Clinical trial results:
Randomized, Phase II Study of Pembrolizumab (MK-3475) versus Chemotherapy in Patients with Advanced Melanoma (KEYNOTE 002)

Summary

EudraCT number	2012-003030-17
Trial protocol	ES DE NO SE IT NL FR Outside EU/EEA
Global end of trial date	31 January 2019

Results information

Result version number	v2 (current)
This version publication date	28 August 2019
First version publication date	22 February 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	P08719

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01704287
WHO universal trial number (UTN)	-
Other trial identifiers	MK-3475-002: Merck Protocol Number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2015
Global end of trial reached?	Yes
Global end of trial date	31 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to compare survival using pembrolizumab (SCH 900475, MK-3475) or standard chemotherapy in participants with advanced melanoma (MEL) who had progressed after prior therapy. Initial Treatment Period: Participants were initially randomized to low-dose (2 mg/kg) pembrolizumab, higher dose (10 mg/kg) pembrolizumab or Investigator-choice chemotherapy (ICC: carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). With Amendment 3, all ongoing pembrolizumab participants were to be treated with open label, fixed dose pembrolizumab 200 mg, instead of a weight-based dosing of pembrolizumab. Switch-to-Pembrolizumab Treatment Period: Participants randomized to ICC who experienced progressive disease (PD) may have been eligible to switch to either pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg. With Amendment 3, all switch-to-pembrolizumab participants were to be treated with open label, fixed dose pembrolizumab 200 mg.

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	20 November 2012
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: 2
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 79
Country: Number of subjects enrolled	Israel: 36
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 36
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 36
Country: Number of subjects enrolled	United States: 279
Worldwide total number of subjects	540
EEA total number of subjects	177

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)	1
Adults (18-64 years)	304
From 65 to 84 years	230
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This end of trial analysis is based on a trial closure database cutoff date of 31-Jan-2019.

Period 1

Period 1 title	Initial Treatment 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 2 mg/kg

Arm description:

Participants were initially randomized to receive pembrolizumab 2 mg/kg intravenously (IV) once every 3 weeks (Q3W). With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 2 mg/kg via IV infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle

Arm title	Pembrolizumab 10 mg/kg

Arm description:

Participants were initially randomized to receive pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 10 mg/kg via IV infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle

Arm title	Investigator-Choice Chemotherapy (ICC)

Arm description:

Participants were initially randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin per institutional standard

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

Dosage and administration details:

Paclitaxel per institutional standard

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	DTIC
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine per institutional standard

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	MK-7365
Other name	TEMODAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide per institutional standard

Number of subjects in period 1	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)
Started	180	181	179
Treated	178	179	171
Completed	33	47	104
Not completed	147	134	75
Consent withdrawn by subject	3	2	4
Death	139	129	71
Lost to follow-up	5	3	-

Period 2

Period 2 title	Switch-to-Pembrolizumab Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ICCPembrolizumab 2 mg/kg

Arm description:

Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 2 mg/kg via IV infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle

Arm title	ICCPembrolizumab 10 mg/kg

Arm description:

Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03,

this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475, SCH 900475
Other name	KEYTRUDA®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab 10 mg/kg via IV infusion on Day 1 of each 3-week cycle

Number of subjects in period 2[1]	ICCPembrolizumab 2 mg/kg	ICCPembrolizumab 10 mg/kg
Started	53	45
Completed	15	7
Not completed	38	38
Consent withdrawn by subject	1	-
Death	35	37
Lost to follow-up	2	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 98 participants who were initially randomized to the ICC treatment group and experienced progressive disease were switched to either the Pembrolizumab 2 mg/kg or Pembrolizumab 10 mg/kg treatment groups.

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab 2 mg/kg
Reporting group description:	
Participants were initially randomized to receive pembrolizumab 2 mg/kg intravenously (IV) once every 3 weeks (Q3W). With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Reporting group title	Pembrolizumab 10 mg/kg
Reporting group description:	
Participants were initially randomized to receive pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Reporting group title	Investigator-Choice Chemotherapy (ICC)
Reporting group description:	
Participants were initially randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	

Reporting group values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)
Number of subjects	180	181	179
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	101	106	97
From 65-84 years	77	72	81
85 years and over	1	3	1
Age Continuous Units: Years			
arithmetic mean	59.5	60.1	60.5
standard deviation	± 14.9	± 13.3	± 12.7
Sex: Female, Male Units: Subjects			
Female	76	72	65
Male	104	109	114
Programmed Cell Death-Ligand 1 (PD-L1) Tumor Expression Status			
Membranous PD-L1 expression in tumor and tumor-associated immune cells was assessed by immunohistochemistry assay and scored on a unique melanoma (Allred Proportion Score [APS]/Melanoma [MEL]) scale of 0 to 5. Participants with an APS score of ≥2 (membranous staining in ≥1% of cells) were considered to be PD-L1 Positive and participants with an APS score of 0 or 1 were considered to be PD-L1 Negative.			
Units: Subjects			
PD-L1 Positive	99	97	98
PD-L1 Negative	48	46	40
Unknown	33	38	41

Reporting group values	Total		
Number of subjects	540		

Age categorical Units: Subjects			
Adolescents (12-17 years)	1		
Adults (18-64 years)	304		
From 65-84 years	230		
85 years and over	5		
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	213		
Male	327		
Programmed Cell Death-Ligand 1 (PD-L1) Tumor Expression Status			
Membranous PD-L1 expression in tumor and tumor-associated immune cells was assessed by immunohistochemistry assay and scored on a unique melanoma (Allred Proportion Score [APS]/Melanoma [MEL]) scale of 0 to 5. Participants with an APS score of ≥2 (membranous staining in ≥1% of cells) were considered to be PD-L1 Positive and participants with an APS score of 0 or 1 were considered to be PD-L1 Negative.			
Units: Subjects			
PD-L1 Positive	294		
PD-L1 Negative	134		
Unknown	112		

End points reporting groups

Reporting group title	Pembrolizumab 2 mg/kg
Reporting group description:	
Participants were initially randomized to receive pembrolizumab 2 mg/kg intravenously (IV) once every 3 weeks (Q3W). With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Reporting group title	Pembrolizumab 10 mg/kg
Reporting group description:	
Participants were initially randomized to receive pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Reporting group title	Investigator-Choice Chemotherapy (ICC)
Reporting group description:	
Participants were initially randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Reporting group title	ICCPembrolizumab 2 mg/kg
Reporting group description:	
Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)	
Reporting group title	ICCPembrolizumab 10 mg/kg
Reporting group description:	
Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)	
Subject analysis set title	Investigator-Choice Chemotherapy (ICC) Only
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants were randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). This treatment group included the participants who remained on ICC through the database cutoff date. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)	
Subject analysis set title	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)	
Subject analysis set title	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	ICCPembrolizumab 2 mg/kg (After Switch to Pembrolizumab)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who were initially randomized to ICC, subsequently experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to PD, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	Pembrolizumab 2 mg/kg PD-L1-Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were initially randomized to receive pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	Pembrolizumab 10 mg/kg PD-L1-Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were initially randomized to receive pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	Investigator-Choice Chemotherapy (ICC) PD-L1 Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). (Up to ~66 months)

Subject analysis set title	Pembrolizumab 2 mg/kg PD-L1-Negative
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were initially randomized to receive pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	Pembrolizumab 10 mg/kg PD-L1-Negative
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were initially randomized to receive pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to ~66 months)

Subject analysis set title	Investigator-Choice Chemotherapy (ICC) PD-L1 Negative

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were randomized to receive 1 of 4 possible chemotherapy regimens decided at the treating institution (carboplatin+paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). (Up to ~66 months)

Primary: Progression-free Survival (PFS) – Initial Treatment Period

End point title	Progression-free Survival (PFS) – Initial Treatment Period

End point description:

PFS was defined as the time from randomization to the 1st documented progressive disease (PD) or death due to any cause, whichever occurred first. Per Response Criteria in Solid Tumors version 1.1 (RECIST 1.1), PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must have also demonstrated an absolute increase of ≥5 mm. Note: The appearance of ≥1 new lesions was also considered PD. Analysis of PFS was based on an integrated radiology & oncology (IRO) assessment & was not planned or conducted for the switch-to-pembrolizumab treatment groups. Median PFS based on the product limit (Kaplan-Meier) method for censored data is presented. This was the final analysis for PFS. The analysis population consisted of all randomized participants. Participants were included in the initial treatment group to which they were randomized for efficacy analysis.

End point type	Primary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	181	179	
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 3.8)	3.0 (2.8 to 5.2)	2.8 (2.6 to 2.8)	

Statistical analyses

Statistical analysis title	PFS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1); lactate dehydrogenase (LDH) levels (normal vs. elevated LDH levels [=110% Upper Limit of Normal (ULN)]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Investigator-Choice Chemotherapy (ICC) v Pembrolizumab 2 mg/kg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.73

Notes:

[1] - Numerator=Pembrolizumab 2 mg/kg Denominator=ICC

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

Statistical analysis title	PFS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 10 mg/kg v Investigator-Choice Chemotherapy (ICC)
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.6

Notes:

[3] - Numerator=Pembrolizumab 10 mg/kg Denominator=ICC

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

Statistical analysis title	PFS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg v Pembrolizumab 10 mg/kg
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.1247 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Notes:

[5] - Numerator=Pembrolizumab 10 mg/kg Denominator=Pembrolizumab 2 mg/kg

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

Primary: Interim Overall Survival (OS) – Initial Treatment Period

End point title	Interim Overall Survival (OS) – Initial Treatment Period

End point description:

OS was defined as the time from randomization to death due to any cause. Analysis of OS was not planned or conducted for the switch-to-pembrolizumab treatment groups. Median OS based on the product-limit (Kaplan-Meier) method for censored data is presented. This was the interim analysis for OS. The analysis population consisted of all randomized participants. Participants were included in the initial treatment group to which they were randomized for the efficacy analysis.

End point type	Primary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	181	179	
Units: Months				
median (confidence interval 95%)	13.4 (11.0 to 16.4)	14.7 (11.3 to 19.5)	11.0 (8.9 to 13.8)	

Statistical analyses

Statistical analysis title	Interim OS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg v Investigator-Choice Chemotherapy (ICC)
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1173 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.1

Notes:

[7] - Numerator=Pembrolizumab 2 mg/kg Denominator=ICC

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

Statistical analysis title	Interim OS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg v Pembrolizumab 10 mg/kg

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.2905 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.12

Notes:

[9] - Numerator=Pembrolizumab 10 mg/kg Denominator=Pembrolizumab 2 mg/kg

[10] - Two-sided p-value based on stratified log rank test

Statistical analysis title	Interim OS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 10 mg/kg v Investigator-Choice Chemotherapy (ICC)
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0106 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.96

Notes:

[11] - Numerator=Pembrolizumab 10 mg/kg Denominator=ICC

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

Primary: Final Overall Survival (OS) – Initial Treatment Period

End point title	Final Overall Survival (OS) – Initial Treatment Period

End point description:

OS was defined as the time from randomization to death due to any cause. Analysis of OS was not planned or conducted for the switch-to-pembrolizumab treatment groups. Median OS based on the product-limit (Kaplan-Meier) method for censored data is presented. This was the final analysis for OS. The analysis population consisted of all randomized participants. Participants were included in the initial treatment group to which they were randomized for the efficacy analysis.

End point type	Primary

End point timeframe:

Up to approximately 75 months (Through End of Trial Analysis database cutoff date of 31-Jan-2019)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	181	179	
Units: Months				
median (confidence interval 95%)	13.4 (11.0 to 16.4)	14.7 (11.3 to 19.5)	11.0 (8.9 to 13.8)	

Statistical analyses

Statistical analysis title	Final OS - Initial Treatment Period
Statistical analysis description:	
Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)	
Comparison groups	Pembrolizumab 2 mg/kg v Investigator-Choice Chemotherapy (ICC)
Number of subjects included in analysis	359
Analysis specification	Post-hoc
Analysis type	superiority[13]
P-value	= 0.1146 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.1

Notes:

[13] - Numerator=Pembrolizumab 2 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS - Initial Treatment Period
Statistical analysis description:	
Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)	
Comparison groups	Pembrolizumab 10 mg/kg v Investigator-Choice Chemotherapy (ICC)
Number of subjects included in analysis	360
Analysis specification	Post-hoc
Analysis type	superiority[15]
P-value	= 0.0023 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.9

Notes:

[15] - Numerator=Pembrolizumab 10 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS - Initial Treatment Period

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg v Pembrolizumab 10 mg/kg
Number of subjects included in analysis	361
Analysis specification	Post-hoc
Analysis type	superiority[17]
P-value	= 0.149 [18]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.07

Notes:

[17] - Numerator=Pembrolizumab 10 mg/kg Denominator=Pembrolizumab 2 mg/kg

[18] - Two-sided p-value based on stratified log rank test

Secondary: Overall Survival (OS) By Programmed Cell Death-Ligand 1 (PD-L1) Tumor Expression Status – Initial Treatment Period

End point title	Overall Survival (OS) By Programmed Cell Death-Ligand 1 (PD-L1) Tumor Expression Status – Initial Treatment Period

End point description:

OS was defined as the time from randomization to death due to any cause. Participants with a Allred Proportion Score (APS) ≥2 (membranous staining in ≥1% of cells for PD-L1) were considered to be PD-L1 Positive and participants with a APS of 0 or 1 were considered to be PD-L1 Negative. Analysis of OS was not planned or conducted for the switch-to-pembrolizumab treatment groups. Median OS based on the product-limit (Kaplan-Meier) method for censored data by PD-L1 tumor expression status is presented. The analysis population consisted of all randomized participants who had a PD-L1 APS assessment. Participants were included in the initial treatment group to which they were randomized for efficacy analysis.

End point type	Secondary

End point timeframe:

Up to approximately 75 months (Through End of Trial Analysis database cutoff date of 31-Jan-2019)

End point values	Pembrolizumab 2 mg/kg PD-L1-Positive	Pembrolizumab 10 mg/kg PD-L1-Positive	Investigator-Choice Chemotherapy (ICC) PD-L1 Positive	Pembrolizumab 2 mg/kg PD-L1-Negative
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	99	97	98	48
Units: Months				
median (confidence interval 95%)	15.0 (10.9 to 20.9)	17.5 (13.7 to 28.9)	12.1 (7.7 to 18.2)	10.5 (6.4 to 13.5)

End point values	Pembrolizumab 10 mg/kg PD-L1-Negative	Investigator-Choice Chemotherapy (ICC) PD-L1 Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	40		
Units: Months				
median (confidence interval 95%)	13.4 (4.6 to 23.3)	9.3 (5.1 to 14.2)		

Statistical analyses

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg PD-L1-Positive v Investigator-Choice Chemotherapy (ICC) PD-L1 Positive
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.3113 [20]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.28

Notes:

[19] - PD-L1-Positive Participants Numerator=Pembrolizumab 2 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 10 mg/kg PD-L1-Positive v Investigator-Choice Chemotherapy (ICC) PD-L1 Positive
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0208 [22]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.99

Notes:

[21] - PD-L1 Positive Participants Numerator=Pembrolizumab 10 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg PD-L1-Positive v Pembrolizumab 10 mg/kg PD-L1-Positive
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.0496 [24]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1

Notes:

[23] - PD-L1 Positive Participants Numerator=Pembrolizumab 10 mg/kg Denominator=Pembrolizumab 2 mg/kg

[24] - Two-sided p-value based on stratified log rank test

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg PD-L1-Negative v Investigator-Choice Chemotherapy (ICC) PD-L1 Negative
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.6043 [26]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.76

Notes:

[25] - PD-L1 Negative Participants Numerator=Pembrolizumab 2 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 10 mg/kg PD-L1-Negative v Investigator-Choice Chemotherapy (ICC) PD-L1 Negative
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0335 [28]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.04

Notes:

[27] - PD-L1 Negative Participants Numerator=Pembrolizumab 10 mg/kg Denominator=ICC

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

Statistical analysis title	Final OS by PD-L1 Tumor Expression Status

Statistical analysis description:

Cox regression model with treatment as covariate stratified by ECOG performance status (0 vs. 1); LDH levels (normal vs. elevated LDH levels [=110% ULN]); & BRAF mutational status (mutant vs. wild-type)

Comparison groups	Pembrolizumab 2 mg/kg PD-L1-Negative v Pembrolizumab 10 mg/kg PD-L1-Negative
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.1504 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.13

Notes:

[29] - PD-L1 Negative Participants Numerator=Pembrolizumab 10 mg/kg Denominator=Pembrolizumab 2 mg/kg

[30] - Two-sided p-value based on stratified log rank test

Secondary: Overall Response Rate (ORR) – Initial Treatment Period

End point title	Overall Response Rate (ORR) – Initial Treatment Period

End point description:

ORR was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions) as assessed using RECIST 1.1. Analysis of ORR was not planned or conducted for the switch-to-pembrolizumab participants. The percentage of participants who experienced a CR or PR is presented. This was the final analysis for ORR. The analysis population consisted of all randomized participants. Participants were included in the initial treatment group to which they were randomized for efficacy analysis.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	181	179	
Units: Percentage of Participants				
number (confidence interval 95%)	22.2 (16.4 to 29.0)	27.6 (21.3 to 34.7)	4.5 (1.9 to 8.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR) - Initial Treatment Period

End point title	Best Overall Response (BOR) - Initial Treatment Period

End point description:

BOR was assessed by independent radiology review using RECIST 1.1 and was recorded from randomization until the last imaging assessment in this period. Response categories included: Complete Response (CR): disappearance of all target lesions; Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions; Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions; and Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. BOR for the Initial Treatment Period was based on IRO and is presented for participants during the Initial Treatment Period. The analysis population consisted of all randomized participants. Participants were included in the initial treatment group to which they were randomized for this efficacy analysis.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	181	179	
Units: Percentage of Participants				
number (not applicable)				
Complete Response	3.3	7.2	0.0	
Partial Response	18.9	20.4	4.5	
Stable Disease	16.7	14.9	19.0	
Progressive Disease	46.7	47.5	61.5	
Not Evaluable	13.3	9.9	15.1	
No Disease	0.6	0.0	0.0	

No Assessment	0.6	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR) - Switch-to-Pembrolizumab Treatment Period

End point title	Best Overall Response (BOR) - Switch-to-Pembrolizumab Treatment Period

End point description:

BOR was assessed using RECIST 1.1 & was recorded from the start of the second line of study drug (pembrolizumab) until the last imaging assessment in this period. Response categories included: Complete Response (CR): disappearance of all target lesions; Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions; Progressive Disease (PD): ≥20% increase in the sum of diameters of target lesions; & Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. For the switch-to-pembrolizumab treatment groups, BOR was based on independent review committee (IRC) assessment and is presented for the switch-to-pembrolizumab treatment groups. The analysis population consisted of all randomized participants in ICC who switched to receiving pembrolizumab. Participants were included in the treatment group to which they were re-randomized (switched) for this efficacy analysis.

End point type	Secondary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	ICCPembrolizumab 2 mg/kg	ICCPembrolizumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	45		
Units: Percentage of Participants				
number (not applicable)				
Complete Response	1.9	4.4		
Partial Response	17.0	13.3		
Stable Disease	15.1	11.1		
Progressive Disease	54.7	55.6		
Not Evaluable	11.3	13.3		
No Assessment	0.0	2.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) – Initial Treatment Period

End point title	Duration of Response (DOR) – Initial Treatment Period

End point description:

For participants who demonstrated a confirmed response (Complete Response [CR]: disappearance of all target lesions or Partial Response [PR]: ≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1, DOR was defined as the time from 1st documented evidence of CR or PR until disease progression or death. DOR for participants who had not progressed or died at the time of analysis was to be censored at the date of their last tumor assessment. DOR analysis was based on IRO assessment. Analysis of DOR was not planned or analyzed for the switch-to-pembrolizumab treatment groups. Median DOR is presented. The analysis population consisted of all randomized participants who demonstrated a confirmed response (CR or PR) per RECIST 1.1. Participants were included in the treatment group to which they were randomized for efficacy. (99999=DOR Median not reached; 99999=DOR Upper Limit not reached: no progressive disease by time of last assessment)

End point type	Secondary

End point timeframe:

Up to approximately 36 months (Through Final Analysis database cutoff date of 16-Nov-2015)

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	50	8	
Units: Months				
median (full range (min-max))	22.8 (1.4 to 25.3)	99999 (1.1 to 99999)	6.8 (2.8 to 11.3)	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants Who Experienced an Adverse Event (AE) - Overall Study[31]

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of study drug, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition which was temporally associated with the use of study drug, was also an AE. Participants were included in the treatment group in which an AE was experienced. The number of participants who experienced at least one AE is presented. The analysis population consisted of all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months (Through End of Trial Analysis database cutoff date of 31-Jan-2019)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The initial ICC treatment group was broken out into 5 treatment groups for analysis of safety.

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC) Only	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	178	179	73	53
Units: Participants	172	179	71	52

End point values	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)	ICCPembrolizumab 2 mg/kg (After Switch to Pembrolizumab)	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	53	45	
Units: Participants	45	53	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an Adverse Event (AE) - Overall Study

End point title	Number of Participants Who Discontinued Study Drug Due to an Adverse Event (AE) - Overall Study[32]

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition which is temporally associated with the use of study drug, was also an AE. The number of participants who discontinued study drug due to an AE is presented. The analysis population consisted of all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months (Through End of Trial Analysis database cutoff date of 31-Jan-2019)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The initial ICC treatment group was broken out into 5 treatment groups for analysis of tolerability.

End point values	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Investigator-Choice Chemotherapy (ICC) Only	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	178	179	73	53
Units: Participants	29	33	13	1

End point values	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)	ICCPembrolizumab 2 mg/kg (After Switch to Pembrolizumab)	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	45	53	45	
Units: Participants	1	4	4	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 75 months (Through End of Trial Analysis database cutoff date of 31-Jan-2019)

Adverse event reporting additional description:

Safety Population: All participants who received ≥1 dose of study drug. Per protocol, disease progression of cancer under study was not considered an AE unless related to study drug. Therefore, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Investigator-Choice Chemotherapy (ICC) Only

Reporting group description:

Participants received one of four possible chemotherapy regimens decided at the treating institution (carboplatin + paclitaxel, paclitaxel alone, dacarbazine, or temozolomide). This treatment group included the participants who remained on ICC through the final analysis. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)

Reporting group description:

Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg in a double-blind fashion. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)

Reporting group description:

Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg in a double-blind fashion. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	Pembrolizumab 2 mg/kg

Reporting group description:

Participants initially received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	Pembrolizumab 10 mg/kg

Reporting group description:

Participants initially received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	ICCPembrolizumab 2 mg/kg (After Switch to Pembrolizumab)

Reporting group description:

Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg in a double-blind fashion. Participants received pembrolizumab 2 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with

fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Reporting group title	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)

Reporting group description:

Participants who were assigned to ICC, experienced confirmed progressive disease (PD) and met all switching criteria at study treatment Week 12, had the opportunity to switch to receive pembrolizumab 2 mg/kg or 10 mg/kg in a double-blind fashion. Participants received pembrolizumab 10 mg/kg IV Q3W. With Amendment 03, this dosing was discontinued and all study participants were to be treated with fixed-dose open label pembrolizumab 200 mg IV Q3W. Participants were to receive study drug until discontinuation due to progression of disease, toxicity, or choice. (Up to approximately 66 months)

Serious adverse events	Investigator-Choice Chemotherapy (ICC) Only	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 73 (45.21%)	9 / 45 (20.00%)	15 / 53 (28.30%)
number of deaths (all causes)	71	0	0
number of deaths resulting from adverse events	7	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oncologic complication			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Prostate cancer			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Intestinal metastasis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell carcinoma			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor venous access			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infusion site extravasation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)	1 / 45 (2.22%)	0 / 53 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 73 (4.11%)	1 / 45 (2.22%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Haemoptysis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Hypoxia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal inflammation			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis allergic			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Delirium			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutrophil count decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Platelet count decreased			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	0 / 53 (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
White blood cell count decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rib fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis noninfective			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenic syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			

subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Aphasia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 73 (4.11%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Thrombocytopenia			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	0 / 53 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye movement disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Constipation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Diverticulum			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal ulcer			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malabsorption			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	3 / 73 (4.11%)	0 / 45 (0.00%)	0 / 53 (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
Pancreatitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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 obstruction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Diverticular perforation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic necrosis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Hyperbilirubinaemia			

subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Bile duct obstruction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Lichenoid keratosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin mass			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purpura			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperparathyroidism			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Groin pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Spondylolisthesis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spine stenosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Appendicitis perforated			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Cellulitis streptococcal			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (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
Erysipelas			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected cyst			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	0 / 53 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Mastitis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 73 (4.11%)	2 / 45 (4.44%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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
Salmonellosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 73 (2.74%)	0 / 45 (0.00%)	0 / 53 (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
Viral infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (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	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral rash			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	ICCPembrolizumab 2 mg/kg (After Switch to Pembrolizumab)
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 178 (51.12%)	78 / 179 (43.58%)	18 / 53 (33.96%)
number of deaths (all causes)	139	129	35
number of deaths resulting from adverse events	11	8	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Colon cancer metastatic			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	3 / 178 (1.69%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Oncologic complication			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Prostate cancer			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Rectal cancer			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal metastasis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Metastasis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Small cell carcinoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Hypotension			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Phlebitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Poor venous access			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Venous thrombosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Thrombosis			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Chest pain			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Cyst			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Death			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	2 / 2	1 / 1	0 / 0
Fatigue			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Gait disturbance			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 178 (0.56%)	6 / 179 (3.35%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 6	0 / 0
deaths causally related to treatment / all	1 / 1	3 / 3	0 / 0
Generalised oedema			

subjects affected / exposed	3 / 178 (1.69%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infusion site extravasation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Oedema			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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	3 / 178 (1.69%)	4 / 179 (2.23%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Hypersensitivity			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cytokine release syndrome			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 178 (1.12%)	5 / 179 (2.79%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Haemoptysis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Hypoxia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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

Interstitial lung disease			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Laryngeal inflammation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Pleural effusion			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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 aspiration			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Pneumonitis			
subjects affected / exposed	1 / 178 (0.56%)	3 / 179 (1.68%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Pulmonary embolism			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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 respiratory failure			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis allergic			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 178 (1.12%)	3 / 179 (1.68%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Mental status changes			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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

Hepatic enzyme increased			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Femur fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower limb fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Rib fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Radiation necrosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Accidental overdose			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
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			
Atrial fibrillation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Atrioventricular block complete			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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 failure			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular disorder			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cardiogenic shock			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Dizziness			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Epilepsy			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Hemiplegia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Lumbar radiculopathy			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Meningitis noninfective			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Myasthenic syndrome			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Paraesthesia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Partial seizures			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Presyncope			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Sciatica			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Aphasia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Brain oedema			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 178 (3.93%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Eye disorders			
Eye movement disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Iritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 178 (0.56%)	4 / 179 (2.23%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Autoimmune colitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Constipation			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Diarrhoea			
subjects affected / exposed	1 / 178 (0.56%)	4 / 179 (2.23%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Dysphagia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric disorder			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Haematemesis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Haematochezia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 178 (0.56%)	2 / 179 (1.12%)	0 / 53 (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
Intestinal obstruction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Large intestinal ulcer			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Large intestine perforation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Malabsorption			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Nausea			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Pancreatitis			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Small intestinal perforation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Vomiting			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Gastritis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cholangitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cholecystitis			
subjects affected / exposed	3 / 178 (1.69%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Hepatic necrosis			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Lichenoid keratosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Rash maculo-papular			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin mass			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Purpura			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Hydronephrosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Postrenal failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Hyperparathyroidism			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Hypopituitarism			
subjects affected / exposed	0 / 178 (0.00%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 178 (0.00%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 178 (0.00%)	2 / 179 (1.12%)	0 / 53 (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
Groin pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Neck pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Osteolysis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Osteoarthritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cervical spine stenosis			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Candida infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Cellulitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Cellulitis streptococcal			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Diverticulitis			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 178 (1.12%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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 cyst			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Mastitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Osteomyelitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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 abscess			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 178 (1.12%)	3 / 179 (1.68%)	3 / 53 (5.66%)
occurrences causally related to treatment / all	0 / 2	2 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (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
Sepsis			
subjects affected / exposed	1 / 178 (0.56%)	1 / 179 (0.56%)	0 / 53 (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
Septic shock			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	2 / 178 (1.12%)	0 / 179 (0.00%)	0 / 53 (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
Soft tissue infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Streptococcal sepsis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Viral rash			

subjects affected / exposed	0 / 178 (0.00%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Dehydration			
subjects affected / exposed	4 / 178 (2.25%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Hypercalcaemia			

subjects affected / exposed	1 / 178 (0.56%)	0 / 179 (0.00%)	0 / 53 (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
Hypocalcaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 178 (0.56%)	3 / 179 (1.68%)	0 / 53 (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
Hyperglycaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 45 (40.00%)		
number of deaths (all causes)	37		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer metastatic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial tumour haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Invasive ductal breast carcinoma				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to lymph nodes				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oncologic complication				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal cancer				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal metastasis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to meninges				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastasis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small cell carcinoma				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Poor venous access				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cyst				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion site extravasation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cytokine release syndrome			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Pelvic pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal inflammation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary thrombosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alveolitis allergic			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Fracture displacement				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiation necrosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac ventricular disorder			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Ataxia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis noninfective				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myasthenic syndrome				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myoclonus				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo positional				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Eye movement disorder				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Abdominal pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric disorder				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intussusception				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestinal ulcer				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malabsorption				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Autoimmune hepatitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic necrosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Lichenoid keratosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin mass				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Purpura				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postrenal failure				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubulointerstitial nephritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal impairment				

subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Addison's disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adrenal insufficiency				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Adrenocortical insufficiency acute				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperparathyroidism				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophysitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypopituitarism				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Secondary adrenocortical insufficiency				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inappropriate antidiuretic hormone secretion				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteolysis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical spine stenosis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis perforated				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis streptococcal				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected cyst				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mastitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral rash				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Investigator-Choice Chemotherapy (ICC) Only	ICCPembrolizumab 10 mg/kg (Before Switch to Pembrolizumab)	ICCPembrolizumab 2 mg/kg (Before Switch to Pembrolizumab)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 73 (90.41%)	44 / 45 (97.78%)	52 / 53 (98.11%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 73 (5.48%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	4	3	4
Melanocytic naevus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 73 (1.37%)	1 / 45 (2.22%)	2 / 53 (3.77%)
occurrences (all)	1	1	2
Deep vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 73 (13.70%)	2 / 45 (4.44%)	4 / 53 (7.55%)
occurrences (all)	11	2	4
Chest pain			
subjects affected / exposed	3 / 73 (4.11%)	1 / 45 (2.22%)	3 / 53 (5.66%)
occurrences (all)	3	1	4
Chills			
subjects affected / exposed	0 / 73 (0.00%)	5 / 45 (11.11%)	3 / 53 (5.66%)
occurrences (all)	0	5	3
Fatigue			

subjects affected / exposed	28 / 73 (38.36%)	26 / 45 (57.78%)	27 / 53 (50.94%)
occurrences (all)	34	33	36
Influenza like illness			
subjects affected / exposed	1 / 73 (1.37%)	1 / 45 (2.22%)	1 / 53 (1.89%)
occurrences (all)	2	1	1
Malaise			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	4 / 73 (5.48%)	1 / 45 (2.22%)	5 / 53 (9.43%)
occurrences (all)	4	1	5
Pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	4 / 53 (7.55%)
occurrences (all)	0	1	5
Pyrexia			
subjects affected / exposed	7 / 73 (9.59%)	5 / 45 (11.11%)	5 / 53 (9.43%)
occurrences (all)	7	6	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 73 (12.33%)	6 / 45 (13.33%)	13 / 53 (24.53%)
occurrences (all)	9	8	13
Dyspnoea			
subjects affected / exposed	9 / 73 (12.33%)	1 / 45 (2.22%)	10 / 53 (18.87%)
occurrences (all)	10	1	10
Pleural effusion			
subjects affected / exposed	4 / 73 (5.48%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences (all)	4	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 73 (5.48%)	1 / 45 (2.22%)	4 / 53 (7.55%)
occurrences (all)	6	1	4
Depression			
subjects affected / exposed	4 / 73 (5.48%)	1 / 45 (2.22%)	4 / 53 (7.55%)
occurrences (all)	4	1	4
Insomnia			

subjects affected / exposed	8 / 73 (10.96%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	8	3	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	0	4	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	1 / 53 (1.89%)
occurrences (all)	0	1	2
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 73 (2.74%)	2 / 45 (4.44%)	1 / 53 (1.89%)
occurrences (all)	2	2	1
Blood bilirubin increased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	3
Blood cholesterol increased			
subjects affected / exposed	0 / 73 (0.00%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	0	3	2
Lymphocyte count decreased			
subjects affected / exposed	4 / 73 (5.48%)	2 / 45 (4.44%)	3 / 53 (5.66%)
occurrences (all)	4	2	4
Neutrophil count decreased			
subjects affected / exposed	3 / 73 (4.11%)	4 / 45 (8.89%)	3 / 53 (5.66%)
occurrences (all)	3	5	4
Platelet count decreased			
subjects affected / exposed	5 / 73 (6.85%)	5 / 45 (11.11%)	4 / 53 (7.55%)
occurrences (all)	7	8	9
Weight decreased			
subjects affected / exposed	1 / 73 (1.37%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	1	3	5
White blood cell count decreased			
subjects affected / exposed	5 / 73 (6.85%)	3 / 45 (6.67%)	3 / 53 (5.66%)
occurrences (all)	6	3	3
Blood creatinine increased			

subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 73 (5.48%)	0 / 45 (0.00%)	2 / 53 (3.77%)
occurrences (all)	4	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 73 (12.33%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	9	3	4
Dysgeusia			
subjects affected / exposed	2 / 73 (2.74%)	4 / 45 (8.89%)	5 / 53 (9.43%)
occurrences (all)	2	4	5
Headache			
subjects affected / exposed	8 / 73 (10.96%)	7 / 45 (15.56%)	9 / 53 (16.98%)
occurrences (all)	8	10	11
Neuropathy peripheral			
subjects affected / exposed	6 / 73 (8.22%)	5 / 45 (11.11%)	7 / 53 (13.21%)
occurrences (all)	6	7	7
Paraesthesia			
subjects affected / exposed	3 / 73 (4.11%)	3 / 45 (6.67%)	5 / 53 (9.43%)
occurrences (all)	3	3	6
Tremor			
subjects affected / exposed	0 / 73 (0.00%)	3 / 45 (6.67%)	1 / 53 (1.89%)
occurrences (all)	0	3	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 73 (1.37%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	1	3	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 73 (28.77%)	10 / 45 (22.22%)	15 / 53 (28.30%)
occurrences (all)	26	10	25
Leukopenia			

subjects affected / exposed	8 / 73 (10.96%)	4 / 45 (8.89%)	3 / 53 (5.66%)
occurrences (all)	8	7	6
Neutropenia			
subjects affected / exposed	2 / 73 (2.74%)	5 / 45 (11.11%)	7 / 53 (13.21%)
occurrences (all)	2	8	14
Thrombocytopenia			
subjects affected / exposed	9 / 73 (12.33%)	2 / 45 (4.44%)	7 / 53 (13.21%)
occurrences (all)	12	2	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 73 (4.11%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences (all)	3	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	3 / 53 (5.66%)
occurrences (all)	1	0	3
Abdominal pain			
subjects affected / exposed	8 / 73 (10.96%)	4 / 45 (8.89%)	1 / 53 (1.89%)
occurrences (all)	10	4	2
Abdominal pain upper			
subjects affected / exposed	2 / 73 (2.74%)	2 / 45 (4.44%)	0 / 53 (0.00%)
occurrences (all)	2	2	0
Constipation			
subjects affected / exposed	16 / 73 (21.92%)	8 / 45 (17.78%)	12 / 53 (22.64%)
occurrences (all)	19	10	17
Diarrhoea			
subjects affected / exposed	13 / 73 (17.81%)	11 / 45 (24.44%)	11 / 53 (20.75%)
occurrences (all)	20	17	17
Dry mouth			
subjects affected / exposed	1 / 73 (1.37%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			

subjects affected / exposed	2 / 73 (2.74%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	2	3	3
Nausea			
subjects affected / exposed	23 / 73 (31.51%)	19 / 45 (42.22%)	29 / 53 (54.72%)
occurrences (all)	30	23	44
Vomiting			
subjects affected / exposed	17 / 73 (23.29%)	13 / 45 (28.89%)	10 / 53 (18.87%)
occurrences (all)	22	14	14
Dysphagia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 73 (13.70%)	11 / 45 (24.44%)	15 / 53 (28.30%)
occurrences (all)	10	11	18
Dry skin			
subjects affected / exposed	4 / 73 (5.48%)	0 / 45 (0.00%)	1 / 53 (1.89%)
occurrences (all)	4	0	1
Night sweats			
subjects affected / exposed	2 / 73 (2.74%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	2	4	5
Erythema			
subjects affected / exposed	2 / 73 (2.74%)	1 / 45 (2.22%)	2 / 53 (3.77%)
occurrences (all)	2	2	2
Pruritus			
subjects affected / exposed	5 / 73 (6.85%)	6 / 45 (13.33%)	4 / 53 (7.55%)
occurrences (all)	6	6	4
Rash			
subjects affected / exposed	6 / 73 (8.22%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	7	3	5
Rash maculo-papular			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	2 / 53 (3.77%)
occurrences (all)	0	1	2

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 73 (0.00%)	1 / 45 (2.22%)	0 / 53 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 73 (6.85%)	7 / 45 (15.56%)	6 / 53 (11.32%)
occurrences (all)	6	9	7
Back pain			
subjects affected / exposed	8 / 73 (10.96%)	6 / 45 (13.33%)	5 / 53 (9.43%)
occurrences (all)	10	6	5
Bone pain			
subjects affected / exposed	1 / 73 (1.37%)	3 / 45 (6.67%)	2 / 53 (3.77%)
occurrences (all)	1	3	10
Muscular weakness			
subjects affected / exposed	3 / 73 (4.11%)	2 / 45 (4.44%)	5 / 53 (9.43%)
occurrences (all)	3	3	6
Myalgia			
subjects affected / exposed	3 / 73 (4.11%)	4 / 45 (8.89%)	4 / 53 (7.55%)
occurrences (all)	3	7	4
Musculoskeletal pain			
subjects affected / exposed	3 / 73 (4.11%)	1 / 45 (2.22%)	4 / 53 (7.55%)
occurrences (all)	3	1	4
Pain in extremity			
subjects affected / exposed	2 / 73 (2.74%)	5 / 45 (11.11%)	6 / 53 (11.32%)
occurrences (all)	2	5	6
Muscle spasms			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 73 (2.74%)	1 / 45 (2.22%)	4 / 53 (7.55%)
occurrences (all)	2	1	4

Upper respiratory tract infection			
subjects affected / exposed	1 / 73 (1.37%)	2 / 45 (4.44%)	1 / 53 (1.89%)
occurrences (all)	1	2	2
Urinary tract infection			
subjects affected / exposed	5 / 73 (6.85%)	2 / 45 (4.44%)	2 / 53 (3.77%)
occurrences (all)	5	2	2
Oral herpes			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	20 / 73 (27.40%)	11 / 45 (24.44%)	8 / 53 (15.09%)
occurrences (all)	21	12	10
Dehydration			
subjects affected / exposed	2 / 73 (2.74%)	3 / 45 (6.67%)	3 / 53 (5.66%)
occurrences (all)	3	4	7
Hyperglycaemia			
subjects affected / exposed	2 / 73 (2.74%)	3 / 45 (6.67%)	5 / 53 (9.43%)
occurrences (all)	2	3	9
Hypertriglyceridaemia			
subjects affected / exposed	0 / 73 (0.00%)	5 / 45 (11.11%)	4 / 53 (7.55%)
occurrences (all)	0	7	5
Hypoalbuminaemia			
subjects affected / exposed	5 / 73 (6.85%)	2 / 45 (4.44%)	3 / 53 (5.66%)
occurrences (all)	5	2	4
Hypokalaemia			
subjects affected / exposed	3 / 73 (4.11%)	3 / 45 (6.67%)	4 / 53 (7.55%)
occurrences (all)	3	3	5
Hyponatraemia			
subjects affected / exposed	4 / 73 (5.48%)	2 / 45 (4.44%)	3 / 53 (5.66%)
occurrences (all)	6	3	3
Hyperkalaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 45 (0.00%)	0 / 53 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	ICCPembrolizumab 2 mg/kg (After Switch to

			Pembrolizumab)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 178 (88.76%)	176 / 179 (98.32%)	48 / 53 (90.57%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 178 (1.12%)	8 / 179 (4.47%)	0 / 53 (0.00%)
occurrences (all)	2	8	0
Melanocytic naevus			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	5
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 178 (2.81%)	11 / 179 (6.15%)	2 / 53 (3.77%)
occurrences (all)	7	11	2
Hypertension			
subjects affected / exposed	2 / 178 (1.12%)	9 / 179 (5.03%)	0 / 53 (0.00%)
occurrences (all)	2	9	0
Deep vein thrombosis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Lymphoedema			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 178 (10.67%)	20 / 179 (11.17%)	2 / 53 (3.77%)
occurrences (all)	25	44	2
Chest pain			
subjects affected / exposed	7 / 178 (3.93%)	11 / 179 (6.15%)	0 / 53 (0.00%)
occurrences (all)	8	15	0
Chills			
subjects affected / exposed	10 / 178 (5.62%)	11 / 179 (6.15%)	0 / 53 (0.00%)
occurrences (all)	11	13	0
Fatigue			
subjects affected / exposed	74 / 178 (41.57%)	91 / 179 (50.84%)	15 / 53 (28.30%)
occurrences (all)	106	117	17

Influenza like illness			
subjects affected / exposed	9 / 178 (5.06%)	14 / 179 (7.82%)	4 / 53 (7.55%)
occurrences (all)	13	17	4
Malaise			
subjects affected / exposed	7 / 178 (3.93%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	9	2	0
Oedema peripheral			
subjects affected / exposed	17 / 178 (9.55%)	21 / 179 (11.73%)	6 / 53 (11.32%)
occurrences (all)	19	24	7
Pain			
subjects affected / exposed	6 / 178 (3.37%)	7 / 179 (3.91%)	3 / 53 (5.66%)
occurrences (all)	7	7	3
Pyrexia			
subjects affected / exposed	23 / 178 (12.92%)	30 / 179 (16.76%)	3 / 53 (5.66%)
occurrences (all)	33	43	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 178 (20.79%)	42 / 179 (23.46%)	7 / 53 (13.21%)
occurrences (all)	50	50	7
Dyspnoea			
subjects affected / exposed	18 / 178 (10.11%)	29 / 179 (16.20%)	7 / 53 (13.21%)
occurrences (all)	20	33	7
Pleural effusion			
subjects affected / exposed	3 / 178 (1.69%)	3 / 179 (1.68%)	4 / 53 (7.55%)
occurrences (all)	3	3	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 178 (5.62%)	8 / 179 (4.47%)	3 / 53 (5.66%)
occurrences (all)	10	8	3
Depression			
subjects affected / exposed	7 / 178 (3.93%)	12 / 179 (6.70%)	0 / 53 (0.00%)
occurrences (all)	7	13	0
Insomnia			
subjects affected / exposed	9 / 178 (5.06%)	11 / 179 (6.15%)	3 / 53 (5.66%)
occurrences (all)	10	12	3
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	9 / 178 (5.06%)	13 / 179 (7.26%)	3 / 53 (5.66%)
occurrences (all)	10	18	4
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 178 (6.18%)	14 / 179 (7.82%)	3 / 53 (5.66%)
occurrences (all)	11	17	4
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 178 (6.74%)	10 / 179 (5.59%)	4 / 53 (7.55%)
occurrences (all)	13	16	4
Blood bilirubin increased			
subjects affected / exposed	6 / 178 (3.37%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	11	5	0
Blood cholesterol increased			
subjects affected / exposed	5 / 178 (2.81%)	7 / 179 (3.91%)	0 / 53 (0.00%)
occurrences (all)	9	14	0
Lymphocyte count decreased			
subjects affected / exposed	6 / 178 (3.37%)	7 / 179 (3.91%)	0 / 53 (0.00%)
occurrences (all)	17	8	0
Neutrophil count decreased			
subjects affected / exposed	2 / 178 (1.12%)	1 / 179 (0.56%)	0 / 53 (0.00%)
occurrences (all)	10	5	0
Platelet count decreased			
subjects affected / exposed	2 / 178 (1.12%)	5 / 179 (2.79%)	0 / 53 (0.00%)
occurrences (all)	9	9	0
Weight decreased			
subjects affected / exposed	12 / 178 (6.74%)	17 / 179 (9.50%)	4 / 53 (7.55%)
occurrences (all)	12	17	5
White blood cell count decreased			
subjects affected / exposed	4 / 178 (2.25%)	3 / 179 (1.68%)	0 / 53 (0.00%)
occurrences (all)	12	3	0
Blood creatinine increased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	7
Lipase increased			

subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 178 (1.69%)	7 / 179 (3.91%)	0 / 53 (0.00%)
occurrences (all)	4	7	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 178 (10.67%)	18 / 179 (10.06%)	3 / 53 (5.66%)
occurrences (all)	25	27	4
Dysgeusia			
subjects affected / exposed	3 / 178 (1.69%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	3	2	0
Headache			
subjects affected / exposed	21 / 178 (11.80%)	30 / 179 (16.76%)	8 / 53 (15.09%)
occurrences (all)	33	45	11
Neuropathy peripheral			
subjects affected / exposed	4 / 178 (2.25%)	3 / 179 (1.68%)	0 / 53 (0.00%)
occurrences (all)	4	3	0
Paraesthesia			
subjects affected / exposed	4 / 178 (2.25%)	4 / 179 (2.23%)	0 / 53 (0.00%)
occurrences (all)	4	4	0
Tremor			
subjects affected / exposed	3 / 178 (1.69%)	5 / 179 (2.79%)	0 / 53 (0.00%)
occurrences (all)	3	5	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 178 (0.56%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 178 (16.85%)	26 / 179 (14.53%)	12 / 53 (22.64%)
occurrences (all)	43	31	13
Leukopenia			
subjects affected / exposed	0 / 178 (0.00%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	0	3	0
Neutropenia			

subjects affected / exposed	1 / 178 (0.56%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	1	4	0
Thrombocytopenia			
subjects affected / exposed	3 / 178 (1.69%)	3 / 179 (1.68%)	0 / 53 (0.00%)
occurrences (all)	5	5	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 178 (2.25%)	10 / 179 (5.59%)	0 / 53 (0.00%)
occurrences (all)	8	11	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	11 / 178 (6.18%)	9 / 179 (5.03%)	0 / 53 (0.00%)
occurrences (all)	13	10	0
Abdominal pain			
subjects affected / exposed	28 / 178 (15.73%)	27 / 179 (15.08%)	7 / 53 (13.21%)
occurrences (all)	38	33	7
Abdominal pain upper			
subjects affected / exposed	6 / 178 (3.37%)	12 / 179 (6.70%)	0 / 53 (0.00%)
occurrences (all)	6	12	0
Constipation			
subjects affected / exposed	40 / 178 (22.47%)	42 / 179 (23.46%)	12 / 53 (22.64%)
occurrences (all)	47	57	14
Diarrhoea			
subjects affected / exposed	40 / 178 (22.47%)	41 / 179 (22.91%)	16 / 53 (30.19%)
occurrences (all)	52	67	23
Dry mouth			
subjects affected / exposed	9 / 178 (5.06%)	7 / 179 (3.91%)	0 / 53 (0.00%)
occurrences (all)	11	10	0
Dyspepsia			
subjects affected / exposed	3 / 178 (1.69%)	4 / 179 (2.23%)	4 / 53 (7.55%)
occurrences (all)	3	5	4
Nausea			

subjects affected / exposed	44 / 178 (24.72%)	49 / 179 (27.37%)	12 / 53 (22.64%)
occurrences (all)	74	56	12
Vomiting			
subjects affected / exposed	19 / 178 (10.67%)	38 / 179 (21.23%)	6 / 53 (11.32%)
occurrences (all)	26	58	7
Dysphagia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 178 (3.93%)	2 / 179 (1.12%)	0 / 53 (0.00%)
occurrences (all)	8	4	0
Dry skin			
subjects affected / exposed	18 / 178 (10.11%)	18 / 179 (10.06%)	0 / 53 (0.00%)
occurrences (all)	24	18	0
Night sweats			
subjects affected / exposed	4 / 178 (2.25%)	10 / 179 (5.59%)	1 / 53 (1.89%)
occurrences (all)	4	11	1
Erythema			
subjects affected / exposed	10 / 178 (5.62%)	7 / 179 (3.91%)	0 / 53 (0.00%)
occurrences (all)	12	8	0
Pruritus			
subjects affected / exposed	49 / 178 (27.53%)	57 / 179 (31.84%)	6 / 53 (11.32%)
occurrences (all)	77	74	7
Rash			
subjects affected / exposed	29 / 178 (16.29%)	33 / 179 (18.44%)	11 / 53 (20.75%)
occurrences (all)	38	49	15
Rash maculo-papular			
subjects affected / exposed	10 / 178 (5.62%)	18 / 179 (10.06%)	3 / 53 (5.66%)
occurrences (all)	11	23	4
Vitiligo			
subjects affected / exposed	14 / 178 (7.87%)	16 / 179 (8.94%)	0 / 53 (0.00%)
occurrences (all)	19	19	0
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	16 / 178 (8.99%)	15 / 179 (8.38%)	4 / 53 (7.55%)
occurrences (all)	17	16	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 178 (20.22%)	24 / 179 (13.41%)	9 / 53 (16.98%)
occurrences (all)	52	37	13
Back pain			
subjects affected / exposed	24 / 178 (13.48%)	21 / 179 (11.73%)	3 / 53 (5.66%)
occurrences (all)	31	27	3
Bone pain			
subjects affected / exposed	2 / 178 (1.12%)	8 / 179 (4.47%)	0 / 53 (0.00%)
occurrences (all)	2	8	0
Muscular weakness			
subjects affected / exposed	5 / 178 (2.81%)	9 / 179 (5.03%)	0 / 53 (0.00%)
occurrences (all)	5	11	0
Myalgia			
subjects affected / exposed	19 / 178 (10.67%)	14 / 179 (7.82%)	3 / 53 (5.66%)
occurrences (all)	23	15	3
Musculoskeletal pain			
subjects affected / exposed	18 / 178 (10.11%)	15 / 179 (8.38%)	4 / 53 (7.55%)
occurrences (all)	20	15	5
Pain in extremity			
subjects affected / exposed	18 / 178 (10.11%)	19 / 179 (10.61%)	4 / 53 (7.55%)
occurrences (all)	25	25	4
Muscle spasms			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	1 / 53 (1.89%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	5 / 53 (9.43%)
occurrences (all)	0	0	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 178 (5.62%)	20 / 179 (11.17%)	4 / 53 (7.55%)
occurrences (all)	11	36	9
Upper respiratory tract infection			

subjects affected / exposed	8 / 178 (4.49%)	18 / 179 (10.06%)	5 / 53 (9.43%)
occurrences (all)	12	25	6
Urinary tract infection			
subjects affected / exposed	17 / 178 (9.55%)	17 / 179 (9.50%)	8 / 53 (15.09%)
occurrences (all)	19	23	8
Oral herpes			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 178 (20.22%)	51 / 179 (28.49%)	9 / 53 (16.98%)
occurrences (all)	43	55	9
Dehydration			
subjects affected / exposed	7 / 178 (3.93%)	6 / 179 (3.35%)	0 / 53 (0.00%)
occurrences (all)	15	7	0
Hyperglycaemia			
subjects affected / exposed	12 / 178 (6.74%)	11 / 179 (6.15%)	3 / 53 (5.66%)
occurrences (all)	21	21	7
Hypertriglyceridaemia			
subjects affected / exposed	7 / 178 (3.93%)	10 / 179 (5.59%)	0 / 53 (0.00%)
occurrences (all)	18	25	0
Hypoalbuminaemia			
subjects affected / exposed	5 / 178 (2.81%)	12 / 179 (6.70%)	0 / 53 (0.00%)
occurrences (all)	6	13	0
Hypokalaemia			
subjects affected / exposed	9 / 178 (5.06%)	8 / 179 (4.47%)	4 / 53 (7.55%)
occurrences (all)	9	10	7
Hyponatraemia			
subjects affected / exposed	19 / 178 (10.67%)	10 / 179 (5.59%)	6 / 53 (11.32%)
occurrences (all)	28	11	11
Hyperkalaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 179 (0.00%)	4 / 53 (7.55%)
occurrences (all)	0	0	4

Non-serious adverse events	ICCPembrolizumab 10 mg/kg (After Switch to Pembrolizumab)		

Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 45 (80.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all) Melanocytic naevus subjects affected / exposed occurrences (all)	 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0		
Vascular disorders Hypotension subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Deep vein thrombosis subjects affected / exposed occurrences (all) Lymphoedema subjects affected / exposed occurrences (all)	 3 / 45 (6.67%) 5 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness	 3 / 45 (6.67%) 3 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 16 / 45 (35.56%) 24		

subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 6 0 / 45 (0.00%) 0 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0 8 / 45 (17.78%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 6 4 / 45 (8.89%) 4 1 / 45 (2.22%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	4			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Blood bilirubin increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Blood cholesterol increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Lymphocyte count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Neutrophil count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Platelet count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Weight decreased				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
White blood cell count decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Lipase increased				

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	7		
Dysgeusia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	10		
Neuropathy peripheral			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	21		
Leukopenia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Neutropenia			

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	22		
Dry mouth			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Nausea			

subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	17		
Vomiting			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	9		
Rash maculo-papular			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vitiligo			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	9		
Back pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	6		
Neck pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		
Dehydration			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	3		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2013	Amendment 01: The primary reasons for the amendment were to: 1) modify the primary and secondary objectives; 2) clarify inclusion and exclusion criteria; 3) modify the standard of care chemotherapy comparators permitted in this trial; and 4) modify the statistical analysis plan.
02 October 2013	Amendment 02: The primary reasons for the amendment were to: 1) modify the primary and secondary objectives; 2) clarify inclusion and exclusion criteria; 3) modify the standard of care chemotherapy comparators permitted in this trial; and 4) modify the statistical analysis plan.
14 July 2016	Amendment 03: The primary reason for the amendment was to modify the dosage of study treatment so that all participants will receive a fixed dose of pembrolizumab 200 mg every 3 weeks.
22 January 2018	Amendment 04: The primary reasons for this amendment were to clarify the follow-up durations for participants and remove the objectives relating to the pharmacokinetics (PK) analyses of pembrolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported