected / exposed	55 / 349 (15.76%)	34 / 302 (11.26%)	0 / 15 (0.00%)
occurrences (all)	62	40	0
Epistaxis			
subjects affected / exposed	22 / 349 (6.30%)	3 / 302 (0.99%)	0 / 15 (0.00%)
occurrences (all)	25	3	0
Hiccups			
subjects affected / exposed	21 / 349 (6.02%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences (all)	29	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	35 / 349 (10.03%)	19 / 302 (6.29%)	0 / 15 (0.00%)
occurrences (all)	40	19	0

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	23 / 349 (6.59%)	17 / 302 (5.63%)	0 / 15 (0.00%)
occurrences (all)	31	19	0
Alanine aminotransferase increased			
subjects affected / exposed	54 / 349 (15.47%)	20 / 302 (6.62%)	0 / 15 (0.00%)
occurrences (all)	106	22	0
Aspartate aminotransferase increased			
subjects affected / exposed	52 / 349 (14.90%)	21 / 302 (6.95%)	0 / 15 (0.00%)
occurrences (all)	93	33	0
Neutrophil count decreased			
subjects affected / exposed	77 / 349 (22.06%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences (all)	174	3	0
Blood creatinine increased			
subjects affected / exposed	68 / 349 (19.48%)	38 / 302 (12.58%)	0 / 15 (0.00%)
occurrences (all)	105	39	0
Platelet count decreased			
subjects affected / exposed	78 / 349 (22.35%)	5 / 302 (1.66%)	0 / 15 (0.00%)
occurrences (all)	159	5	0
White blood cell count decreased			
subjects affected / exposed	55 / 349 (15.76%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences (all)	136	1	0
Weight decreased			
subjects affected / exposed	38 / 349 (10.89%)	38 / 302 (12.58%)	0 / 15 (0.00%)
occurrences (all)	43	39	0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	24 / 349 (6.88%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences (all)	32	2	0
Dizziness			
subjects affected / exposed	45 / 349 (12.89%)	19 / 302 (6.29%)	0 / 15 (0.00%)
occurrences (all)	54	23	0
Dysgeusia			
subjects affected / exposed	25 / 349 (7.16%)	8 / 302 (2.65%)	0 / 15 (0.00%)
occurrences (all)	28	8	0
Headache			

subjects affected / exposed	42 / 349 (12.03%)	17 / 302 (5.63%)	0 / 15 (0.00%)
occurrences (all)	52	23	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	86 / 349 (24.64%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences (all)	175	2	0
Neutropenia			
subjects affected / exposed	126 / 349 (36.10%)	2 / 302 (0.66%)	0 / 15 (0.00%)
occurrences (all)	274	2	0
Anaemia			
subjects affected / exposed	227 / 349 (65.04%)	75 / 302 (24.83%)	0 / 15 (0.00%)
occurrences (all)	334	103	0
Leukopenia			
subjects affected / exposed	31 / 349 (8.88%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences (all)	60	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	102 / 349 (29.23%)	58 / 302 (19.21%)	0 / 15 (0.00%)
occurrences (all)	136	81	0
Dyspepsia			
subjects affected / exposed	14 / 349 (4.01%)	6 / 302 (1.99%)	0 / 15 (0.00%)
occurrences (all)	16	6	0
Gastrooesophageal reflux disease			
subjects affected / exposed	19 / 349 (5.44%)	1 / 302 (0.33%)	0 / 15 (0.00%)
occurrences (all)	20	1	0
Nausea			
subjects affected / exposed	180 / 349 (51.58%)	43 / 302 (14.24%)	0 / 15 (0.00%)
occurrences (all)	279	53	0
Constipation			
subjects affected / exposed	124 / 349 (35.53%)	56 / 302 (18.54%)	0 / 15 (0.00%)
occurrences (all)	155	70	0
Abdominal pain upper			
subjects affected / exposed	12 / 349 (3.44%)	9 / 302 (2.98%)	0 / 15 (0.00%)
occurrences (all)	15	11	0
Abdominal pain			

subjects affected / exposed	41 / 349 (11.75%)	29 / 302 (9.60%)	0 / 15 (0.00%)
occurrences (all)	51	35	0
Stomatitis			
subjects affected / exposed	22 / 349 (6.30%)	13 / 302 (4.30%)	0 / 15 (0.00%)
occurrences (all)	28	14	0
Vomiting			
subjects affected / exposed	91 / 349 (26.07%)	33 / 302 (10.93%)	0 / 15 (0.00%)
occurrences (all)	142	43	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	82 / 349 (23.50%)	40 / 302 (13.25%)	0 / 15 (0.00%)
occurrences (all)	108	57	0
Alopecia			
subjects affected / exposed	26 / 349 (7.45%)	0 / 302 (0.00%)	0 / 15 (0.00%)
occurrences (all)	26	0	0
Dry skin			
subjects affected / exposed	12 / 349 (3.44%)	18 / 302 (5.96%)	0 / 15 (0.00%)
occurrences (all)	13	19	0
Pruritus			
subjects affected / exposed	80 / 349 (22.92%)	66 / 302 (21.85%)	1 / 15 (6.67%)
occurrences (all)	109	89	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	19 / 349 (5.44%)	9 / 302 (2.98%)	0 / 15 (0.00%)
occurrences (all)	22	10	0
Haematuria			
subjects affected / exposed	53 / 349 (15.19%)	31 / 302 (10.26%)	0 / 15 (0.00%)
occurrences (all)	66	33	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	34 / 349 (9.74%)	30 / 302 (9.93%)	0 / 15 (0.00%)
occurrences (all)	43	33	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	45 / 349 (12.89%)	35 / 302 (11.59%)	0 / 15 (0.00%)
occurrences (all)	70	41	0

Back pain			
subjects affected / exposed	50 / 349 (14.33%)	37 / 302 (12.25%)	0 / 15 (0.00%)
occurrences (all)	67	43	0
Pain in extremity			
subjects affected / exposed	32 / 349 (9.17%)	24 / 302 (7.95%)	0 / 15 (0.00%)
occurrences (all)	36	27	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 349 (5.44%)	14 / 302 (4.64%)	0 / 15 (0.00%)
occurrences (all)	27	20	0
Upper respiratory tract infection			
subjects affected / exposed	26 / 349 (7.45%)	10 / 302 (3.31%)	0 / 15 (0.00%)
occurrences (all)	31	14	0
Urinary tract infection			
subjects affected / exposed	70 / 349 (20.06%)	62 / 302 (20.53%)	0 / 15 (0.00%)
occurrences (all)	109	93	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	31 / 349 (8.88%)	25 / 302 (8.28%)	0 / 15 (0.00%)
occurrences (all)	47	36	0
Hypomagnesaemia			
subjects affected / exposed	39 / 349 (11.17%)	9 / 302 (2.98%)	0 / 15 (0.00%)
occurrences (all)	53	10	0
Hypokalaemia			
subjects affected / exposed	33 / 349 (9.46%)	19 / 302 (6.29%)	1 / 15 (6.67%)
occurrences (all)	61	28	1
Hypoalbuminaemia			
subjects affected / exposed	19 / 349 (5.44%)	19 / 302 (6.29%)	0 / 15 (0.00%)
occurrences (all)	28	22	0
Hyperkalaemia			
subjects affected / exposed	34 / 349 (9.74%)	24 / 302 (7.95%)	0 / 15 (0.00%)
occurrences (all)	60	36	0
Hyperglycaemia			
subjects affected / exposed	23 / 349 (6.59%)	14 / 302 (4.64%)	0 / 15 (0.00%)
occurrences (all)	54	16	0
Decreased appetite			

subjects affected / exposed	121 / 349 (34.67%)	72 / 302 (23.84%)	0 / 15 (0.00%)
occurrences (all)	147	79	0

Non-serious adverse events	Pembrolizumab + ST Chemotherapy (Pembro Combo) Second Course	ST Chemotherapy (Chemo) First Course	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	337 / 342 (98.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	10 / 342 (2.92%)	
occurrences (all)	0	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	84 / 342 (24.56%)	
occurrences (all)	0	120	
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	122 / 342 (35.67%)	
occurrences (all)	0	150	
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	20 / 342 (5.85%)	
occurrences (all)	0	23	
Mucosal inflammation			
subjects affected / exposed	0 / 14 (0.00%)	9 / 342 (2.63%)	
occurrences (all)	0	15	
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	44 / 342 (12.87%)	
occurrences (all)	0	48	
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	41 / 342 (11.99%)	
occurrences (all)	0	62	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 14 (0.00%)	28 / 342 (8.19%)	
occurrences (all)	0	30	
Dyspnoea			

subjects affected / exposed	0 / 14 (0.00%)	36 / 342 (10.53%)	
occurrences (all)	0	40	
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	23 / 342 (6.73%)	
occurrences (all)	0	31	
Hiccups			
subjects affected / exposed	0 / 14 (0.00%)	14 / 342 (4.09%)	
occurrences (all)	0	22	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	16 / 342 (4.68%)	
occurrences (all)	0	18	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 14 (0.00%)	11 / 342 (3.22%)	
occurrences (all)	0	21	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	21 / 342 (6.14%)	
occurrences (all)	0	35	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	20 / 342 (5.85%)	
occurrences (all)	0	23	
Neutrophil count decreased			
subjects affected / exposed	0 / 14 (0.00%)	69 / 342 (20.18%)	
occurrences (all)	0	152	
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	39 / 342 (11.40%)	
occurrences (all)	0	51	
Platelet count decreased			
subjects affected / exposed	0 / 14 (0.00%)	79 / 342 (23.10%)	
occurrences (all)	0	169	
White blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)	51 / 342 (14.91%)	
occurrences (all)	0	109	
Weight decreased			

subjects affected / exposed	0 / 14 (0.00%)	22 / 342 (6.43%)	
occurrences (all)	0	23	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 14 (0.00%)	20 / 342 (5.85%)	
occurrences (all)	0	23	
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	36 / 342 (10.53%)	
occurrences (all)	0	41	
Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	28 / 342 (8.19%)	
occurrences (all)	0	30	
Headache			
subjects affected / exposed	0 / 14 (0.00%)	27 / 342 (7.89%)	
occurrences (all)	0	33	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 14 (0.00%)	89 / 342 (26.02%)	
occurrences (all)	0	180	
Neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	129 / 342 (37.72%)	
occurrences (all)	0	281	
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	210 / 342 (61.40%)	
occurrences (all)	0	303	
Leukopenia			
subjects affected / exposed	0 / 14 (0.00%)	25 / 342 (7.31%)	
occurrences (all)	0	55	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	73 / 342 (21.35%)	
occurrences (all)	0	91	
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	22 / 342 (6.43%)	
occurrences (all)	0	27	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 14 (0.00%)	6 / 342 (1.75%)	
occurrences (all)	0	7	
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	154 / 342 (45.03%)	
occurrences (all)	0	247	
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	107 / 342 (31.29%)	
occurrences (all)	0	140	
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	26 / 342 (7.60%)	
occurrences (all)	0	26	
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	29 / 342 (8.48%)	
occurrences (all)	0	31	
Stomatitis			
subjects affected / exposed	0 / 14 (0.00%)	18 / 342 (5.26%)	
occurrences (all)	0	20	
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	72 / 342 (21.05%)	
occurrences (all)	0	108	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 14 (0.00%)	24 / 342 (7.02%)	
occurrences (all)	0	33	
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	28 / 342 (8.19%)	
occurrences (all)	0	29	
Dry skin			
subjects affected / exposed	0 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences (all)	0	7	
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	17 / 342 (4.97%)	
occurrences (all)	0	21	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences (all)	0	10	
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	18 / 342 (5.26%)	
occurrences (all)	0	19	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 342 (0.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	24 / 342 (7.02%)	
occurrences (all)	0	25	
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	19 / 342 (5.56%)	
occurrences (all)	0	22	
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	14 / 342 (4.09%)	
occurrences (all)	0	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	16 / 342 (4.68%)	
occurrences (all)	0	16	
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	10 / 342 (2.92%)	
occurrences (all)	0	10	
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	48 / 342 (14.04%)	
occurrences (all)	0	55	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	16 / 342 (4.68%)	
occurrences (all)	0	23	
Hypomagnesaemia			
subjects affected / exposed	0 / 14 (0.00%)	24 / 342 (7.02%)	
occurrences (all)	0	26	

Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	11 / 342 (3.22%)	
occurrences (all)	0	12	
Hypoalbuminaemia			
subjects affected / exposed	0 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences (all)	0	8	
Hyperkalaemia			
subjects affected / exposed	0 / 14 (0.00%)	17 / 342 (4.97%)	
occurrences (all)	0	22	
Hyperglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	7 / 342 (2.05%)	
occurrences (all)	0	14	
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	95 / 342 (27.78%)	
occurrences (all)	0	122	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2017	Major changes of Amendment (AM) 2 included revision and simplification of the Statistical Analysis Plan.
16 March 2018	Major changes of AM 4 included a recommendation from the external Data Monitoring Committee to stop accrual to the pembrolizumab monotherapy arm for participants whose tumors are PD-L1 CPS<10%.
23 October 2019	Major changes of AM 6 included a revision the Statistical Analysis Plan in order to account for a potential delayed treatment effect, which was observed with immunotherapy study data external to this study.
15 May 2020	Major changes of AM 8 included the removal of the requirement for the final analysis of approximately 532 PFS events in the combo and chemo arms in all participants, due to a significant drop off in the accrual of PFS events.
30 June 2021	Major changes of AM 10 included updating the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported