Clinical trial results:
A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence (CheckMate 238: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 2238)

Summary

EudraCT number	2014-002351-26
Trial protocol	BE IE GB NO FI SE CZ ES AT NL FR HU GR PL RO Outside EU/EEA IT
Global end of trial date	18 October 2024
Results information	
Result version number	v1 (current)
This version publication date	20 April 2025
First version publication date	20 April 2025

Trial information

Trial identification	
Sponsor protocol code	CA209-238
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, mg-gsm-ct@bms.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	12 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy, as measured by RFS, provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	United States: 211
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Italy: 137
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	United Kingdom: 68
Country: Number of subjects enrolled	Czechia: 28
Country: Number of subjects enrolled	Hungary: 4

Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 25
Country: Number of subjects enrolled	Japan: 28
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Australia: 78
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	South Africa: 4
Worldwide total number of subjects	906
EEA total number of subjects	447

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)	672
From 65 to 84 years	233
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

906 participants randomized and 905 treated.

Period 1

Period 1 title	Pre-Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 3 mg/kg

Arm description:

Nivolumab 3 mg/kg IV q2 wks and Ipilimumab placebo IV q3 wks for 4 doses then q12 wks starting at Wk 24

Arm type	Experimental
Investigational medicinal product name	ipilimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

placebo

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

Dosage and administration details:

3mg/kg

Arm title	Ipilimumab 10 mg/kg

Arm description:

Ipilimumab 10 mg/kg IV q3 wks for 4 doses then q12 wks starting at Wk 24 and Nivolumab placebo IV q2 wks

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

10mg/kg

Investigational medicinal product name	nivolumab placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

placebo

Number of subjects in period 1	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg
Started	453	453
Completed	452	453
Not completed	1	0
Participant withdrew consent	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 3 mg/kg

Arm description:

Nivolumab 3 mg/kg IV q2 wks and Ipilimumab placebo IV q3 wks for 4 doses then q12 wks starting at Wk 24

Arm type	Experimental
Investigational medicinal product name	ipilimumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

placebo

Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

3mg/kg

Arm title	Ipilimumab 10 mg/kg

Arm description:	
Ipilimumab 10 mg/kg IV q3 wks for 4 doses then q12 wks starting at Wk 24 and Nivolumab placebo IV q2 wks	
Arm type	Experimental
Investigational medicinal product name	nivolumab placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use
Dosage and administration details:	
placebo	
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use
Dosage and administration details:	
10mg/kg	

Number of subjects in period 2	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg
Started	452	453
Completed	275	123
Not completed	177	330
Disease progression	121	100
Adverse Event (AE) unrelated to study drug	5	5
Participant request to stop treatment	5	9
Participant withdrew consent	2	3
Study drug toxicity	41	208
Participant no longer meets study criteria	-	1
Other reasons	3	3
Poor/non-compliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab 3 mg/kg
Reporting group description:	
Nivolumab 3 mg/kg IV q2 wks and Ipilimumab placebo IV q3 wks for 4 doses then q12 wks starting at Wk 24	
Reporting group title	Ipilimumab 10 mg/kg
Reporting group description:	
Ipilimumab 10 mg/kg IV q3 wks for 4 doses then q12 wks starting at Wk 24 and Nivolumab placebo IV q2 wks	

Reporting group values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg	Total
Number of subjects	453	453	906
Age categorical Units: Subjects			
Adults (18-64 years)	333	339	672
From 65-84 years	120	113	233
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	54.4	53.6	
standard deviation	± 13.34	± 13.50	-
Sex: Female, Male Units: Participants			
Female	195	184	379
Male	258	269	527
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	25	18	43
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	0	0
White	425	434	859
More than one race	0	0	0
Unknown or Not Reported	2	1	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	8	14
Not Hispanic or Latino	215	208	423
Unknown or Not Reported	232	237	469

End points

End points reporting groups

Reporting group title	Nivolumab 3 mg/kg
Reporting group description:	
Nivolumab 3 mg/kg IV q2 wks and Ipilimumab placebo IV q3 wks for 4 doses then q12 wks starting at Wk 24	
Reporting group title	Ipilimumab 10 mg/kg
Reporting group description:	
Ipilimumab 10 mg/kg IV q3 wks for 4 doses then q12 wks starting at Wk 24 and Nivolumab placebo IV q2 wks	
Reporting group title	Nivolumab 3 mg/kg
Reporting group description:	
Nivolumab 3 mg/kg IV q2 wks and Ipilimumab placebo IV q3 wks for 4 doses then q12 wks starting at Wk 24	
Reporting group title	Ipilimumab 10 mg/kg
Reporting group description:	
Ipilimumab 10 mg/kg IV q3 wks for 4 doses then q12 wks starting at Wk 24 and Nivolumab placebo IV q2 wks	

Primary: Recurrence-free survival (RFS)

End point title	Recurrence-free survival (RFS)
End point description:	
RFS is defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. Here "99999 and -99999" = NA	
End point type	Primary
End point timeframe:	
up to 36 months	

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	453		
Units: Months				
median (confidence interval 95%)	61.04 (42.51 to 68.63)	24.15 (16.56 to 35.09)		

Statistical analyses

Statistical analysis title	Statistical Analysis for RFS
Comparison groups	Nivolumab 3 mg/kg v Ipilimumab 10 mg/kg

Number of subjects included in analysis	906
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.87

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as as the time between the date of randomization and the date of death.

Here "99999 and -99999" = NA

End point type	Secondary

End point timeframe:

up to 106.6 months

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	453		
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
Comparison groups	Nivolumab 3 mg/kg v Ipilimumab 10 mg/kg
Number of subjects included in analysis	906
Analysis specification	Pre-specified
Analysis type	
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88

Confidence interval	
level	95.03 %
sides	2-sided
lower limit	0.69
upper limit	1.11

Secondary: The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of adverse events

End point title	The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of adverse events

End point description:

the safety and tolerability of Nivolumab and Ipilimumab was measured by the incidence of adverse events

End point type	Secondary

End point timeframe:

reported between first dose and 30 days after last dose of study therapy

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	453		
Units: Participants				
Grade 3-4	116	251		
Any grade	440	446		

Statistical analyses

No statistical analyses for this end point

Secondary: The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of serious adverse events

End point title	The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of serious adverse events

End point description:

The Safety and Tolerability of nivolumab and ipilimumab was measured by the incidence of serious adverse events

End point type	Secondary

End point timeframe:

reported between the first dose and 30 days after last dose of study therapy

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	453		
Units: Participants				
Grade 3-4	48	145		
Any grade	80	184		

Statistical analyses

No statistical analyses for this end point

Secondary: the safety and tolerability of Nivolumab and Ipilimumab measured by the incidence of Deaths

End point title	the safety and tolerability of Nivolumab and Ipilimumab measured by the incidence of Deaths

End point description:

the safety and tolerability of Nivolumab and Ipilimumab wasmeasured by the incidence of Deaths

End point type	Secondary

End point timeframe:

reported between first dose and 30 to 100 days after last dose of study therapy

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	453		
Units: Participants	128	142		

Statistical analyses

No statistical analyses for this end point

Secondary: The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of Laboratory abnormalities

End point title	The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of Laboratory abnormalities

End point description:

The Safety and Tolerability of Nivolumab and Ipilimumab measured by the incidence of Laboratory abnormalities.

End point type	Secondary

End point timeframe:

reported after first dose and within 30 days of last dose of the study therapy

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	452	453		
Units: Participants				
Heamoglobin (grade1-4)	114	148		
Heamoglobin (Grade 3-4)	0	2		
Platelet count (grade1-4)	27	25		
Platelet count (grade 3-4)	0	1		
Leukocytes (grade1-4)	62	12		
Leukocytes (grade 3-4)	0	1		
Lymphocytes (grade1-4)	118	54		
Lymphocytes (grade 3-4)	2	4		
Absolute Neutrophil count (Grade1-4)	56	26		
Absolute Neutrophil count (Grade3-4)	0	2		
Alkaline Phosphatase (grade1-4)	35	69		
Alkaline Phosphatase (Grade3-4)	1	3		
Aspartate Aminotransferase (grade 1-4)	105	144		
Aspartate Aminotransferase(grade 3-4)	6	39		
Alkaline Aminotransferase (grade 1-4)	113	176		
Alkaline Aminotransferase(grade 3-4)	8	52		
Total Bilirubin (grade 1-4)	33	43		
Total Bilirubin (grade 3-4)	0	5		
Creatinine (grade1-4)	55	56		
Creatinine (grade 3-4)	0	0		
Total Amylase (grade1-4)	68	52		
Total Amylase (grade 3-4)	13	12		
Total Lipase (grade1-4)	109	100		
Total Lipase (grade 3-4)	31	38		
Hypernatremia (grade1-4)	35	20		
Hypernatremia (grade 3-4)	0	0		
Hyponatremia (grade1-4)	72	96		
Hyponatremia (grade 3-4)	5	14		
Hyperkalemia (grade1-4)	55	39		
Hyperkalemia (grade 3-4)	1	2		
Hypokalemia (grade1-4)	37	45		
Hypokalemia(grade 3-4)	5	9		
Hypercalcemia (grade1-4)	14	18		
Hypercalcemia(grade 3-4)	0	0		
Hypocalcemia (grade1-4)	46	73		
Hypocalcemia(grade 3-4)	3	2		
Hypermagnesemia (grade1-4)	20	7		
Hypermagnesemia(grade 3-4)	2	1		
Hypomagnesemia (grade1-4)	39	32		
Hypomagnesemia(grade 3-4)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence-free survival by PD-L1 Expression

End point title	Recurrence-free survival by PD-L1 Expression

End point description:

Recurrence-free survival by PD-L1 Expression(5% tumor cell membrane expression)

Here "99999 and -99999" = NA

End point type	Secondary

End point timeframe:

up to 106.6 months

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	453	453		
Units: Months				
median (confidence interval 95%)				
Participants with >= 5% PD-L1 Expression,	70.41 (67.65 to 84.80)	54.67 (24.15 to 84.40)		
< 5% PD-L1 Expression,	38.67 (22.05 to 61.04)	16.56 (11.14 to 26.51)		
Non-quantifiable PD-L1 Expression	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HRQoL) evaluation

End point title	Health Related Quality of Life (HRQoL) evaluation

End point description:

HRQoL was measured by mean changes from baseline in EORTC-QLQ-C30 global health status/QoL composite scale and in remaining EORTC QLQ-C30 scales in all randomized participants.

EORTC QLQ-C30 is the most commonly used QoL instrument in melanoma clinical studies, is a 30-item instrument that has gained wide acceptance in oncology clinical studies and comprises 5 functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4 point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales for which higher score reflects higher health status/quality of life for the 7-point Likert scale.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	308		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical functioning	-2.04 (± 15.134)	-4.88 (± 15.713)		
Role functioning	-2.43 (± 25.219)	-3.85 (± 29.951)		
Emotional functioning	0.18 (± 20.282)	1.43 (± 17.911)		
Cognitive functioning	-3.74 (± 18.364)	-4.67 (± 16.664)		
Social functioning	-0.51 (± 22.085)	-3.53 (± 26.391)		
Global health status	-5.81 (± 20.046)	-7.00 (± 23.109)		
Fatigue	6.45 (± 21.605)	9.05 (± 23.475)		
Nausea and vomiting	2.23 (± 12.622)	1.90 (± 11.473)		
Pain	1.66 (± 23.314)	4.38 (± 23.641)		
Dyspnea	7.32 (± 22.741)	5.45 (± 20.364)		
Insomnia	1.82 (± 28.692)	3.05 (± 28.785)		
Appetite loss	4.07 (± 22.660)	2.61 (± 19.257)		
Constipation	1.11 (± 17.904)	0.33 (± 18.373)		
Diarrhea	1.31 (± 20.831)	3.38 (± 21.242)		
Financial difficulties	-1.41 (± 23.348)	0.54 (± 20.282)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: (From first dose to last dose + 100 days): approximately up to 16 Months

All-Cause mortality (From first dose to end of study): Approximately up to 114 Months

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Ipilimumab 10 mg/kg

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions).

Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses

Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Reporting group title	Nivolumab 3 mg/kg

Reporting group description:

Nivolumab: specified dose on specified days; IV (intravenous) infusion
Temozolomide: 75 mg (milligram)/meter squared daily during Radiotherapy, 4 week treatment break, 150 mg/meter squared Day 1-5 for Cycle 1 and increased to 200 mg/meter squared Day 1-5 for Cycle2-Cycle 6 as tolerated; orally (additional cycles may be permitted with approval of sponsor)
Radiotherapy: 2 gray units (joule of radiation energy per kilogram) 5 times per week for 6 weeks

Serious adverse events	Ipilimumab 10 mg/kg	Nivolumab 3 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	215 / 453 (47.46%)	106 / 452 (23.45%)	
number of deaths (all causes)	142	128	
number of deaths resulting from adverse events	4	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 453 (0.66%)	3 / 452 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	3 / 453 (0.66%)	4 / 452 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Melanoma recurrent			

subjects affected / exposed	1 / 453 (0.22%)	10 / 452 (2.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 453 (0.22%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm malignant			
subjects affected / exposed	0 / 453 (0.00%)	3 / 452 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm recurrence			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 453 (0.22%)	5 / 452 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis limb			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell arteritis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 453 (0.44%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 453 (2.43%)	8 / 452 (1.77%)	
occurrences causally related to treatment / all	7 / 11	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune lung disease			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 453 (0.22%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung infiltration			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 453 (1.10%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 453 (0.88%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Dependence			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 453 (1.10%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal volume increased			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	3 / 453 (0.66%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	5 / 453 (1.10%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bradycardia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Bell's palsy			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	4 / 453 (0.88%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IVth nerve disorder			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miller Fisher syndrome			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosarcoidosis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 453 (0.66%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node pain			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	3 / 453 (0.66%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Autoimmune colitis			
subjects affected / exposed	5 / 453 (1.10%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 453 (0.66%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	41 / 453 (9.05%)	5 / 452 (1.11%)	
occurrences causally related to treatment / all	50 / 52	3 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 453 (0.66%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glossitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intussusception			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 453 (0.66%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	37 / 453 (8.17%)	5 / 452 (1.11%)	
occurrences causally related to treatment / all	39 / 43	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 453 (0.44%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	7 / 453 (1.55%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disease			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	3 / 453 (0.66%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acne			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			

subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	4 / 453 (0.88%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 453 (0.22%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 453 (0.22%)	3 / 452 (0.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	5 / 453 (1.10%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal suppression			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucocorticoid deficiency			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 453 (0.22%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			

subjects affected / exposed	18 / 453 (3.97%)	3 / 452 (0.66%)	
occurrences causally related to treatment / all	19 / 19	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothalamo-pituitary disorder			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	5 / 453 (1.10%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporomandibular pain and dysfunction syndrome			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 453 (0.66%)	7 / 452 (1.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	3 / 453 (0.66%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			

subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 453 (1.32%)	4 / 452 (0.88%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 453 (0.22%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 453 (0.66%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinobronchitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 453 (0.00%)	2 / 452 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 453 (0.66%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 453 (0.88%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fulminant type 1 diabetes mellitus			

subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 453 (0.22%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 453 (0.44%)	0 / 452 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 453 (0.44%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 453 (0.00%)	1 / 452 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab 10 mg/kg	Nivolumab 3 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	438 / 453 (96.69%)	421 / 452 (93.14%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 453 (5.30%)	33 / 452 (7.30%)	
occurrences (all)	48	60	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	197 / 453 (43.49%)	193 / 452 (42.70%)	
occurrences (all)	239	263	
Asthenia			
subjects affected / exposed	72 / 453 (15.89%)	74 / 452 (16.37%)	
occurrences (all)	98	105	
Chills			
subjects affected / exposed	31 / 453 (6.84%)	11 / 452 (2.43%)	
occurrences (all)	37	11	
Pyrexia			
subjects affected / exposed	105 / 453 (23.18%)	39 / 452 (8.63%)	
occurrences (all)	146	45	
Oedema peripheral			
subjects affected / exposed	29 / 453 (6.40%)	24 / 452 (5.31%)	
occurrences (all)	32	29	
Influenza like illness			
subjects affected / exposed	39 / 453 (8.61%)	32 / 452 (7.08%)	
occurrences (all)	50	41	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	37 / 453 (8.17%)	30 / 452 (6.64%)	
occurrences (all)	47	36	
Nasal congestion			
subjects affected / exposed	17 / 453 (3.75%)	24 / 452 (5.31%)	
occurrences (all)	19	26	
Cough			
subjects affected / exposed	83 / 453 (18.32%)	84 / 452 (18.58%)	
occurrences (all)	106	107	

Dyspnoea			
subjects affected / exposed	45 / 453 (9.93%)	34 / 452 (7.52%)	
occurrences (all)	52	36	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	21 / 453 (4.64%)	25 / 452 (5.53%)	
occurrences (all)	21	25	
Insomnia			
subjects affected / exposed	43 / 453 (9.49%)	35 / 452 (7.74%)	
occurrences (all)	51	36	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	88 / 453 (19.43%)	38 / 452 (8.41%)	
occurrences (all)	109	45	
Amylase increased			
subjects affected / exposed	26 / 453 (5.74%)	29 / 452 (6.42%)	
occurrences (all)	31	49	
Aspartate aminotransferase increased			
subjects affected / exposed	75 / 453 (16.56%)	31 / 452 (6.86%)	
occurrences (all)	101	37	
Blood alkaline phosphatase increased			
subjects affected / exposed	26 / 453 (5.74%)	4 / 452 (0.88%)	
occurrences (all)	33	7	
Lipase increased			
subjects affected / exposed	41 / 453 (9.05%)	36 / 452 (7.96%)	
occurrences (all)	49	55	
Weight decreased			
subjects affected / exposed	35 / 453 (7.73%)	11 / 452 (2.43%)	
occurrences (all)	39	12	
Nervous system disorders			
Dizziness			
subjects affected / exposed	39 / 453 (8.61%)	47 / 452 (10.40%)	
occurrences (all)	45	58	
Headache			
subjects affected / exposed	148 / 453 (32.67%)	109 / 452 (24.12%)	
occurrences (all)	181	149	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 453 (5.74%)	13 / 452 (2.88%)	
occurrences (all)	45	19	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	30 / 453 (6.62%)	10 / 452 (2.21%)	
occurrences (all)	34	10	
Constipation			
subjects affected / exposed	46 / 453 (10.15%)	47 / 452 (10.40%)	
occurrences (all)	47	61	
Diarrhoea			
subjects affected / exposed	250 / 453 (55.19%)	171 / 452 (37.83%)	
occurrences (all)	471	341	
Dry mouth			
subjects affected / exposed	23 / 453 (5.08%)	33 / 452 (7.30%)	
occurrences (all)	28	34	
Dyspepsia			
subjects affected / exposed	27 / 453 (5.96%)	21 / 452 (4.65%)	
occurrences (all)	34	23	
Nausea			
subjects affected / exposed	135 / 453 (29.80%)	110 / 452 (24.34%)	
occurrences (all)	171	153	
Vomiting			
subjects affected / exposed	68 / 453 (15.01%)	39 / 452 (8.63%)	
occurrences (all)	88	44	
Abdominal pain upper			
subjects affected / exposed	21 / 453 (4.64%)	33 / 452 (7.30%)	
occurrences (all)	25	39	
Abdominal pain			
subjects affected / exposed	78 / 453 (17.22%)	53 / 452 (11.73%)	
occurrences (all)	99	70	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	23 / 453 (5.08%)	31 / 452 (6.86%)	
occurrences (all)	25	42	
Rash maculo-papular			

subjects affected / exposed	52 / 453 (11.48%)	27 / 452 (5.97%)	
occurrences (all)	77	35	
Rash			
subjects affected / exposed	166 / 453 (36.64%)	122 / 452 (26.99%)	
occurrences (all)	225	157	
Pruritus			
subjects affected / exposed	179 / 453 (39.51%)	136 / 452 (30.09%)	
occurrences (all)	257	188	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	35 / 453 (7.73%)	53 / 452 (11.73%)	
occurrences (all)	36	57	
Hypophysitis			
subjects affected / exposed	42 / 453 (9.27%)	6 / 452 (1.33%)	
occurrences (all)	45	6	
Hyperthyroidism			
subjects affected / exposed	22 / 453 (4.86%)	37 / 452 (8.19%)	
occurrences (all)	22	37	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	80 / 453 (17.66%)	103 / 452 (22.79%)	
occurrences (all)	94	122	
Back pain			
subjects affected / exposed	46 / 453 (10.15%)	49 / 452 (10.84%)	
occurrences (all)	51	59	
Myalgia			
subjects affected / exposed	35 / 453 (7.73%)	60 / 452 (13.27%)	
occurrences (all)	39	69	
Pain in extremity			
subjects affected / exposed	36 / 453 (7.95%)	42 / 452 (9.29%)	
occurrences (all)	41	46	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	32 / 453 (7.06%)	43 / 452 (9.51%)	
occurrences (all)	46	54	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	24 / 453 (5.30%) 33	53 / 452 (11.73%) 65	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 69 / 453 (15.23%) 85	 43 / 452 (9.51%) 46	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2015	1) The main purpose of this global amendment is to clarify the age requirement to participate in the study as the inclusion of adolescents may not be appropriate per local regulations. 2) Additional clarifications have been made to other inclusion/exclusion criteria. 3) There is also a new requirement regarding additional sample collection (serum, and biopsy of affected organ) for biomarker analysis. This collection will be done upon occurrence of Grade 3 drug-related AE and lab abnormalities regarded as a drug related SAE when clinically safe and feasible 4) This amendment will also be used to implement recent changes in the program level protocol template as well as changes to the standard protocol model document 5) This amendment applies to all subjects
24 February 2016	The main purpose of this global amendment is to: 1) Increase the visit window from 2 days to 3 days for all dosing visits, except for Week 24, Week 36 and Week 48 where the visit window will increase from 2 days to 7 days. 2) Clarify that the minimum time between dosing visits is 12 days 3) Revise and clarify the Prohibited and /or Restricted Treatments 4) Update the acceptable methods of contraception
04 August 2016	The main purpose of this global amendment is to: Addition of Adrenocorticotropic hormone (ACTH) test at Week 45 in subjects receiving ipilimumab/ipilimumab-placebo at Week 48 (Note: All subjects will have completed 36 weeks of treatment prior to implementation of this amendment.) Clarify that the minimum time between dosing visits is 12 days between Nivolumab administrations Add information on surveillance scan requirements in case the patient discontinues and starts new systemic therapy. Update the contraception section Updates in the treatment algorithms
06 August 2016	The main purpose of this global amendment is to: 1) Incorporate the definition of immune-mediated adverse events 2) Incorporate the Adverse Event Management Algorithms for Immuno-oncology Agents as an appendix, and updated terminology to be consistent throughout document 3) Clarify that follow-up of laboratory toxicities will continue until toxicities resolve, return to baseline, or are deemed irreversible based on on-site/local laboratory results. 4) Clarify that follow-up of immune-mediated adverse drug reactions will continue until toxicities resolve, return to baseline, or are deemed irreversible 5) Revise the discontinuation criteria to be consistent with the Nivolumab USPI 6) Revise the definition of recurrence free survival to include new primary melanoma 7) Add censoring rules for primary analysis of recurrence free survival 8) Clarify that subjects will continue to be followed for recurrences (until local or regional recurrences for all subjects and until distant recurrence for Stage III subjects) and survival

26 January 2017	The main purpose of this global amendment is to: Add an interim analysis of RFS after all subjects have a minimum of 18 months of follow-up (approximately 350 RFS events are anticipated at this analysis). Change the name and coordinates of the new Medical Monitor Add the Mechanism for Action for Ipilimumab Confirm that also blood samples from subjects receiving Ipilimumab will also be evaluated for development of Anti-Drug Antibody (ADA).
14 October 2020	The primary purpose of Revised Protocol 06 is to extend the collection of Overall Survival (OS) data for approximately 5 additional years. In addition, data associated with the primary, secondary, and exploratory efficacy outcomes (eg, melanoma recurrence data, data on development of new primary melanomas and non-melanoma cancers, subsequent anticancer therapies) will continue to be collected on Case Report Forms. Study drug-related serious adverse events (SAEs) will continue to be collected, whereas follow-up surveillance imaging assessments, plasma biomarker samples, and the EQ-5D questionnaire will no longer be required during extended follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported