Clinical trial results:
An Open Label, Randomized, Two Arm Phase III Study of Nivolumab in Combination with Ipilimumab versus Extreme Study Regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as First Line Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Summary

EudraCT number	2016-000725-39
Trial protocol	ES GR AT DE PL GB IE IT
Global end of trial date	22 September 2022

Results information

Result version number	v1 (current)
This version publication date	16 September 2023
First version publication date	16 September 2023

Trial information

Trial identification

Sponsor protocol code	CA209-651

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	EU Study Start-Up Unit, ristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@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	31 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the OS of participants with PD-L1 CPS ≥ 20 who are receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen and to compare the OS of all study participants receiving nivolumab combined with ipilimumab to those receiving EXTREME regimen.

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 participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	France: 155
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	Japan: 71
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Australia: 77
Country: Number of subjects enrolled	Brazil: 86
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Mexico: 54

Worldwide total number of subjects	947
EEA total number of subjects	450

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)	605
From 65 to 84 years	339
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

947 participants randomized to receive study treatment. 909 participants received study treatment.

Period 1

Period 1 title	Pre-Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Ipilimumab

Arm description:

Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg IV every 6 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg IV every 2 weeks

Arm title	EXTREME Regimen

Arm description:

Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.

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

Dosage and administration details:

400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 per day for 4 days every 3 weeks

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

Dosage and administration details:

AUC of 5 mg per milliliter per minute on Day 1

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

Dosage and administration details:

100mg/m2 on Day 1

Number of subjects in period 1	Nivolumab + Ipilimumab	EXTREME Regimen
Started	472	475
Completed	468	441
Not completed	4	34
Adverse event, serious fatal	-	1
Disease progression	-	1
Participant withdrew consent	-	18
Participant no longer meets study criteria	3	6
Adverse event unrelated to study drug	1	-
Other reasons	-	3
Lost to follow-up	-	2
Poor/non-compliance	-	1
Participant request to discontinue study treatment	-	2

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Ipilimumab

Arm description:

Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg IV every 6 weeks

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg IV every 2 weeks

Arm title	EXTREME Regimen

Arm description:

Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.

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

Dosage and administration details:

400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 per day for 4 days every 3 weeks

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use
Dosage and administration details: AUC of 5 mg per milliliter per minute on Day 1	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100mg/m2 on Day 1	

Number of subjects in period 2	Nivolumab + Ipilimumab	EXTREME Regimen
Started	468	441
Completed	0	0
Not completed	468	441
Participant request to discontinue treatment	8	23
Adverse event, serious fatal	9	7
Disease progression	294	301
Participant withdrew consent	9	13
Study drug toxicity	55	47
Maximum clinical benefit	4	6
Adverse event unrelated to study drug	41	26
Other reasons	47	12
Lost to follow-up	1	3
Poor/non-compliance	-	2
Administrative reason by sponsor	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.	
Reporting group title	EXTREME Regimen
Reporting group description:	
Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.	

Reporting group values	Nivolumab + Ipilimumab	EXTREME Regimen	Total
Number of subjects	472	475	947
Age Categorical Units: Participants			
< 65	310	295	605
>= 65 AND < 75	134	151	285
>= 75 AND < 85	26	28	54
>= 85	2	1	3
Age Continuous Units: Years			
arithmetic mean	60.4	60.9	
standard deviation	± 9.7	± 9.5	-
Sex: Female, Male Units: Participants			
Female	92	78	170
Male	380	397	777
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	7	5	12
Asian	58	55	113
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	15	7	22
White	379	401	780
More than one race	0	0	0
Unknown or Not Reported	12	7	19
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	40	43	83
Not Hispanic or Latino	199	207	406
Unknown or Not Reported	233	225	458

End points

End points reporting groups

Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.	
Reporting group title	EXTREME Regimen
Reporting group description:	
Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.	
Reporting group title	EXTREME Regimen
Reporting group description:	
Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.	

Primary: Overall Survival (OS) in Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥20

End point title	Overall Survival (OS) in Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥20
End point description:	
Overall survival (OS) is defined as the time between randomization and death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive. Overall survival will be censored at the date of randomization for participants who were randomized but had no follow-up. Survival follow-up will be conducted every 3 months after participants off-treatment date. (Based on Kaplan-Meier estimates)	
End point type	Primary
End point timeframe:	
From randomization to date of death or date the participant was last known to be alive (Up to approximately 55 months)	

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	178		
Units: Months				
median (confidence interval 95%)	17.58 (13.77 to 21.98)	14.59 (12.32 to 15.97)		

Statistical analyses

Statistical analysis title	OS (Participants with PD-L1 CPS ≥20)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0469
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	Other: 97.51 %
sides	2-sided
lower limit	0.59
upper limit	1.03

Primary: Overall Survival (OS) in All Randomized Participants

End point title	Overall Survival (OS) in All Randomized Participants

End point description:

Overall survival (OS) is defined as the time between randomization and death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive. Overall survival will be censored at the date of randomization for participants who were randomized but had no follow-up. Survival follow-up will be conducted every 3 months after participants off-treatment date. (Based on Kaplan-Meier estimates)

End point type	Primary

End point timeframe:

From randomization to date of death or date the participant was last known to be alive (Up to approximately 55 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	472	475		
Units: Months				
median (confidence interval 95%)	13.90 (12.12 to 15.77)	13.50 (12.55 to 15.21)		

Statistical analyses

Statistical analysis title	OS (All Randomized Participants)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen
Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4951
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	Other: 97.9 %
sides	2-sided
lower limit	0.8
upper limit	1.13

Secondary: Overall Survival (OS) in Randomized Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥ 1

End point title	Overall Survival (OS) in Randomized Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥ 1

End point description:

Overall survival (OS) is defined as the time between randomization and death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive. Overall survival will be censored at the date of randomization for participants who were randomized but had no follow-up. Survival follow-up will be conducted every 3 months after participants off-treatment date. (Based on Kaplan-Meier estimates)

End point type	Secondary

End point timeframe:

From randomization to date of death or date the participant was last known to be alive (Up to approximately 65 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	355	372		
Units: Months				
median (confidence interval 95%)	15.67 (13.70 to 18.79)	13.24 (11.07 to 14.59)		

Statistical analyses

Statistical analysis title	OS (Participants with PD-L1 CPS ≥1)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen

Number of subjects included in analysis	727
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.95

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time between the date of randomization and the date of first documented tumor progression, based on Blinded Independent Central Review (BICR) assessments (per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria), or death due to any cause, whichever occurs first. Participants who neither progress nor die will be censored on the date of their last tumor assessment. Participants who receive subsequent anti-cancer therapy prior to documented progression, will be censored on the date of their last tumor assessment prior to subsequent therapy. (Based on Kaplan-Meier Estimates)

Progression is defined as at least a 20% increase in the sum of diameters of target lesions, in addition the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

End point type	Secondary

End point timeframe:

From randomization to disease progression or death (Up to approximately 65 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	472	475		
Units: Months				
median (confidence interval 95%)				
Randomized participants	3.29 (2.83 to 4.17)	6.77 (5.78 to 7.00)		
Randomized PD-L1 CPS >= 20 participants	5.39 (3.09 to 6.93)	6.97 (5.78 to 8.67)		

Statistical analyses

Statistical analysis title	PFS (Participants with PD-L1 CPS ≥20)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen

Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.3

Statistical analysis title	PFS (All Randomized Participants)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen
Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.63

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)

End point description:

The time between the first documented response (Complete response (CR) or partial response (PR)) and progression or death, per RECIST 1.1 by blinded independent central review (BICR) assessment. (Based on Kaplan-Meier Estimates) 99999= N/A - Insufficient number of participants with events to make calculation.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization to the first documented response (CR or PR) and progression (up to approximately 65 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	176		
Units: Months				
median (confidence interval 95%)				
All randomized participants	16.59 (9.69 to 29.40)	5.88 (5.45 to 6.97)		
Randomized PD-L1 CPS >= 20 participants	33.51 (12.12 to 99999)	6.97 (5.65 to 10.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate (ORR) is defined as the number of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). Based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria by blinded independent central review (BICR) assessment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From randomization up to approximately 65 months

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	472	475		
Units: Percent				
number (confidence interval 95%)				
All randomized participants	24.2 (20.4 to 28.3)	37.1 (32.7 to 41.6)		
Randomized PD-L1 CPS >= 20 participants	34.1 (27.3 to 41.4)	35.4 (28.4 to 42.9)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival (OS) in Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥20 - Extended Collection

End point title	Overall Survival (OS) in Participants with Programmed Death-Ligand 1 (PD-L1) with a Combined Positive Score (CPS) ≥20 - Extended Collection

End point description:

Overall survival (OS) is defined as the time between randomization and death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive. Overall survival will be censored at the date of randomization for participants who were randomized but had no follow-up. Survival follow-up will be conducted every 3 months after participants off-treatment date. (Based on Kaplan-Meier estimates)

End point type	Post-hoc

End point timeframe:

From randomization to date of death or date the participant was last known to be alive (Up to approximately 65 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	178		
Units: Months				
median (confidence interval 95%)	17.74 (13.77 to 21.98)	14.59 (12.32 to 15.97)		

Statistical analyses

Statistical analysis title	OS (Participants with PD-L1 CPS ≥20)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen
Number of subjects included in analysis	363
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.97

Post-hoc: Overall Survival (OS) in All Randomized Participants - Extended Collection

End point title	Overall Survival (OS) in All Randomized Participants - Extended Collection

End point description:

Overall survival (OS) is defined as the time between randomization and death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive. Overall survival will be censored at the date of randomization for participants who were randomized but had no follow-up. Survival follow-up will be conducted every 3 months after participants off-treatment date. (Based on Kaplan-Meier estimates)

End point type	Post-hoc

End point timeframe:

From randomization to date of death or date the participant was last known to be alive (Up to approximately 65 months)

End point values	Nivolumab + Ipilimumab	EXTREME Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	472	475		
Units: Months				
median (confidence interval 95%)	13.90 (12.12 to 15.77)	13.50 (12.48 to 15.11)		

Statistical analyses

Statistical analysis title	OS (All Randomized Participants)
Comparison groups	Nivolumab + Ipilimumab v EXTREME Regimen
Number of subjects included in analysis	947
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.08

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from participants first dose to their study completion (up to approximately 65 months). SAEs and Other AEs were assessed from first dose to 100 days following last dose (up to approximately 63 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	EXTREME Regimen

Reporting group description:

Cetuximab 400 mg/m2 IV for the initial dose only, then 250 mg/m2 weekly + cisplatin (100mg/m2) or carboplatin (AUC of 5 mg per milliliter per minute) on Day 1 and fluorouracil (1000 mg/m2 per day for 4 days) every 3 weeks for maximum of 6 cycles followed by maintenance cetuximab at 250 mg/m2 weekly (or every 2 weeks, per local prescribing information) until disease progression or unacceptable toxicity; the choice of cisplatin or carboplatin is at the discretion of the investigator.

Reporting group title	Nivolumab + Ipilimumab

Reporting group description:

Nivolumab 3 mg/kg IV every 2 weeks + Ipilimumab 1 mg/kg IV every 6 weeks until progression, unacceptable toxicity, or a maximum of 24 months from first nivolumab treatment.

Serious adverse events	EXTREME Regimen	Nivolumab + Ipilimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	290 / 441 (65.76%)	313 / 468 (66.88%)	
number of deaths (all causes)	381	385	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 441 (0.45%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lentigo maligna			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	100 / 441 (22.68%)	101 / 468 (21.58%)	
occurrences causally related to treatment / all	0 / 107	2 / 111	
deaths causally related to treatment / all	0 / 79	1 / 91	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			

subjects affected / exposed	2 / 441 (0.45%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Non-small cell lung cancer			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma			
subjects affected / exposed	1 / 441 (0.23%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular lymphoma			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	9 / 441 (2.04%)	21 / 468 (4.49%)	
occurrences causally related to treatment / all	0 / 10	1 / 22	
deaths causally related to treatment / all	0 / 3	0 / 4	
Tumour pain			
subjects affected / exposed	1 / 441 (0.23%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arterial haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 441 (0.68%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hypertension			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 441 (0.68%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular rupture			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral ischaemia			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 441 (0.68%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disease progression			

subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Face oedema			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 441 (1.36%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	2 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Inflammation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lithiasis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	7 / 441 (1.59%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 441 (0.45%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 441 (0.45%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprapubic pain			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	8 / 441 (1.81%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 8	0 / 7	
Sudden cardiac death			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stenosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 441 (2.04%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	2 / 12	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Infusion related hypersensitivity reaction			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal dyspnoea			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asphyxia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			

subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumopathy			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 441 (0.68%)	14 / 468 (2.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemoptysis			
subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal fistula			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract congestion			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	3 / 441 (0.68%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	2 / 441 (0.45%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	3 / 441 (0.68%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (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	0 / 441 (0.00%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	0 / 0	7 / 9	
deaths causally related to treatment / all	0 / 0	2 / 3	
Pneumothorax			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 441 (1.59%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	1 / 7	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary mass			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory disorder			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 441 (0.68%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Laryngeal oedema			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Delirium tremens			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eating disorder			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	2 / 441 (0.45%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 441 (0.68%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device placement issue			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Radiation injury			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site inflammation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site ulcer			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintentional medical device removal			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Immune-mediated myocarditis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	2 / 441 (0.45%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 441 (0.23%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac tamponade			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	5 / 441 (1.13%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Complex regional pain syndrome			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraparesis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 441 (0.68%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
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	18 / 441 (4.08%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	12 / 23	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (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 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cytopenia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	24 / 441 (5.44%)	6 / 468 (1.28%)	
occurrences causally related to treatment / all	24 / 25	0 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (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	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 441 (0.68%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			

subjects affected / exposed	3 / 441 (0.68%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal perforation			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 441 (0.23%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic pancreatitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 441 (0.45%)	10 / 468 (2.14%)	
occurrences causally related to treatment / all	2 / 2	10 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			

subjects affected / exposed	3 / 441 (0.68%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 441 (1.81%)	9 / 468 (1.92%)	
occurrences causally related to treatment / all	7 / 9	5 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Duodenal perforation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	10 / 441 (2.27%)	8 / 468 (1.71%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	3 / 441 (0.68%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	4 / 441 (0.91%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	1 / 441 (0.23%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic failure			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	6 / 441 (1.36%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	4 / 441 (0.91%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	4 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric haematoma			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hepatic function abnormal			

subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystocholangitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis			
subjects affected / exposed	1 / 441 (0.23%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 441 (0.00%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 441 (0.23%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatic cytolysis			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pemphigus			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pemphigoid			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	7 / 441 (1.59%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 441 (0.68%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephropathy			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 441 (0.00%)	4 / 468 (0.85%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hypophysitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Back pain			
subjects affected / exposed	1 / 441 (0.23%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immobilisation syndrome			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fistula			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 441 (0.45%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 441 (0.68%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Actinomycosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (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	3 / 441 (0.68%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Catheter site infection			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 441 (0.91%)	5 / 468 (1.07%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous cystitis			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	2 / 441 (0.45%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective spondylitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal infection			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (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	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 441 (0.23%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	7 / 441 (1.59%)	8 / 468 (1.71%)	
occurrences causally related to treatment / all	0 / 15	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pneumonia			
subjects affected / exposed	31 / 441 (7.03%)	25 / 468 (5.34%)	
occurrences causally related to treatment / all	6 / 34	0 / 27	
deaths causally related to treatment / all	3 / 8	0 / 6	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy viral			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 441 (0.68%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	10 / 441 (2.27%)	10 / 468 (2.14%)	
occurrences causally related to treatment / all	5 / 10	0 / 10	
deaths causally related to treatment / all	3 / 4	0 / 6	
Septic shock			
subjects affected / exposed	3 / 441 (0.68%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Stoma site infection			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
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	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	3 / 441 (0.68%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 441 (0.00%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 441 (0.00%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site cellulitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site infection			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 441 (0.91%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	2 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 3	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte depletion			
subjects affected / exposed	1 / 441 (0.23%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	5 / 441 (1.13%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperamylasaemia			

subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 441 (0.45%)	7 / 468 (1.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 441 (0.23%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipasaemia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 441 (0.23%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	7 / 441 (1.59%)	2 / 468 (0.43%)	
occurrences causally related to treatment / all	3 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypomagnesaemia			
subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 441 (0.91%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	4 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	2 / 441 (0.45%)	0 / 468 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	3 / 441 (0.68%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour lysis syndrome			
subjects affected / exposed	0 / 441 (0.00%)	1 / 468 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Decreased appetite			
subjects affected / exposed	4 / 441 (0.91%)	3 / 468 (0.64%)	
occurrences causally related to treatment / all	3 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EXTREME Regimen	Nivolumab + Ipilimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	429 / 441 (97.28%)	420 / 468 (89.74%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	25 / 441 (5.67%)	13 / 468 (2.78%)	
occurrences (all)	31	15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	106 / 441 (24.04%)	73 / 468 (15.60%)	
occurrences (all)	146	94	
Fatigue			
subjects affected / exposed	154 / 441 (34.92%)	123 / 468 (26.28%)	
occurrences (all)	199	154	
Mucosal inflammation			

subjects affected / exposed	137 / 441 (31.07%)	27 / 468 (5.77%)	
occurrences (all)	200	31	
Oedema peripheral			
subjects affected / exposed	29 / 441 (6.58%)	30 / 468 (6.41%)	
occurrences (all)	36	31	
Pain			
subjects affected / exposed	15 / 441 (3.40%)	26 / 468 (5.56%)	
occurrences (all)	20	26	
Pyrexia			
subjects affected / exposed	46 / 441 (10.43%)	49 / 468 (10.47%)	
occurrences (all)	65	59	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	31 / 441 (7.03%)	5 / 468 (1.07%)	
occurrences (all)	38	5	
Dyspnoea			
subjects affected / exposed	53 / 441 (12.02%)	59 / 468 (12.61%)	
occurrences (all)	58	64	
Cough			
subjects affected / exposed	34 / 441 (7.71%)	63 / 468 (13.46%)	
occurrences (all)	38	73	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	37 / 441 (8.39%)	35 / 468 (7.48%)	
occurrences (all)	45	37	
Investigations			
Amylase increased			
subjects affected / exposed	18 / 441 (4.08%)	32 / 468 (6.84%)	
occurrences (all)	28	44	
Alanine aminotransferase increased			
subjects affected / exposed	23 / 441 (5.22%)	35 / 468 (7.48%)	
occurrences (all)	29	42	
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 441 (4.31%)	27 / 468 (5.77%)	
occurrences (all)	24	38	
Aspartate aminotransferase increased			

subjects affected / exposed	18 / 441 (4.08%)	39 / 468 (8.33%)	
occurrences (all)	29	51	
Blood creatinine increased			
subjects affected / exposed	34 / 441 (7.71%)	17 / 468 (3.63%)	
occurrences (all)	47	24	
White blood cell count decreased			
subjects affected / exposed	36 / 441 (8.16%)	12 / 468 (2.56%)	
occurrences (all)	75	31	
Weight decreased			
subjects affected / exposed	81 / 441 (18.37%)	57 / 468 (12.18%)	
occurrences (all)	94	66	
Lipase increased			
subjects affected / exposed	19 / 441 (4.31%)	50 / 468 (10.68%)	
occurrences (all)	32	94	
Neutrophil count decreased			
subjects affected / exposed	66 / 441 (14.97%)	19 / 468 (4.06%)	
occurrences (all)	135	29	
Platelet count decreased			
subjects affected / exposed	60 / 441 (13.61%)	7 / 468 (1.50%)	
occurrences (all)	128	14	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	34 / 441 (7.71%)	10 / 468 (2.14%)	
occurrences (all)	34	11	
Headache			
subjects affected / exposed	31 / 441 (7.03%)	30 / 468 (6.41%)	
occurrences (all)	40	33	
Dizziness			
subjects affected / exposed	32 / 441 (7.26%)	20 / 468 (4.27%)	
occurrences (all)	43	23	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	131 / 441 (29.71%)	11 / 468 (2.35%)	
occurrences (all)	221	11	
Lymphopenia			

subjects affected / exposed	25 / 441 (5.67%)	17 / 468 (3.63%)	
occurrences (all)	38	29	
Anaemia			
subjects affected / exposed	190 / 441 (43.08%)	102 / 468 (21.79%)	
occurrences (all)	271	130	
Leukopenia			
subjects affected / exposed	35 / 441 (7.94%)	6 / 468 (1.28%)	
occurrences (all)	64	6	
Thrombocytopenia			
subjects affected / exposed	109 / 441 (24.72%)	7 / 468 (1.50%)	
occurrences (all)	186	12	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	27 / 441 (6.12%)	4 / 468 (0.85%)	
occurrences (all)	28	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	36 / 441 (8.16%)	34 / 468 (7.26%)	
occurrences (all)	39	35	
Constipation			
subjects affected / exposed	157 / 441 (35.60%)	95 / 468 (20.30%)	
occurrences (all)	203	113	
Diarrhoea			
subjects affected / exposed	141 / 441 (31.97%)	104 / 468 (22.22%)	
occurrences (all)	219	155	
Dyspepsia			
subjects affected / exposed	29 / 441 (6.58%)	12 / 468 (2.56%)	
occurrences (all)	37	12	
Dysphagia			
subjects affected / exposed	49 / 441 (11.11%)	52 / 468 (11.11%)	
occurrences (all)	52	59	
Nausea			
subjects affected / exposed	226 / 441 (51.25%)	101 / 468 (21.58%)	
occurrences (all)	357	132	
Vomiting			

subjects affected / exposed	121 / 441 (27.44%)	57 / 468 (12.18%)	
occurrences (all)	178	79	
Stomatitis			
subjects affected / exposed	104 / 441 (23.58%)	24 / 468 (5.13%)	
occurrences (all)	158	27	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	79 / 441 (17.91%)	35 / 468 (7.48%)	
occurrences (all)	103	38	
Alopecia			
subjects affected / exposed	40 / 441 (9.07%)	6 / 468 (1.28%)	
occurrences (all)	40	6	
Skin fissures			
subjects affected / exposed	65 / 441 (14.74%)	4 / 468 (0.85%)	
occurrences (all)	86	4	
Rash			
subjects affected / exposed	177 / 441 (40.14%)	90 / 468 (19.23%)	
occurrences (all)	239	111	
Pruritus			
subjects affected / exposed	38 / 441 (8.62%)	88 / 468 (18.80%)	
occurrences (all)	42	118	
Dermatitis acneiform			
subjects affected / exposed	147 / 441 (33.33%)	23 / 468 (4.91%)	
occurrences (all)	179	25	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	19 / 441 (4.31%)	86 / 468 (18.38%)	
occurrences (all)	19	97	
Hyperthyroidism			
subjects affected / exposed	2 / 441 (0.45%)	40 / 468 (8.55%)	
occurrences (all)	3	45	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 441 (4.76%)	26 / 468 (5.56%)	
occurrences (all)	21	29	
Arthralgia			

subjects affected / exposed	21 / 441 (4.76%)	58 / 468 (12.39%)	
occurrences (all)	22	68	
Neck pain			
subjects affected / exposed	38 / 441 (8.62%)	38 / 468 (8.12%)	
occurrences (all)	40	43	
Infections and infestations			
Folliculitis			
subjects affected / exposed	33 / 441 (7.48%)	6 / 468 (1.28%)	
occurrences (all)	55	7	
Oral candidiasis			
subjects affected / exposed	29 / 441 (6.58%)	19 / 468 (4.06%)	
occurrences (all)	35	21	
Paronychia			
subjects affected / exposed	95 / 441 (21.54%)	9 / 468 (1.92%)	
occurrences (all)	115	9	
Pneumonia			
subjects affected / exposed	25 / 441 (5.67%)	41 / 468 (8.76%)	
occurrences (all)	25	53	
Upper respiratory tract infection			
subjects affected / exposed	19 / 441 (4.31%)	26 / 468 (5.56%)	
occurrences (all)	23	35	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	34 / 441 (7.71%)	10 / 468 (2.14%)	
occurrences (all)	47	12	
Hyponatraemia			
subjects affected / exposed	35 / 441 (7.94%)	39 / 468 (8.33%)	
occurrences (all)	50	68	
Hypomagnesaemia			
subjects affected / exposed	146 / 441 (33.11%)	34 / 468 (7.26%)	
occurrences (all)	230	57	
Hypokalaemia			
subjects affected / exposed	93 / 441 (21.09%)	27 / 468 (5.77%)	
occurrences (all)	153	35	
Hypocalcaemia			

subjects affected / exposed	45 / 441 (10.20%)	13 / 468 (2.78%)	
occurrences (all)	62	19	
Hypoalbuminaemia			
subjects affected / exposed	26 / 441 (5.90%)	33 / 468 (7.05%)	
occurrences (all)	34	44	
Hyperglycaemia			
subjects affected / exposed	20 / 441 (4.54%)	24 / 468 (5.13%)	
occurrences (all)	25	41	
Hypercalcaemia			
subjects affected / exposed	14 / 441 (3.17%)	31 / 468 (6.62%)	
occurrences (all)	16	37	
Dehydration			
subjects affected / exposed	26 / 441 (5.90%)	5 / 468 (1.07%)	
occurrences (all)	27	5	
Decreased appetite			
subjects affected / exposed	115 / 441 (26.08%)	73 / 468 (15.60%)	
occurrences (all)	153	88	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2016	Week 7 biopsy optional instead of required, Section 5.8 "Additional Research" added, PK and IMG Follow up visit samples no longer required to be collected.
26 October 2017	A maximum duration of nivolumab and ipilimumab treatment of 24 months from the start of treatment was added. Duration of response has been changed to a secondary objective. Response to first therapy after disease progression was changed to an exploratory endpoint.
01 May 2018	The primary objectives were changed from PFS and OS in all randomized subjects to PFS and OS in subjects with PD-L1 expressing tumors. PFS and OS in all study subjects moved to secondary endpoints. Added that nivolumab should be permanently discontinued in case of grade 3 drug-related myocarditis.
20 June 2019	The primary objectives were changed to compare: OS for participants who are receiving nivolumab + ipilimumab versus EXTREME regimen in participants with PD-L1 CPS ≥ 20 (changed from tumor PD-L1 ≥ 1) and OS for participants who are receiving nivolumab + ipilimumab versus EXTREME regimen in all study participants (irrespective of PD-L1 expression). Description of the statistical analyses were changed based on the changes in objectives. Key secondary objective was changed to OS in subject with PD-L1 CPS ≥ 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported