Clinical trial results:
A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients With Advanced Melanoma

Summary

EudraCT number	2012-004907-10
Trial protocol	GB SE AT BE ES FR DE NL NO
Global end of trial date	03 June 2019

Results information

Result version number	v1 (current)
This version publication date	23 May 2020
First version publication date	23 May 2020

Trial information

Trial identification

Sponsor protocol code	3475-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01866319
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-3475-006

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2015
Global end of trial reached?	Yes
Global end of trial date	03 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the safety and efficacy of 2 different dosing schedules of pembrolizumab (MK-3475), every 2 weeks (Q2W) and every 3 weeks (Q3W), and compared the 2 schedules to treatment with ipilimumab in ipilimumab-naïve participants with unresectable or metastatic melanoma. The primary hypotheses were that pembrolizumab is superior to ipilimumab with respect to progression-free survival (PFS) and overall survival (OS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 104
Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Israel: 70
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	Norway: 19
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	United Kingdom: 86
Country: Number of subjects enrolled	United States: 161

Worldwide total number of subjects	834
EEA total number of subjects	415

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	471
From 65 to 84 years	341
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

Participants with advanced melanoma were recruited to receive ipilimumab once every 3 weeks (Q3W), or a primary course of pembrolizumab administered every 2 weeks (Q2W) or every 3 weeks (Q3W).

Pre-assignment

Screening details:

834 participants were randomized 1:1:1 to receive ipilimumab Q3W, pembrolizumab Q2W, or pembrolizumab Q3W. For participants receiving pembrolizumab, all safety and efficacy results data reported are for the primary pembrolizumab course received.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab

Arm description:

Participants received ipilimumab, 3 mg/kg intravenously (IV), once every 3 weeks (Q3W) for a total of 4 doses (up to approximately 3 months).

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

Dosage and administration details:

10 mg/kg IV, administered Q2W or Q3W based upon randomization.

Arm title	Pembrolizumab Q2W

Arm description:

Participants received pembrolizumab, 10 mg/kg IV, once every 2 weeks (Q2W) for up to approximately 24 months.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg IV, administered Q2W or Q3W based upon randomization.

Arm title	Pembrolizumab Q3W

Arm description:

Participants received pembrolizumab, 10 mg/kg IV, Q3W for up to approximately 24 months.

Arm type	Experimental

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg IV, administered Q2W or Q3W based upon randomization.

Number of subjects in period 1	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W
Started	278	279	277
Treated	256	278	277
Completed	71	101	97
Not completed	207	178	180
Clinical progression	3	2	2
Adverse event, serious fatal	153	154	147
Physician decision	1	-	1
Consent withdrawn by subject	32	14	12
Adverse event, non-fatal	12	5	9
Lost to follow-up	6	3	8
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab
Reporting group description:	
Participants received ipilimumab, 3 mg/kg intravenously (IV), once every 3 weeks (Q3W) for a total of 4 doses (up to approximately 3 months).	
Reporting group title	Pembrolizumab Q2W
Reporting group description:	
Participants received pembrolizumab, 10 mg/kg IV, once every 2 weeks (Q2W) for up to approximately 24 months.	
Reporting group title	Pembrolizumab Q3W
Reporting group description:	
Participants received pembrolizumab, 10 mg/kg IV, Q3W for up to approximately 24 months.	

Reporting group values	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W
Number of subjects	278	279	277
Age categorical Units: Subjects			
Age Continuous Units: Years arithmetic mean standard deviation	 59.9 ± 14.2	 59.9 ± 14.6	 61.2 ± 13.6
Sex: Female, Male Units:			
Female Male	116 162	118 161	103 174

Reporting group values	Total		
Number of subjects	834		
Age categorical Units: Subjects			
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units:			
Female Male	337 497		

End points

End points reporting groups

Reporting group title	Ipilimumab
Reporting group description:	
Participants received ipilimumab, 3 mg/kg intravenously (IV), once every 3 weeks (Q3W) for a total of 4 doses (up to approximately 3 months).	
Reporting group title	Pembrolizumab Q2W
Reporting group description:	
Participants received pembrolizumab, 10 mg/kg IV, once every 2 weeks (Q2W) for up to approximately 24 months.	
Reporting group title	Pembrolizumab Q3W
Reporting group description:	
Participants received pembrolizumab, 10 mg/kg IV, Q3W for up to approximately 24 months.	

Primary: Progression-free Survival (PFS) According to Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Independent Radiology Plus Oncology Review (IRO)

End point title	Progression-free Survival (PFS) According to Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Independent Radiology Plus Oncology Review (IRO)
End point description:	
PFS was defined as the time from randomization to the first documented disease progression, based on blinded Independent Radiology plus Oncology review (IRO) using RECIST 1.1, or death due to any cause, whichever occurred first. Disease progression was defined as a 20% or greater increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of new lesions. The primary analysis of PFS was performed at the time of the first protocol pre-specified statistical analysis, with data cut-off of 03-Sep-2014. The Intent To Treat (ITT) population, comprising all participants as randomized to a study arm, was analysed for this endpoint.	
End point type	Primary
End point timeframe:	
Up to approximately 12 months (through first pre-specified statistical analysis cut-off date of 03-Sep-2014)	

End point values	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	279	277	
Units: Months				
median (confidence interval 95%)	2.8 (2.8 to 2.9)	5.5 (3.4 to 6.9)	4.1 (2.9 to 6.9)	

Statistical analyses

Statistical analysis title	PFS: IPI vs. Pembrolizumab Q2W
Statistical analysis description:	
Statistical testing was stratified by line of therapy (1st vs. 2nd), programmed cell death ligand 1 (PD-L1) status (positive vs. negative) and Eastern Cooperative Oncology Group (ECOG) performance status (0	

vs. 1)

Comparison groups	Ipilimumab v Pembrolizumab Q2W
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.72

Statistical analysis title	PFS: IPI vs. Pembrolizumab Q3W

Statistical analysis description:

Statistical testing was stratified by line of therapy (1st vs. 2nd), programmed cell death ligand 1 (PD-L1) status (positive vs. negative) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1)

Comparison groups	Ipilimumab v Pembrolizumab Q3W
Number of subjects included in analysis	555
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.72

Statistical analysis title	PFS: Pembrolizumab Q2W vs. Pembrolizumab Q3W

Statistical analysis description:

Statistical testing was stratified by line of therapy (1st vs. 2nd), programmed cell death ligand 1 (PD-L1) status (positive vs. negative) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1)

Comparison groups	Pembrolizumab Q2W v Pembrolizumab Q3W
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.75869
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.21

Primary: Percentage of Participants with Overall Survival (OS) at 12 Months

End point title	Percentage of Participants with Overall Survival (OS) at 12 Months

End point description:

OS was defined as the time from randomization to death due to any cause. The percentage of participants with OS (OS rate) at 12 months was reported for each arm. The reported percentage was estimated using a product-limit (Kaplan-Meier) method for censored data; data were censored at the date of cut-off. The primary analysis of OS was performed at the time of the second protocol pre-specified statistical analysis, with data cut-off of 03-Mar-2015. The ITT population, comprising all participants as randomized to a study arm, was analysed for this endpoint.

End point type	Primary

End point timeframe:

Month 12

End point values	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	279	277	
Units: Percentage of participants				
number (confidence interval 95%)	58.2 (51.8 to 64.0)	74.1 (68.5 to 78.9)	68.4 (62.5 to 73.6)	

Statistical analyses

Statistical analysis title	OS: IPI vs. Pembrolizumab Q2W

Statistical analysis description:

Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1).

Comparison groups	Ipilimumab v Pembrolizumab Q2W
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00052
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.83

Statistical analysis title	OS: IPI vs. Pembrolizumab Q3W
Statistical analysis description:	
Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1).	
Comparison groups	Ipilimumab v Pembrolizumab Q3W
Number of subjects included in analysis	555
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00358
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.9

Statistical analysis title	OS: Pembrolizumab Q2W vs. Pembrolizumab Q3W
Statistical analysis description:	
Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1).	
Comparison groups	Pembrolizumab Q2W v Pembrolizumab Q3W
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.51319
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.22

Secondary: Objective Response Rate (ORR) According to RECIST 1.1 as Assessed by IRO

End point title	Objective Response Rate (ORR) According to RECIST 1.1 as Assessed by IRO

End point description:

ORR was defined as the percentage of the participants with a best tumor response of complete response (CR: disappearance of all target lesions with any pathological lymph nodes having a reduction in short axis to <10 mm) or partial response (PR: ≥30% decrease in the sum of diameters of target lesions), based on IRO using RECIST 1.1. The primary analysis of ORR was performed at the time of the first

protocol pre-specified statistical analysis, with data cut-off of 03-Sep-2014. The ITT population, comprising all participants as randomized to a study arm, was analysed for this endpoint.

End point type	Secondary

End point timeframe:

Up to approximately 12 months (through first pre-specified statistical analysis cut-off date of 03-Sep-2014)

End point values	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	279	277	
Units: Percentage of Participants				
number (confidence interval 95%)	11.9 (8.3 to 16.3)	33.7 (28.2 to 39.6)	32.9 (27.4 to 38.7)	

Statistical analyses

Statistical analysis title	ORR: IPI vs. Pembrolizumab Q2W

Statistical analysis description:

Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1)

Comparison groups	Ipilimumab v Pembrolizumab Q2W
Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00013
Method	Miettinen & Nurmimen
Parameter estimate	Percent difference
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.8
upper limit	24.5

Statistical analysis title	ORR: IPI vs. Pembrolizumab Q3W

Statistical analysis description:

Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1)

Comparison groups	Ipilimumab v Pembrolizumab Q3W

Number of subjects included in analysis	555
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00002
Method	Miettinen & Nurmimen
Parameter estimate	Percent difference
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.5
upper limit	25.6

Statistical analysis title	ORR: Pembrolizumab Q2W vs. Pembrolizumab Q3W
Statistical analysis description:	
Statistical testing was stratified by line of therapy (1st vs. 2nd), PD-L1) status (positive vs. negative) and ECOG performance status (0 vs. 1)	
Comparison groups	Pembrolizumab Q2W v Pembrolizumab Q3W
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.82636
Method	Miettinen & Nurmimen
Parameter estimate	Percent difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	8.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 69 months (through End of Trial Analysis data cut-off date of 03-Jun-2019)

Adverse event reporting additional description:

Serious and Other adverse events (AEs) tables include all randomized participants who received ≥1 dose of study drug. Per protocol, disease progression on study not considered AE unless related to drug. Thus, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to drug excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Participants received ipilimumab 3 mg/kg IV Q3W for a total of 4 doses (up to approximately 3 months). The number of deaths (all causes) was reported out of all randomized participants (N=278).

Reporting group title	Pembrolizumab Q2W

Reporting group description:

Participants received pembrolizumab 10 mg/kg IV Q2W for up to approximately 24 months. The number of deaths (all causes) was reported out of all randomized participants (N=279).

Reporting group title	Pembrolizumab Q3W

Reporting group description:

Participants received pembrolizumab 10 mg/kg IV Q3W for up to approximately 24 months. The number of deaths (all causes) was reported out of all randomized participants (N=277).

Serious adverse events	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 256 (30.08%)	89 / 278 (32.01%)	90 / 277 (32.49%)
number of deaths (all causes)	173	166	162
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	5 / 278 (1.80%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal squamous cell carcinoma			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Desmoplastic melanoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Epidermoid carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Huerthle cell carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intra-epidermal carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 bleeding			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Lymphangiosis carcinomatosa			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Melanoma			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to brain			
subjects affected / exposed	2 / 256 (0.78%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Signet-ring cell adenocarcinoma gastric			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 256 (0.39%)	2 / 278 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial basal cell carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid papillary carcinoma			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour bleeding			
subjects affected / exposed	3 / 256 (1.17%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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			
Aortic stenosis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Arterial stenosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Arterial thrombosis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Haematoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Lymphoedema			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor venous access			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Superior vena cava occlusion			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombosis leg			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Vein disorder			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
General disorders and administration site conditions			
Anasarca			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
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 death			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Face oedema			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Fatigue aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	4 / 256 (1.56%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General body pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reduced general condition			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Unknown cause of death			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Anaphylactoid reaction			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 reaction			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Chronic obstructive pulmonary disease exacerbation			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exacerbated			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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	0 / 256 (0.00%)	1 / 278 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	1 / 1	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	4 / 277 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute delirium			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Completed suicide			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Confusion			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphoria			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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	2 / 256 (0.78%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin total increased			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure decreased			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Liver function test abnormal			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Shoulder injury			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 breakdown			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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 congestive			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Congestive cardiac failure aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decompensation cardiac			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Heart attack			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Paroxysmal atrial fibrillation			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
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 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Nervous system disorders			
Bell's palsy			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Carotid artery stenosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebral ischaemia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral oedema			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsions aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Epilepsy			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Guillain-Barre syndrome			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage brain			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Horner's syndrome			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Hydrocephalus			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraneoplastic limbic encephalitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Partial seizures			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Sciatica			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Syncope			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Vasogenic cerebral oedema			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph nodes enlarged			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Thrombocytopenia			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Neovascular glaucoma			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Papilloedema			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 256 (0.78%)	1 / 278 (0.36%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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

Anal fistula			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune pancreatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood in stool			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	16 / 256 (6.25%)	6 / 278 (2.16%)	6 / 277 (2.17%)
occurrences causally related to treatment / all	18 / 18	6 / 6	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	9 / 256 (3.52%)	7 / 278 (2.52%)	3 / 277 (1.08%)
occurrences causally related to treatment / all	9 / 9	6 / 7	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Enterocolitis			

subjects affected / exposed	2 / 256 (0.78%)	0 / 278 (0.00%)	0 / 277 (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
Gastritis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophagitis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage of digestive tract			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
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 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal stenosis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Intussusception			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal bleeding			

subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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 gastrointestinal haemorrhage			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Mouth necrosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis aggravated			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial small intestinal obstruction			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Reflux oesophagitis			

subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Sigmoiditis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 256 (0.78%)	0 / 278 (0.00%)	0 / 277 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 256 (0.78%)	4 / 278 (1.44%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 2	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Biliary colic			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dilatation			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Cholecystitis			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	0 / 277 (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
Cytolytic hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cytolysis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Obstructive jaundice			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Skin and subcutaneous tissue disorders			
Bullous lichen planus			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Bullous pemphigoid			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug rash			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Rash			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute renal insufficiency			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
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	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Nephritis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Nephritis interstitial			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal disorder			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal insufficiency			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 256 (0.39%)	2 / 278 (0.72%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenomegaly			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	2 / 256 (0.78%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	0 / 277 (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
Hypothyroidism			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Panhypopituitarism			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain aggravated			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hips osteoarthritis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low back pain			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Pain in heel			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 leg			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathologic fracture of femur			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathologic fracture of humerus			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	0 / 277 (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
Pathological fracture			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prolapsed lumbar disc			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Psoriatic arthritis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seronegative arthritis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Unilateral leg pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bladder infection			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Bronchial infection			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis aggravated			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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 of oral soft tissues			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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 of upper arm			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central line infection			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Colonic abscess			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Gastroenteritis			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	0 / 277 (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
Infection			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Klebsiella sepsis			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Meningoencephalitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Myelitis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 256 (0.39%)	2 / 278 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Pseudomembranous colitis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Pyelonephritis			

subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 256 (0.78%)	2 / 278 (0.72%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septicaemia gram-negative NOS			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Sinusitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	1 / 256 (0.39%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Failure to thrive			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Hypercalcaemia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	0 / 277 (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
Hypoalbuminaemia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Hypokalaemia			
subjects affected / exposed	0 / 256 (0.00%)	2 / 278 (0.72%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 278 (0.00%)	2 / 277 (0.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia aggravated			

subjects affected / exposed	0 / 256 (0.00%)	1 / 278 (0.36%)	0 / 277 (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
Metabolic disorder			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 256 (0.00%)	0 / 278 (0.00%)	1 / 277 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ipilimumab	Pembrolizumab Q2W	Pembrolizumab Q3W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 256 (85.94%)	257 / 278 (92.45%)	247 / 277 (89.17%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 256 (4.69%)	21 / 278 (7.55%)	16 / 277 (5.78%)
occurrences (all)	13	32	19
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 256 (4.69%)	22 / 278 (7.91%)	12 / 277 (4.33%)
occurrences (all)	13	35	17
Lactate dehydrogenase increased			
subjects affected / exposed	6 / 256 (2.34%)	14 / 278 (5.04%)	6 / 277 (2.17%)
occurrences (all)	6	25	11
Weight decreased			
subjects affected / exposed	13 / 256 (5.08%)	20 / 278 (7.19%)	26 / 277 (9.39%)
occurrences (all)	13	21	28
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 256 (3.52%)	27 / 278 (9.71%)	22 / 277 (7.94%)
occurrences (all)	9	34	26
Headache			

subjects affected / exposed	27 / 256 (10.55%)	45 / 278 (16.19%)	33 / 277 (11.91%)
occurrences (all)	29	72	58
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 256 (4.69%)	34 / 278 (12.23%)	23 / 277 (8.30%)
occurrences (all)	14	44	28
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 256 (10.16%)	45 / 278 (16.19%)	41 / 277 (14.80%)
occurrences (all)	29	92	56
Fatigue			
subjects affected / exposed	73 / 256 (28.52%)	90 / 278 (32.37%)	85 / 277 (30.69%)
occurrences (all)	78	125	116
Fever			
subjects affected / exposed	20 / 256 (7.81%)	29 / 278 (10.43%)	21 / 277 (7.58%)
occurrences (all)	22	40	35
Flu-like symptoms			
subjects affected / exposed	8 / 256 (3.13%)	21 / 278 (7.55%)	14 / 277 (5.05%)
occurrences (all)	9	23	27
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 256 (6.25%)	29 / 278 (10.43%)	18 / 277 (6.50%)
occurrences (all)	19	37	19
Constipation			
subjects affected / exposed	29 / 256 (11.33%)	53 / 278 (19.06%)	39 / 277 (14.08%)
occurrences (all)	32	78	47
Diarrhoea			
subjects affected / exposed	69 / 256 (26.95%)	82 / 278 (29.50%)	76 / 277 (27.44%)
occurrences (all)	91	162	116
Dry mouth			
subjects affected / exposed	1 / 256 (0.39%)	26 / 278 (9.35%)	20 / 277 (7.22%)
occurrences (all)	1	27	21
Nausea			
subjects affected / exposed	55 / 256 (21.48%)	73 / 278 (26.26%)	70 / 277 (25.27%)
occurrences (all)	66	90	88
Vomiting			

subjects affected / exposed	31 / 256 (12.11%)	45 / 278 (16.19%)	27 / 277 (9.75%)
occurrences (all)	35	66	32
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 256 (6.25%)	58 / 278 (20.86%)	43 / 277 (15.52%)
occurrences (all)	17	75	48
Dry cough			
subjects affected / exposed	2 / 256 (0.78%)	9 / 278 (3.24%)	15 / 277 (5.42%)
occurrences (all)	2	10	16
Dyspnoea			
subjects affected / exposed	15 / 256 (5.86%)	30 / 278 (10.79%)	27 / 277 (9.75%)
occurrences (all)	16	32	27
Sore throat			
subjects affected / exposed	4 / 256 (1.56%)	16 / 278 (5.76%)	5 / 277 (1.81%)
occurrences (all)	5	16	5
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 256 (2.34%)	19 / 278 (6.83%)	17 / 277 (6.14%)
occurrences (all)	6	20	17
Pruritus			
subjects affected / exposed	65 / 256 (25.39%)	68 / 278 (24.46%)	59 / 277 (21.30%)
occurrences (all)	76	99	83
Rash			
subjects affected / exposed	28 / 256 (10.94%)	37 / 278 (13.31%)	36 / 277 (13.00%)
occurrences (all)	29	55	51
Rash maculo-papular			
subjects affected / exposed	8 / 256 (3.13%)	17 / 278 (6.12%)	10 / 277 (3.61%)
occurrences (all)	8	23	15
Vitiligo			
subjects affected / exposed	4 / 256 (1.56%)	34 / 278 (12.23%)	42 / 277 (15.16%)
occurrences (all)	4	36	45
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 256 (1.56%)	14 / 278 (5.04%)	10 / 277 (3.61%)
occurrences (all)	4	14	10
Insomnia			

subjects affected / exposed	14 / 256 (5.47%)	28 / 278 (10.07%)	20 / 277 (7.22%)
occurrences (all)	14	33	20
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	6 / 256 (2.34%)	17 / 278 (6.12%)	12 / 277 (4.33%)
occurrences (all)	6	19	12
Hypothyroidism			
subjects affected / exposed	5 / 256 (1.95%)	29 / 278 (10.43%)	25 / 277 (9.03%)
occurrences (all)	5	31	26
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 256 (7.03%)	41 / 278 (14.75%)	39 / 277 (14.08%)
occurrences (all)	18	63	42
Back pain			
subjects affected / exposed	8 / 256 (3.13%)	29 / 278 (10.43%)	11 / 277 (3.97%)
occurrences (all)	8	32	12
Knee pain			
subjects affected / exposed	6 / 256 (2.34%)	15 / 278 (5.40%)	8 / 277 (2.89%)
occurrences (all)	6	21	8
Low back pain			
subjects affected / exposed	5 / 256 (1.95%)	17 / 278 (6.12%)	12 / 277 (4.33%)
occurrences (all)	5	19	14
Myalgia			
subjects affected / exposed	8 / 256 (3.13%)	32 / 278 (11.51%)	15 / 277 (5.42%)
occurrences (all)	8	38	18
Shoulder pain			
subjects affected / exposed	8 / 256 (3.13%)	21 / 278 (7.55%)	12 / 277 (4.33%)
occurrences (all)	9	26	12
Infections and infestations			
Common cold syndrome			
subjects affected / exposed	9 / 256 (3.52%)	21 / 278 (7.55%)	15 / 277 (5.42%)
occurrences (all)	9	32	18
Upper respiratory tract infection			
subjects affected / exposed	11 / 256 (4.30%)	31 / 278 (11.15%)	21 / 277 (7.58%)
occurrences (all)	11	43	25
Urinary tract infection			

subjects affected / exposed	10 / 256 (3.91%)	22 / 278 (7.91%)	14 / 277 (5.05%)
occurrences (all)	11	33	19
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	24 / 256 (9.38%)	31 / 278 (11.15%)	35 / 277 (12.64%)
occurrences (all)	27	39	36
Hypokalaemia			
subjects affected / exposed	5 / 256 (1.95%)	16 / 278 (5.76%)	13 / 277 (4.69%)
occurrences (all)	7	34	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2013	Major changes of Amendment (AM) 1 include 1) changing the primary endpoint of the study from OS to PFS and OS, 2) changing the study to a 3-arm trial testing two dosing regimens of pembrolizumab against ipilimumab, and 3) changing the study to prospectively evaluate participants for PD-L1 expression.
25 February 2014	Major changes of Amendment AM 2 include incorporation of feedback from the FDA and adjusting the interim analysis timing.
21 August 2014	Major changes of Amendment AM 3 include changing pharmacokinetic (PK) collection timepoints to reflect the timepoints in AM1, as all participants were enrolled prior to the finalization of AM2.
12 January 2015	Major changes of Amendment AM 4 included updating the in-house blinding plan.
12 August 2016	Major changes of Amendment AM 5 included changing the pembrolizumab dose for ongoing Second Course participants to a fixed dose of 200 mg every 3 weeks (not weight-based).
19 January 2018	Major changes of Amendment AM 6 included specifying the timepoints for survival status assessment during the course of the study, during the study follow-up period, and after study discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported