Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer (KEYNOTE-826)

Summary

EudraCT number	2018-001440-53
Trial protocol	DE FR ES PL IT
Global end of trial date	04 June 2024

Results information

Result version number	v1 (current)
This version publication date	24 May 2025
First version publication date	24 May 2025

Trial information

Trial identification

Sponsor protocol code	MK-3475-826

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03635567
WHO universal trial number (UTN)	-
Other trial identifiers	JAPAC-CTI: 184183, MSD: KEYNOTE-826

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.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	04 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2022
Global end of trial reached?	Yes
Global end of trial date	04 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of pembrolizumab (MK-3475) plus one of four platinum-based chemotherapy regimens compared to the efficacy and safety of placebo plus one of four platinum-based chemotherapy regimens in the treatment of adult women with persistent, recurrent, or metastatic cervical cancer. Possible chemotherapy regimens include: paclitaxel plus cisplatin with or without bevacizumab and paclitaxel plus carboplatin with or without bevacizumab. The primary study hypotheses are that the combination of pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy with respect to: 1) Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the Investigator, or, 2) Overall Survival (OS).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 40
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Chile: 57
Country: Number of subjects enrolled	Colombia: 43
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Japan: 57
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Peru: 41
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Taiwan: 16

Country: Number of subjects enrolled	Türkiye: 24
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	617
EEA total number of subjects	97

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)	517
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

883 participants were screened and 617 participants were randomized to receive either Pembrolizumab+Chemotherapy or Placebo+Chemotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab+Chemotherapy

Arm description:

On Day 1 of each 21-day cycle, participants received an intravenous (IV) infusion of pembrolizumab 200 mg for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin Area Under the Curve (AUC) 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

Arm title	Placebo+Chemotherapy

Arm description:

On Day 1 of each 21-day cycle, participants received an IV infusion of placebo (Normal Saline or Dextrose solution) for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin AUC 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity.

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

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

Dosage and administration details:

IV infusion

Investigational medicinal product name	Placebo to pembrolizumab
Investigational medicinal product code	
Other name	Normal Saline or Dextrose solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion

Number of subjects in period 1	Pembrolizumab+Chemotherapy	Placebo+Chemotherapy
Started	308	309
Treated	307	309
Received Second Course of Pembrolizumab	12	0
Completed	0	0
Not completed	308	309
Consent withdrawn by subject	11	16
Death	194	235
Sponsor Decision	99	57
Lost to follow-up	4	1

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an intravenous (IV) infusion of pembrolizumab 200 mg for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin Area Under the Curve (AUC) 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Placebo+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an IV infusion of placebo (Normal Saline or Dextrose solution) for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin AUC 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity.

Reporting group values	Pembrolizumab+Chemotherapy	Placebo+Chemotherapy	Total
Number of subjects	308	309	617
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	260	257	517
From 65-84 years	48	52	100
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.7	50.7	
standard deviation	± 11.9	± 12.7	-
Sex: Female, Male Units: Participants			
Female	308	309	617
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	18	21	39
Asian	65	45	110
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	2	6

White	170	190	360
More than one race	32	34	66
Unknown or Not Reported	19	17	36
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	109	121	230
Not Hispanic or Latino	193	184	377
Unknown or Not Reported	6	4	10
Programmed Cell Death-Ligand 1 (PD-L1) Combined Positive Score (CPS) Status			
Participants were assessed for their PD-L1 tumor expression level by immunohistochemistry assay using tumor tissue. Randomization of participants in the study were stratified by their PD-L1 CPS at baseline (PD-L1 CPS<1, 1≤ PD-L1 CPS<10, or PD-L1 CPS≥10).			
Units: Subjects			
PD-L1 CPS<1	35	34	69
1≤ PD-L1 CPS<10	115	116	231
PD-L1 CPS≥10	158	159	317
Metastatic at Initial Diagnosis			
Randomization of participants was stratified by whether they were metastatic at initial diagnosis (Yes or No). Metastatic was defined as Stage IVB based on the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) (2009).			
Units: Subjects			
Metastatic at Initial Diagnosis = Yes	94	96	190
Metastatic at Initial Diagnosis = No	214	213	427
Investigator Choice to Use Bevacizumab			
Randomization of participants was stratified by the Investigator's choice for the participant to receive bevacizumab (Yes or No).			
Units: Subjects			
Received Bevacizumab = Yes	196	193	389
Received Bevacizumab = No	112	116	228

End points

End points reporting groups

Reporting group title	Pembrolizumab+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an intravenous (IV) infusion of pembrolizumab 200 mg for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin Area Under the Curve (AUC) 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Placebo+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an IV infusion of placebo (Normal Saline or Dextrose solution) for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin AUC 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity.

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

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

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 as assessed by Investigator for all randomized participants with PD-L1 CPS ≥1 is presented. All randomized participants with PD-L1 CPS ≥1 based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	275		
Units: Months				
median (confidence interval 95%)	10.5 (9.7 to 12.3)	8.2 (6.3 to 8.5)		

Statistical analyses

Statistical analysis title	PFS in CPS ≥1 Participants

Statistical analysis description:

Treatment comparison (hazard ratio [HR]) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.71

Notes:

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

Primary: PFS per RECIST 1.1 as Assessed by Investigator in All Participants

End point title	PFS per RECIST 1.1 as Assessed by Investigator in All Participants

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 as assessed by Investigator for all randomized participants is presented. All randomized participants based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	309		
Units: Months				
median (confidence interval 95%)	10.4 (9.1 to	8.2 (6.4 to 8.4)		

12.2)

Statistical analyses

Statistical analysis title	PFS in All Participants

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.74

Notes:

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

Primary: PFS per RECIST 1.1 as Assessed by Investigator in Participants with PD-L1 CPS ≥10

End point title	PFS per RECIST 1.1 as Assessed by Investigator in Participants with PD-L1 CPS ≥10

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 as assessed by Investigator for all randomized participants with PD-L1 CPS ≥10 is presented. All randomized participants with PD-L1 CPS ≥10 based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	159		
Units: Months				
median (confidence interval 95%)	10.4 (8.9 to 15.1)	8.1 (6.2 to 8.8)		

Statistical analyses

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

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [3]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.68

Notes:

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

Primary: Overall Survival (OS) in Participants with PD-L1 CPS ≥1

End point title	Overall Survival (OS) in Participants with PD-L1 CPS ≥1

End point description:

OS was defined as the time from randomization to death due to any cause. The OS for all randomized participants with PD-L1 CPS ≥1 is presented. All randomized participants with PD-L1 CPS ≥1 based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	275		
Units: Months				
median (confidence interval 95%)	28.6 (22.1 to 38.0)	16.5 (14.5 to 20.0)		

Statistical analyses

Statistical analysis title	OS in Participants with PD-L1 CPS ≥1

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [4]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.74

Notes:

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

Primary: OS in All Participants

End point title	OS in All Participants

End point description:

OS was defined as the time from randomization to death due to any cause. The OS for all randomized participants is presented. All randomized participants based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	309		
Units: Months				
median (confidence interval 95%)	26.4 (21.3 to 32.5)	16.8 (14.6 to 19.4)		

Statistical analyses

Statistical analysis title	OS in All Participants

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [5]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.77

Notes:

[5] - No formal hypothesis testing performed; nominal p-value based on log-rank test provided for treatment comparison.

Primary: OS in Participants with PD-L1 CPS ≥10

End point title	OS in Participants with PD-L1 CPS ≥10

End point description:

OS was defined as the time from randomization to death due to any cause. The OS for all randomized participants with PD-L1 CPS ≥10 is presented. A value of 9999 means that the upper limit not reached at time of data cut-off due to insufficient number of participants with an event. All randomized participants with PD-L1 CPS ≥10 based on the treatment group to which they were randomized were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	159		
Units: Months				
median (confidence interval 95%)	29.6 (20.6 to 9999)	17.4 (14.0 to 24.7)		

Statistical analyses

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

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [6]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.78

Notes:

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

Secondary: Objective Response Rate (ORR) Per RECIST 1.1 as Assessed by Investigator

End point title	Objective Response Rate (ORR) Per RECIST 1.1 as Assessed by Investigator

End point description:

ORR was defined as the percentage of the participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters). The ORR per RECIST 1.1 as assessed by Investigator is presented. All randomized participants based on the treatment group to which they were randomized were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	309		
Units: Percentage of Participants				
number (confidence interval 95%)	66.2 (60.7 to 71.5)	51.5 (45.7 to 57.2)		

Statistical analyses

Statistical analysis title	ORR - Pembro+Chemo vs. Placebo+Chemo

Statistical analysis description:

Treatment comparison was based on Miettinen & Nurminen method stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001 [7]
Method	Miettinen & Nurminen method
Parameter estimate	Difference in Percentage
Point estimate	14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.4
upper limit	22.3

Notes:

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

Secondary: Duration of Response (DOR) Per RECIST 1.1 as Assessed by Investigator

End point title	Duration of Response (DOR) Per RECIST 1.1 as Assessed by Investigator

End point description:

For participants who demonstrate CR or PR, DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. The DOR per RECIST 1.1 as assessed by Investigator is presented. All randomized participants based on the treatment group to which they were randomized who demonstrated CR or PR were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	159		
Units: Months				
median (confidence interval 95%)	18.0 (10.5 to 32.3)	10.4 (8.3 to 13.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants that were PFS Event-Free (PFS Rate) at Month 12 Per RECIST 1.1 as Assessed by Investigator

End point title	Percentage of Participants that were PFS Event-Free (PFS Rate) at Month 12 Per RECIST 1.1 as Assessed by Investigator

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS Rate was defined as the percentage of participants that were PFS event-free at Month 12. The PFS Rate per RECIST 1.1 as assessed by Investigator at Month 12 is presented. All randomized participants based on the treatment group to which they were randomized were analyzed.

End point type	Secondary

End point timeframe:

12 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	309		
Units: Percentage of Participants				
number (confidence interval 95%)	44.7 (38.9 to 50.4)	33.1 (27.7 to 38.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per RECIST 1.1 as Assessed by Blinded Independent Central Review (BICR)

End point title	PFS per 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 PD or death due to any cause,

whichever occurs first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 as assessed by BICR is presented. All randomized participants based on the treatment group to which they were randomized were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	309		
Units: Months				
median (confidence interval 95%)	12.3 (10.3 to 17.9)	8.3 (8.1 to 9.0)		

Statistical analyses

Statistical analysis title	PFS per RECIST 1.1 as Assessed by BICR

Statistical analysis description:

Treatment comparison (HR) was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS<1, CPS 1 to <10, or CPS ≥10).

Comparison groups	Pembrolizumab+Chemotherapy v Placebo+Chemotherapy
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [8]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.74

Notes:

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

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

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

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who experienced an AE is presented. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	309		
Units: Number of participants	305	307		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Serious AE (SAE)

End point title	Number of Participants Who Experienced a Serious AE (SAE)

End point description:

An SAE was defined as any untoward medical occurrence that, at any dose: a.) Resulted in death; b.) Was life-threatening; c.) Required inpatient hospitalization or prolongation of existing hospitalization; d.) Resulted in persistent or significant disability/incapacity; e.) Was a congenital anomaly/birth defect; f.) Other important medical events; h.) Was a new cancer (that is not a condition of the study) or i.) Was associated with an overdose. The number of participants who experienced an SAE is presented. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	309		
Units: Number of Participants	157	132		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Immune-related AE (irAE)

End point title	Number of Participants Who Experienced an Immune-related AE (irAE)

End point description:

AEs associated with pembrolizumab exposure may be a result of an immune response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and

may affect more than one body system simultaneously. For this study irAEs included, but were not limited to: -Pneumonitis;
-Diarrhea/Colitis;
-Aspartate transaminase (AST)/Alanine transaminase (ALT) elevation or Increased bilirubin;
-Type 1 diabetes mellitus or Hyperglycemia;
-Hypophysitis;
-Hyperthyroidism;
-Hypothyroidism;
-Nephritis and Renal dysfunction; and
-Myocarditis.
The number of participants who experienced an irAE is presented. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 66 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	309		
Units: Number of Participants	134	92		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to an AE

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

End point description:

The number of participants who discontinued study treatment due to an AE is presented. All randomized participants who received at least one dose of study treatment were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 63 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	309		
Units: Number of Participants	126	92		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a 10-point Change from Baseline in Quality of Life (QoL) Based on the European Organisation for the Research & Treatment of Cancer (EORTC) QoL Questionnaire-30 (QLQ-C30) Combined Global Score

End point title	Number of Participants with a 10-point Change from Baseline in Quality of Life (QoL) Based on the European Organisation for the Research & Treatment of Cancer (EORTC) QoL Questionnaire-30 (QLQ-C30) Combined Global Score

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the QoL of participants. Responses to "How would you rate your overall health during the past week?" (Item 29) & "How would you rate your overall quality of life during the past week?" (Item 30) are scored on a 7-point scale (1= Very poor to 7=Excellent). Raw scores are standardized with linear transformation from 0-100. A higher combined score indicates a better overall health status. Participant post-baseline scores were classified as "Improved": a ≥10-point improvement in score & confirmed by the next visit; "Stable": a ≥10-point increase or <10-point change in score OR a <10-point change in score & a ≥10-point increase in score at the next visit; or "Deteriorated": a ≥10-point deterioration in score when the criteria for improvement/stability weren't met. Participants who didn't meet the above criteria were reported as "Other". All randomized participants who received ≥1 dose of treatment & completed ≥1 EORTC QLQ-C30 were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1: Predose) and up to approximately 46 months

End point values	Pembrolizumab +Chemotherapy	Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279	282		
Units: Number of Participants				
Improved	122	86		
Stable	106	139		
Deteriorated	42	48		
Other	9	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 66 months

Adverse event reporting additional description:

AEs included all participants who received ≥1 dose of study drug. All-Cause Mortality included all randomized participants. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" not related to study treatment are excluded as AEs. Data are reported by treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Pembrolizumab+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an intravenous (IV) infusion of pembrolizumab 200 mg for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin Area Under the Curve (AUC) 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity. Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	Placebo+Chemotherapy

Reporting group description:

On Day 1 of each 21-day cycle, participants received an IV infusion of placebo (Normal Saline or Dextrose solution) for up to 35 cycles (up to approximately 2 years) PLUS Investigator choice of chemotherapy for up to 6 cycles (paclitaxel 175 mg/m^2 PLUS cisplatin 50 mg/m^2 WITH or WITHOUT bevacizumab 15 mg/kg per local label OR paclitaxel 175 mg/m^2 PLUS carboplatin AUC 5 for up to 6 cycles, WITH or WITHOUT bevacizumab 15 mg/kg per local label). All treatments were administered until disease progression or toxicity.

Reporting group title	Pembrolizumab (Second Course)

Reporting group description:

Eligible participants received up to 17 additional administrations (up to approximately 1 year) of pembrolizumab 200 mg IV on Day 1 of each 21-day cycle.

Serious adverse events	Pembrolizumab+Chemotherapy	Placebo+Chemotherapy	Pembrolizumab (Second Course)
Total subjects affected by serious adverse events			
subjects affected / exposed	157 / 307 (51.14%)	132 / 309 (42.72%)	4 / 12 (33.33%)
number of deaths (all causes)	195	241	4
number of deaths resulting from adverse events	16	15	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Tumour haemorrhage			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Ovarian cancer recurrent			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 307 (0.65%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hypertension			
subjects affected / exposed	0 / 307 (0.00%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	4 / 307 (1.30%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Hypertensive urgency			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Vena cava embolism			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Subclavian vein thrombosis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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			
Chest pain			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Asthenia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Death			

subjects affected / exposed	3 / 307 (0.98%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 0
Pseudocyst			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Pyrexia			
subjects affected / exposed	9 / 307 (2.93%)	5 / 309 (1.62%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 9	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site extravasation			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Malaise			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site laceration			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 307 (0.00%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media allergy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Anaphylactic shock			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Anaphylactic reaction			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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	1 / 307 (0.33%)	3 / 309 (0.97%)	0 / 12 (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
Intermenstrual bleeding			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heavy menstrual bleeding			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Female genital tract fistula			
subjects affected / exposed	8 / 307 (2.61%)	10 / 309 (3.24%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	5 / 8	4 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Uterine haemorrhage			
subjects affected / exposed	3 / 307 (0.98%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vaginal fistula			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (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
Vulval ulceration			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Vaginal haemorrhage			
subjects affected / exposed	5 / 307 (1.63%)	4 / 309 (1.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 5	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Oropharyngeal pain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Pneumonitis			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Pneumothorax			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Pulmonary embolism			
subjects affected / exposed	4 / 307 (1.30%)	6 / 309 (1.94%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 4	2 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Delirium			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Stent malfunction			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	2 / 307 (0.65%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Alanine aminotransferase increased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Urine output decreased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Platelet count decreased			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutrophil count decreased			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Weight decreased			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Fall			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cystitis radiation			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Ankle fracture			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Fibula fracture			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Hip fracture			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Humerus fracture			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Infusion related reaction			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Pelvic fracture			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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 urine leak			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Foot fracture			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Gastroenteritis radiation			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Procedural pneumothorax			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Radiation proctitis			
subjects affected / exposed	4 / 307 (1.30%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Urinary tract stoma complication			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (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
Tibia fracture			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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 haemorrhage			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Atrial fibrillation			
subjects affected / exposed	4 / 307 (1.30%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Mitral valve stenosis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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

Supraventricular tachycardia			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Stress cardiomyopathy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Myocarditis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Myocardial infarction			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Cerebellar infarction			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Ischaemic stroke			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Idiopathic intracranial hypertension			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Hypoaesthesia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Hemiparesis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Headache			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Encephalitis autoimmune			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Seizure			
subjects affected / exposed	3 / 307 (0.98%)	0 / 309 (0.00%)	0 / 12 (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
Posterior reversible encephalopathy syndrome			

subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (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
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Peripheral motor neuropathy			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 307 (4.56%)	12 / 309 (3.88%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	7 / 14	9 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Lymphadenitis			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Leukopenia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	21 / 307 (6.84%)	13 / 309 (4.21%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	25 / 25	13 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 307 (1.30%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	4 / 5	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 307 (0.65%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 307 (0.98%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic neuropathy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Anal fistula			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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 pain upper			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 307 (0.65%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal ulcer			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Colitis			
subjects affected / exposed	3 / 307 (0.98%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 12 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Enterovesical fistula			

subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Duodenal perforation			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Diarrhoea			
subjects affected / exposed	5 / 307 (1.63%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	4 / 5	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Gastritis			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Gastric ulcer			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Ileus			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			

subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	3 / 307 (0.98%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Nausea			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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 intestine perforation			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 12 (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
Large intestinal obstruction			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Pancreatitis acute			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	0 / 12 (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
Small intestinal obstruction			

subjects affected / exposed	0 / 307 (0.00%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	3 / 307 (0.98%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Small intestinal perforation			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Subileus			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 12 (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
Volvulus			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Vomiting			

subjects affected / exposed	3 / 307 (0.98%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Cholelithiasis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Cholecystitis acute			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Autoimmune hepatitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Hepatotoxicity			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated cholangitis			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	3 / 307 (0.98%)	0 / 309 (0.00%)	0 / 12 (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
Skin ulcer			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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	11 / 307 (3.58%)	5 / 309 (1.62%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	6 / 13	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder diverticulum			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Haematuria			
subjects affected / exposed	5 / 307 (1.63%)	4 / 309 (1.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 6	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Nephrolithiasis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Hydronephrosis			
subjects affected / exposed	4 / 307 (1.30%)	4 / 309 (1.29%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Urinary tract obstruction			
subjects affected / exposed	1 / 307 (0.33%)	3 / 309 (0.97%)	0 / 12 (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
Urethral fistula			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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 stenosis			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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 failure			
subjects affected / exposed	1 / 307 (0.33%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinoma			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Urogenital fistula			
subjects affected / exposed	5 / 307 (1.63%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 5	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Adrenal insufficiency			
subjects affected / exposed	3 / 307 (0.98%)	0 / 309 (0.00%)	0 / 12 (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
Hypophysitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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

Osteoporosis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Myositis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Muscular weakness			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Back pain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Autoimmune myositis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	0 / 12 (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
Abdominal wall abscess			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Abscess			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 307 (0.33%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
COVID-19			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Anal abscess			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Acute hepatitis B			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Diverticulitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Cytomegalovirus infection			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Cellulitis			
subjects affected / exposed	1 / 307 (0.33%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Erysipelas			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Infection			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected lymphocele			

subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Infected fistula			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Herpes zoster meningoradiculitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Herpes zoster			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Groin abscess			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Fournier's gangrene			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	0 / 12 (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
Pelvic infection			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Lower respiratory tract infection			

subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Pneumonia			
subjects affected / exposed	1 / 307 (0.33%)	7 / 309 (2.27%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoas abscess			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Sepsis			
subjects affected / exposed	8 / 307 (2.61%)	5 / 309 (1.62%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 8	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pyometra			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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	2 / 307 (0.65%)	3 / 309 (0.97%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	4 / 307 (1.30%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Urosepsis			
subjects affected / exposed	2 / 307 (0.65%)	4 / 309 (1.29%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	16 / 307 (5.21%)	20 / 309 (6.47%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	3 / 17	2 / 23	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 307 (0.65%)	2 / 309 (0.65%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			

subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	0 / 12 (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
Cachexia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Decreased appetite			
subjects affected / exposed	0 / 307 (0.00%)	1 / 309 (0.32%)	0 / 12 (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
Dehydration			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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
Diabetic ketoacidosis			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	0 / 12 (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
Electrolyte imbalance			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 307 (0.33%)	1 / 309 (0.32%)	0 / 12 (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

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

Non-serious adverse events	Pembrolizumab+Chemotherapy	Placebo+Chemotherapy	Pembrolizumab (Second Course)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	298 / 307 (97.07%)	299 / 309 (96.76%)	8 / 12 (66.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	80 / 307 (26.06%)	71 / 309 (22.98%)	0 / 12 (0.00%)
occurrences (all)	117	117	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	64 / 307 (20.85%)	66 / 309 (21.36%)	0 / 12 (0.00%)
occurrences (all)	122	128	0
Fatigue			
subjects affected / exposed	88 / 307 (28.66%)	85 / 309 (27.51%)	0 / 12 (0.00%)
occurrences (all)	148	150	0
Pyrexia			
subjects affected / exposed	51 / 307 (16.61%)	44 / 309 (14.24%)	0 / 12 (0.00%)
occurrences (all)	78	61	0
Oedema peripheral			
subjects affected / exposed	32 / 307 (10.42%)	30 / 309 (9.71%)	0 / 12 (0.00%)
occurrences (all)	38	36	0
Mucosal inflammation			
subjects affected / exposed	23 / 307 (7.49%)	10 / 309 (3.24%)	0 / 12 (0.00%)
occurrences (all)	32	14	0
Facial pain			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	17 / 307 (5.54%)	24 / 309 (7.77%)	0 / 12 (0.00%)
occurrences (all)	18	26	0
Pelvic pain			

subjects affected / exposed	16 / 307 (5.21%)	33 / 309 (10.68%)	0 / 12 (0.00%)
occurrences (all)	18	39	0
Vaginal haemorrhage			
subjects affected / exposed	25 / 307 (8.14%)	32 / 309 (10.36%)	1 / 12 (8.33%)
occurrences (all)	40	40	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	22 / 307 (7.17%)	30 / 309 (9.71%)	1 / 12 (8.33%)
occurrences (all)	28	34	1
Cough			
subjects affected / exposed	40 / 307 (13.03%)	32 / 309 (10.36%)	1 / 12 (8.33%)
occurrences (all)	48	41	1
Asthma			
subjects affected / exposed	2 / 307 (0.65%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Epistaxis			
subjects affected / exposed	31 / 307 (10.10%)	43 / 309 (13.92%)	1 / 12 (8.33%)
occurrences (all)	53	65	1
Oropharyngeal discomfort			
subjects affected / exposed	0 / 307 (0.00%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 307 (11.07%)	27 / 309 (8.74%)	2 / 12 (16.67%)
occurrences (all)	35	29	2
Anxiety			
subjects affected / exposed	16 / 307 (5.21%)	13 / 309 (4.21%)	0 / 12 (0.00%)
occurrences (all)	16	14	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 307 (14.66%)	29 / 309 (9.39%)	3 / 12 (25.00%)
occurrences (all)	67	37	3
Aspartate aminotransferase increased			
subjects affected / exposed	35 / 307 (11.40%)	24 / 309 (7.77%)	3 / 12 (25.00%)
occurrences (all)	57	32	3
Blood alkaline phosphatase increased			

subjects affected / exposed	27 / 307 (8.79%)	18 / 309 (5.83%)	1 / 12 (8.33%)
occurrences (all)	33	20	1
White blood cell count decreased			
subjects affected / exposed	37 / 307 (12.05%)	22 / 309 (7.12%)	1 / 12 (8.33%)
occurrences (all)	109	62	1
Weight decreased			
subjects affected / exposed	35 / 307 (11.40%)	37 / 309 (11.97%)	0 / 12 (0.00%)
occurrences (all)	35	38	0
Platelet count decreased			
subjects affected / exposed	49 / 307 (15.96%)	42 / 309 (13.59%)	1 / 12 (8.33%)
occurrences (all)	99	69	1
Neutrophil count decreased			
subjects affected / exposed	56 / 307 (18.24%)	48 / 309 (15.53%)	0 / 12 (0.00%)
occurrences (all)	152	143	0
Blood creatinine increased			
subjects affected / exposed	28 / 307 (9.12%)	34 / 309 (11.00%)	0 / 12 (0.00%)
occurrences (all)	44	42	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	17 / 307 (5.54%)	12 / 309 (3.88%)	0 / 12 (0.00%)
occurrences (all)	24	17	0
Gastroenteritis radiation			
subjects affected / exposed	8 / 307 (2.61%)	3 / 309 (0.97%)	1 / 12 (8.33%)
occurrences (all)	8	3	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 307 (7.17%)	26 / 309 (8.41%)	0 / 12 (0.00%)
occurrences (all)	27	33	0
Dysgeusia			
subjects affected / exposed	15 / 307 (4.89%)	20 / 309 (6.47%)	0 / 12 (0.00%)
occurrences (all)	17	24	0
Headache			
subjects affected / exposed	50 / 307 (16.29%)	57 / 309 (18.45%)	0 / 12 (0.00%)
occurrences (all)	76	99	0
Peripheral sensory neuropathy			

subjects affected / exposed	70 / 307 (22.80%)	78 / 309 (25.24%)	0 / 12 (0.00%)
occurrences (all)	81	89	0
Paraesthesia			
subjects affected / exposed	28 / 307 (9.12%)	26 / 309 (8.41%)	0 / 12 (0.00%)
occurrences (all)	38	34	0
Neuropathy peripheral			
subjects affected / exposed	81 / 307 (26.38%)	80 / 309 (25.89%)	0 / 12 (0.00%)
occurrences (all)	105	97	0
Migraine			
subjects affected / exposed	2 / 307 (0.65%)	1 / 309 (0.32%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	15 / 307 (4.89%)	7 / 309 (2.27%)	1 / 12 (8.33%)
occurrences (all)	29	7	1
Leukopenia			
subjects affected / exposed	40 / 307 (13.03%)	33 / 309 (10.68%)	2 / 12 (16.67%)
occurrences (all)	71	55	2
Anaemia			
subjects affected / exposed	182 / 307 (59.28%)	159 / 309 (51.46%)	2 / 12 (16.67%)
occurrences (all)	264	247	2
Neutropenia			
subjects affected / exposed	71 / 307 (23.13%)	58 / 309 (18.77%)	0 / 12 (0.00%)
occurrences (all)	142	115	0
Thrombocytopenia			
subjects affected / exposed	60 / 307 (19.54%)	60 / 309 (19.42%)	0 / 12 (0.00%)
occurrences (all)	90	101	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 307 (0.00%)	2 / 309 (0.65%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	50 / 307 (16.29%)	52 / 309 (16.83%)	0 / 12 (0.00%)
occurrences (all)	66	78	0
Abdominal pain lower			

subjects affected / exposed	16 / 307 (5.21%)	12 / 309 (3.88%)	0 / 12 (0.00%)
occurrences (all)	18	13	0
Constipation			
subjects affected / exposed	89 / 307 (28.99%)	101 / 309 (32.69%)	1 / 12 (8.33%)
occurrences (all)	143	147	1
Abdominal pain upper			
subjects affected / exposed	30 / 307 (9.77%)	30 / 309 (9.71%)	0 / 12 (0.00%)
occurrences (all)	43	41	0
Diarrhoea			
subjects affected / exposed	111 / 307 (36.16%)	93 / 309 (30.10%)	1 / 12 (8.33%)
occurrences (all)	203	174	1
Dyspepsia			
subjects affected / exposed	20 / 307 (6.51%)	15 / 309 (4.85%)	1 / 12 (8.33%)
occurrences (all)	24	19	2
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 307 (3.58%)	13 / 309 (4.21%)	1 / 12 (8.33%)
occurrences (all)	11	14	1
Nausea			
subjects affected / exposed	122 / 307 (39.74%)	135 / 309 (43.69%)	1 / 12 (8.33%)
occurrences (all)	265	287	1
Stomatitis			
subjects affected / exposed	22 / 307 (7.17%)	22 / 309 (7.12%)	1 / 12 (8.33%)
occurrences (all)	26	30	1
Rectal haemorrhage			
subjects affected / exposed	16 / 307 (5.21%)	15 / 309 (4.85%)	0 / 12 (0.00%)
occurrences (all)	26	20	0
Vomiting			
subjects affected / exposed	81 / 307 (26.38%)	85 / 309 (27.51%)	1 / 12 (8.33%)
occurrences (all)	127	142	1
Cheilitis			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Food poisoning			
subjects affected / exposed	1 / 307 (0.33%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Colitis			

subjects affected / exposed	10 / 307 (3.26%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	11	0	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	16 / 307 (5.21%)	9 / 309 (2.91%)	1 / 12 (8.33%)
occurrences (all)	20	13	2
Rash			
subjects affected / exposed	47 / 307 (15.31%)	36 / 309 (11.65%)	2 / 12 (16.67%)
occurrences (all)	66	48	2
Pruritus			
subjects affected / exposed	40 / 307 (13.03%)	26 / 309 (8.41%)	0 / 12 (0.00%)
occurrences (all)	58	39	0
Dry skin			
subjects affected / exposed	18 / 307 (5.86%)	9 / 309 (2.91%)	0 / 12 (0.00%)
occurrences (all)	18	10	0
Alopecia			
subjects affected / exposed	173 / 307 (56.35%)	179 / 309 (57.93%)	0 / 12 (0.00%)
occurrences (all)	173	181	0
Dermatitis			
subjects affected / exposed	5 / 307 (1.63%)	6 / 309 (1.94%)	1 / 12 (8.33%)
occurrences (all)	8	7	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	22 / 307 (7.17%)	23 / 309 (7.44%)	0 / 12 (0.00%)
occurrences (all)	27	29	0
Incontinence			
subjects affected / exposed	3 / 307 (0.98%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	1
Leukocyturia			
subjects affected / exposed	5 / 307 (1.63%)	1 / 309 (0.32%)	2 / 12 (16.67%)
occurrences (all)	8	1	2
Proteinuria			
subjects affected / exposed	54 / 307 (17.59%)	33 / 309 (10.68%)	0 / 12 (0.00%)
occurrences (all)	87	52	0
Haematuria			

subjects affected / exposed	20 / 307 (6.51%)	15 / 309 (4.85%)	0 / 12 (0.00%)
occurrences (all)	25	20	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	59 / 307 (19.22%)	31 / 309 (10.03%)	0 / 12 (0.00%)
occurrences (all)	65	33	0
Hyperthyroidism			
subjects affected / exposed	24 / 307 (7.82%)	9 / 309 (2.91%)	0 / 12 (0.00%)
occurrences (all)	26	10	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	82 / 307 (26.71%)	78 / 309 (25.24%)	0 / 12 (0.00%)
occurrences (all)	128	126	0
Back pain			
subjects affected / exposed	44 / 307 (14.33%)	48 / 309 (15.53%)	0 / 12 (0.00%)
occurrences (all)	55	64	0
Bone pain			
subjects affected / exposed	21 / 307 (6.84%)	18 / 309 (5.83%)	0 / 12 (0.00%)
occurrences (all)	22	22	0
Myalgia			
subjects affected / exposed	57 / 307 (18.57%)	61 / 309 (19.74%)	1 / 12 (8.33%)
occurrences (all)	98	115	1
Pain in extremity			
subjects affected / exposed	38 / 307 (12.38%)	27 / 309 (8.74%)	0 / 12 (0.00%)
occurrences (all)	60	52	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	67 / 307 (21.82%)	74 / 309 (23.95%)	0 / 12 (0.00%)
occurrences (all)	123	111	0
Upper respiratory tract infection			
subjects affected / exposed	13 / 307 (4.23%)	16 / 309 (5.18%)	0 / 12 (0.00%)
occurrences (all)	19	21	0
Nasopharyngitis			
subjects affected / exposed	20 / 307 (6.51%)	11 / 309 (3.56%)	1 / 12 (8.33%)
occurrences (all)	26	13	1
Influenza			

subjects affected / exposed	3 / 307 (0.98%)	13 / 309 (4.21%)	1 / 12 (8.33%)
occurrences (all)	3	14	1
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	18 / 307 (5.86%)	11 / 309 (3.56%)	1 / 12 (8.33%)
occurrences (all)	19	11	1
Hyperglycaemia			
subjects affected / exposed	13 / 307 (4.23%)	19 / 309 (6.15%)	1 / 12 (8.33%)
occurrences (all)	19	28	1
Hypokalaemia			
subjects affected / exposed	30 / 307 (9.77%)	29 / 309 (9.39%)	1 / 12 (8.33%)
occurrences (all)	43	34	1
Decreased appetite			
subjects affected / exposed	62 / 307 (20.20%)	52 / 309 (16.83%)	1 / 12 (8.33%)
occurrences (all)	97	77	1
Hypomagnesaemia			
subjects affected / exposed	27 / 307 (8.79%)	19 / 309 (6.15%)	0 / 12 (0.00%)
occurrences (all)	38	31	0
Hyponatraemia			
subjects affected / exposed	21 / 307 (6.84%)	15 / 309 (4.85%)	0 / 12 (0.00%)
occurrences (all)	27	16	0
Hypoproteinaemia			
subjects affected / exposed	3 / 307 (0.98%)	0 / 309 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2019	Amendment 2: The purpose of this amendment was to clarify the stratification factors and treatment duration of the study.
25 February 2020	Amendment 3: The purpose of this amendment was to modify objectives and hypotheses with an updated multiplicity strategy based on updated results.
20 May 2020	Amendment 4: The purpose of this amendment was to modify objectives and hypotheses with an updated multiplicity strategy based on updated results.
01 December 2020	Amendment 5: The purpose of this amendment was to modify objectives including primary efficacy endpoints.
21 July 2021	Amendment 6: The purpose of this amendment was to update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
01 February 2022	Amendment 7: The purpose of this amendment was to state that the preplanned second interim analysis (IA2) will not be performed.
12 July 2022	Amendment 8: The purpose of this amendment was to update the Sponsor name.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported