Clinical trial results:
A Randomized Double-Blind Phase III Study of Ipilimumab Administered at 3 mg/kg vs at 10 mg/kg in Subjects with Previously Treated or Untreated Unresectable or Metastatic Melanoma

Summary

EudraCT number	2011-004029-28
Trial protocol	DE SE AT HU ES BE PL IT DK NL CZ NO GB
Global end of trial date	17 August 2017

Results information

Result version number	v1 (current)
This version publication date	31 August 2018
First version publication date	31 August 2018

Trial information

Trial identification

Sponsor protocol code	CA184-169

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, Bristol-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	17 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) of ipilimumab monotherapy at doses of 3 versus (vs) 10 mg/kg in subjects with previously treated (excluding prior BRAF, CTLA-4 and PD-1 inhibitors) or untreated unresectable Stage III or Stage IV melanoma.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 83
Country: Number of subjects enrolled	Denmark: 42
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	France: 140
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 175
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Norway: 19
Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Sweden: 21

Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	South Africa: 8
Worldwide total number of subjects	831
EEA total number of subjects	691

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)	492
From 65 to 84 years	324
85 years and over	15

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

831 subjects were enrolled; 727 were randomized to a treatment group; 726 received at least one dose of study treatment. Of the 105 subjects not treated, 81 no longer met study criteria, 11 withdrew consent, 4 suffered an Adverse Event, 4 died, and 5 were not treated due to investigator decision or other reasons.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab (10 mg/kg)

Arm description:

Ipilimumab 10 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity

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

Dosage and administration details:

Each subject received ipilimumab (3 or 10 mg/kg) as a single dose via IV infusion. During the Induction Period, subjects received ipilimumab at a dose of 3 or 10 mg/kg via IV infusion every 3 weeks x 4 doses (Weeks 1, 4, 7, and 10) unless there was confirmed disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment. Eligible subjects received ipilimumab again during the Re-induction Phase. During Re-induction, ipilimumab was administered at the same dose level as assigned at randomization once every 3 weeks x 4 for a total of 4 separate doses unless there was disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment.

Arm title	Ipilimumab (3 mg/kg)

Arm description:

Ipilimumab 3 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity

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

Dosage and administration details:

Each subject received ipilimumab (3 or 10 mg/kg) as a single dose via IV infusion. During the Induction Period, subjects received ipilimumab at a dose of 3 or 10 mg/kg via IV infusion every 3 weeks x 4 doses (Weeks 1, 4, 7, and 10) unless there was confirmed disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment. Eligible subjects received ipilimumab again during the Re-induction Phase. During Re-induction, ipilimumab was administered at the same dose

level as assigned at randomization once every 3 weeks x 4 for a total of 4 separate doses unless there was disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment.

Number of subjects in period 1[1]	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)
Started	365	362
Completed	128	130
Not completed	237	232
Adverse event, serious fatal	24	17
Consent withdrawn by subject	3	9
Disease progression	109	155
Adverse event, non-fatal	14	9
Study drug toxicity	86	36
No longer meets study criteria	-	2
Unspecified	-	4
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial as out of 831 subjects who were enrolled only 727 were randomised. 726 received at least one dose of study treatment. Of the 105 subjects not treated, 81 no longer met study criteria, 11 withdrew consent, 4 suffered an Adverse Event, 4 died, and 5 were not treated due to investigator decision or other reasons.

Period 2

Period 2 title	First Re-Induction Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab (10 mg/kg)

Arm description:

Ipilimumab 10 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity

Arm type	Experimental

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

Dosage and administration details:

Each subject received ipilimumab (3 or 10 mg/kg) as a single dose via IV infusion. During the Induction Period, subjects received ipilimumab at a dose of 3 or 10 mg/kg via IV infusion every 3 weeks x 4 doses (Weeks 1, 4, 7, and 10) unless there was confirmed disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment. Eligible subjects received ipilimumab again during the Re-induction Phase. During Re-induction, ipilimumab was administered at the same dose level as assigned at randomization once every 3 weeks x 4 for a total of 4 separate doses unless there was disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment.

Arm title	Ipilimumab (3 mg/kg)

Arm description:

Ipilimumab 3 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity

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

Dosage and administration details:

Each subject received ipilimumab (3 or 10 mg/kg) as a single dose via IV infusion. During the Induction Period, subjects received ipilimumab at a dose of 3 or 10 mg/kg via IV infusion every 3 weeks x 4 doses (Weeks 1, 4, 7, and 10) unless there was confirmed disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment. Eligible subjects received ipilimumab again during the Re-induction Phase. During Re-induction, ipilimumab was administered at the same dose level as assigned at randomization once every 3 weeks x 4 for a total of 4 separate doses unless there was disease progression (per irRC), unacceptable toxicity, or the subject requested to stop study treatment.

Number of subjects in period 2[2]	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)
Started	23	32
Completed	9	17
Not completed	14	15
Consent withdrawn by subject	1	1
Disease progression	6	14
Study drug toxicity	5	-
No longer meets study criteria	1	-
Unspecified	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Out of 258 subjects who completed the induction period, 55 subjects continued directly into the first re-induction phase.

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab (10 mg/kg)
Reporting group description:	
Ipilimumab 10 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab (3 mg/kg)
Reporting group description:	
Ipilimumab 3 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	

Reporting group values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)	Total
Number of subjects	365	362	727
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	224	208	432
>=65 years	141	154	295
Age Continuous Units: years			
arithmetic mean	58.6	60.7	
standard deviation	± 14.52	± 13.22	-
Sex: Female, Male Units: Subjects			
Female	146	131	277
Male	219	231	450

End points

End points reporting groups

Reporting group title	Ipilimumab (10 mg/kg)
Reporting group description:	
Ipilimumab 10 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab (3 mg/kg)
Reporting group description:	
Ipilimumab 3 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab (10 mg/kg)
Reporting group description:	
Ipilimumab 10 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab (3 mg/kg)
Reporting group description:	
Ipilimumab 3 mg/kg solution intravenously once every 3 weeks for 4 doses or until disease progression or unacceptable toxicity	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined for each subject as the time between randomization date and death due to any cause. The survival time for subjects who had not died was censored at the last known alive date. Median and associated 2-sided 95% confidence intervals were calculated using the method of Brookmeyer and Crowley.	
End point type	Primary
End point timeframe:	
Approximately 48 months (assessed up to February 2016)	

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: months				
median (confidence interval 95%)	15.70 (11.63 to 17.84)	11.53 (9.86 to 13.27)		

Statistical analyses

Statistical analysis title	Overall Survival Hazard Ratio
Comparison groups	Ipilimumab (10 mg/kg) v Ipilimumab (3 mg/kg)

Number of subjects included in analysis	727
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.99

Notes:

[1] - Analysis stratified by ECOG performance status (0 vs. 1), prior treatment for metastatic melanoma (yes vs. no) and M-stage (M0/M1a/M1b vs. M1c without brain metastases vs. M1c with brain metastases).

Secondary: Progression Free Survival (PFS) by mWHO Criteria

End point title	Progression Free Survival (PFS) by mWHO Criteria

End point description:

PFS was defined as the time between randomization date and the date of progression or death, whichever occurred first. A subject who died without reported prior progression was considered to have progressed on the date of death. For a subject who underwent resection post randomization, PFS was censored on last tumor assessment date prior to resection. For those who remained alive and had not progressed, PFS was censored on last evaluable tumor assessment date. Subjects who had not died and had no recorded post-baseline tumor assessment were censored at the day of randomization. For subjects who had Progressive Disease (PD) prior to Week 12 and a subsequent assessment of Stable Disease (SD), Partial Response (PR), or Complete Response (CR), the date of PD following response was used in the analysis of PFS; otherwise these subjects were censored on the date of their last tumor assessment. Median and 2-sided 95% CIs were calculated with Brookmeyer Crowley method.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: months				
median (confidence interval 95%)	2.83 (2.79 to 2.99)	2.79 (2.76 to 2.83)		

Statistical analyses

Statistical analysis title	Progression Free Survival Hazard Ratio
Comparison groups	Ipilimumab (10 mg/kg) v Ipilimumab (3 mg/kg)

Number of subjects included in analysis	727
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1548 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.04

Notes:

[2] - Analysis stratified by ECOG performance status (0 vs. 1), prior treatment for metastatic melanoma (yes vs. no) and M-stage (M0/M1a/M1b vs. M1c without brain metastases vs. M1c with brain metastases).

Secondary: Best Overall Response Rate (BORR) by mWHO Criteria

End point title	Best Overall Response Rate (BORR) by mWHO Criteria

End point description:

BORR by treatment arm was defined as the total number of randomized subjects in the arm whose BOR is CR or PR, divided by the total number of randomized subjects in the arm. Any subject who was unevaluable for BOR, e.g. on account of missing or "not evaluable" assessments, was included in the denominator of the calculation (i.e. was considered a non-responder with respect to the BORR endpoint). 95% 2-sided exact confidence intervals were computed using the method of Clopper and Pearson.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: percentage of subjects with BORR				
number (confidence interval 95%)	15.3 (11.8 to 19.5)	12.2 (9.0 to 16.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by mWHO Criteria

End point title	Disease Control Rate (DCR) by mWHO Criteria

End point description:

DCR by treatment arm was defined as the total number of randomized subjects in the arm whose BOR is CR, PR or SD, divided by the total number of randomized subjects in the arm. Any subject who was unevaluable for Disease Control (DC), (e.g. on account of missing or "not evaluable" assessments), was included in the denominator of the calculation (i.e. was considered a non-responder with respect to the DCR endpoint). 95% 2-sided exact confidence intervals were computed using the Clopper and Pearson

method.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: percentage of subjects with DC				
number (confidence interval 95%)	31.5 (26.8 to 36.5)	27.9 (23.3 to 32.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by mWHO Criteria

End point title	Duration of Response (DOR) by mWHO Criteria

End point description:

Duration of response for subjects whose BOR was CR or PR was defined as the time between the date measurement criteria were first met for overall response of PR or CR (whichever status was recorded first) and the date of disease progression or death (whichever occurred first). For subjects who underwent tumor resection following response but prior to disease progression, duration of response was censored on the date of last evaluable tumor assessment prior to resection. For subjects who had BOR of SD, PR or CR at Week 12, or a confirmed response of PR or CR before Week 12, the date of PD following thereafter (where available) was used in the analysis of duration of response. For those subjects who remained alive and had not progressed following response, duration of response was censored on the date of last evaluable tumor assessment. Median and associated 2-sided 95% confidence intervals were calculated using the Brookmeyer Crowley method.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: months				
median (confidence interval 95%)	16.33 (5.98 to 23.98)	15.90 (10.35 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease by mWHO Criteria

End point title	Duration of Stable Disease by mWHO Criteria

End point description:

Duration of stable disease was defined for subjects whose BOR was SD as the time between when SD was first documented and the date of PD or death (whichever occurred first). For a subject who underwent tumor resection following Week 12 but prior to disease progression, duration of stable disease was censored on the date of the last evaluable tumor assessment prior to resection. For subjects who had BOR of SD at Week 12, the date of PD following thereafter (where available) was used in the analysis of duration of stable disease. For subjects with BOR of SD who had not subsequently progressed and who remained alive, duration of stable disease was censored on the date of last evaluable tumor assessment. Median and associated 2-sided 95% confidence intervals were calculated using the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: months				
median (confidence interval 95%)	5.55 (3.02 to 8.02)	3.19 (2.73 to 5.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Overall Survival

End point title	Rate of Overall Survival

End point description:

OS is defined for each subject as the time between randomization date and death due to any cause. The survival time for subjects who had not died was censored at the last known alive date. Survival rates were calculated based on Kaplan-Meier estimation with log-log transformed confidence intervals. The survival rate at x year(s) is defined as the probability that a subject is alive at x year(s) following randomization.

End point type	Secondary

End point timeframe:

Approximately 66 months

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	362		
Units: percentage of subjects				
number (confidence interval 95%)				
Survival rate at 1 year|	54.28 (49.01 to 59.25)	47.62 (42.35 to 52.70)		
Survival rate at 2 years|	38.46 (33.44 to 43.45)	30.97 (26.21 to 35.84)		
Survival rate at 3 years|	31.16 (26.44 to 35.98)	23.15 (18.88 to 27.69)		
Survival rate at 4 years|	26.63 (22.17 to 31.28)	20.25 (16.21 to 24.62)		
Survival rate at 5 years|	24.90 (20.54 to 29.48)	18.78 (14.87 to 23.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival of Subjects with Brain Metastases at Baseline

End point title	Overall Survival of Subjects with Brain Metastases at Baseline

End point description:

OS for each subject with brain metastases at baseline was measured as the time between randomization date and death due to any cause. The survival time for subjects who had not died was censored at the last known alive date. Median OS, and associated 2-sided 95% confidence intervals were calculated using the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

From date of randomization until 540 death events occurred (approximately 48 months)

End point values	Ipilimumab (10 mg/kg)	Ipilimumab (3 mg/kg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	62		
Units: months				
median (confidence interval 95%)	7.00 (3.98 to 12.78)	5.67 (4.21 to 6.97)		

Statistical analyses

Statistical analysis title	Overall Survival Hazard Ratio
Comparison groups	Ipilimumab (10 mg/kg) v Ipilimumab (3 mg/kg)

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events occurring on or after Day 1 of study treatment and no later than 90 days following the last day of study treatment were considered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	10 mg/kg Ipilimumab

Reporting group description:

Subjects received intravenous (IV) infusion of 10 milligram per kilogram (mg/kg) Ipilimumab at every 3 weeks (Day 1, 22, 43 and 64 ± 3 days) for total of 4 separate doses.

Reporting group title	3 mg/kg Ipilimumab

Reporting group description:

Subjects received IV infusion of 3 mg/kg Ipilimumab at every 3 weeks (Day 1, 22, 43 and 64 ± 3 days) for total of 4 separate doses.

Serious adverse events	10 mg/kg Ipilimumab	3 mg/kg Ipilimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	245 / 364 (67.31%)	194 / 362 (53.59%)	
number of deaths (all causes)	68	72	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			

subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma in situ			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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	54 / 364 (14.84%)	60 / 362 (16.57%)	
occurrences causally related to treatment / all	0 / 54	0 / 63	
deaths causally related to treatment / all	0 / 45	0 / 47	
Metastases to central nervous system			
subjects affected / exposed	1 / 364 (0.27%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Metastases to eye			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to muscle			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to skin			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 364 (0.00%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Neoplasm swelling			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 364 (0.00%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fatigue			
subjects affected / exposed	5 / 364 (1.37%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	10 / 364 (2.75%)	12 / 362 (3.31%)	
occurrences causally related to treatment / all	2 / 10	2 / 12	
deaths causally related to treatment / all	0 / 3	0 / 4	
Generalised oedema			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 364 (0.27%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
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 / 364 (2.47%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	3 / 9	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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	6 / 364 (1.65%)	6 / 362 (1.66%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 3	
Epistaxis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 364 (1.37%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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	4 / 364 (1.10%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	9 / 364 (2.47%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pulmonary microemboli			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	2 / 364 (0.55%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 364 (1.65%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (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	3 / 364 (0.82%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation dysphagia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Carney complex			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	5 / 364 (1.37%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	5 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
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	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 364 (0.82%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 364 (1.37%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	4 / 364 (1.10%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	6 / 6	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 364 (0.55%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancreatitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	33 / 364 (9.07%)	13 / 362 (3.59%)	
occurrences causally related to treatment / all	40 / 40	17 / 18	
deaths causally related to treatment / all	2 / 2	0 / 0	
Colitis ulcerative			
subjects affected / exposed	2 / 364 (0.55%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 364 (0.27%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	42 / 364 (11.54%)	22 / 362 (6.08%)	
occurrences causally related to treatment / all	51 / 53	24 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ascites			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	2 / 364 (0.55%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (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	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	3 / 364 (0.82%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	4 / 364 (1.10%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced liver injury			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	6 / 364 (1.65%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	5 / 6	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	5 / 364 (1.37%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	2 / 364 (0.55%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
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			
Dermatitis allergic			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage subcutaneous			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 364 (0.27%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	3 / 364 (0.82%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocortical insufficiency acute			
subjects affected / exposed	2 / 364 (0.55%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes insipidus			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	5 / 364 (1.37%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	16 / 364 (4.40%)	9 / 362 (2.49%)	
occurrences causally related to treatment / all	17 / 17	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothalamo-Pituitary disorder			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
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 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 364 (0.27%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyrotoxic crisis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
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	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 364 (0.55%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 364 (0.55%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myalgia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholinitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 364 (0.55%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 364 (1.37%)	4 / 362 (1.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	2 / 364 (0.55%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 364 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 364 (0.82%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	3 / 364 (0.82%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 364 (0.27%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 364 (0.82%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 364 (0.27%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 364 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	10 mg/kg Ipilimumab	3 mg/kg Ipilimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	319 / 364 (87.64%)	302 / 362 (83.43%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 364 (7.42%)	12 / 362 (3.31%)	
occurrences (all)	32	14	
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 364 (7.42%)	8 / 362 (2.21%)	
occurrences (all)	29	9	
Weight decreased			
subjects affected / exposed	29 / 364 (7.97%)	25 / 362 (6.91%)	
occurrences (all)	30	27	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 364 (4.40%)	22 / 362 (6.08%)	
occurrences (all)	16	23	
Headache			
subjects affected / exposed	56 / 364 (15.38%)	66 / 362 (18.23%)	
occurrences (all)	63	72	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 364 (6.59%)	17 / 362 (4.70%)	
occurrences (all)	25	19	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	86 / 364 (23.63%)	95 / 362 (26.24%)	
occurrences (all)	95	106	
Asthenia			
subjects affected / exposed	68 / 364 (18.68%)	60 / 362 (16.57%)	
occurrences (all)	76	69	
Pyrexia			

subjects affected / exposed	59 / 364 (16.21%)	43 / 362 (11.88%)	
occurrences (all)	72	56	
Oedema peripheral			
subjects affected / exposed	25 / 364 (6.87%)	22 / 362 (6.08%)	
occurrences (all)	26	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 364 (9.07%)	34 / 362 (9.39%)	
occurrences (all)	36	36	
Constipation			
subjects affected / exposed	38 / 364 (10.44%)	40 / 362 (11.05%)	
occurrences (all)	39	44	
Diarrhoea			
subjects affected / exposed	140 / 364 (38.46%)	105 / 362 (29.01%)	
occurrences (all)	213	152	
Nausea			
subjects affected / exposed	59 / 364 (16.21%)	74 / 362 (20.44%)	
occurrences (all)	67	84	
Vomiting			
subjects affected / exposed	43 / 364 (11.81%)	34 / 362 (9.39%)	
occurrences (all)	51	48	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 364 (9.07%)	32 / 362 (8.84%)	
occurrences (all)	34	35	
Dyspnoea			
subjects affected / exposed	27 / 364 (7.42%)	26 / 362 (7.18%)	
occurrences (all)	28	32	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	98 / 364 (26.92%)	103 / 362 (28.45%)	
occurrences (all)	119	117	
Rash			
subjects affected / exposed	106 / 364 (29.12%)	64 / 362 (17.68%)	
occurrences (all)	135	79	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	19 / 364 (5.22%)	17 / 362 (4.70%)	
occurrences (all)	19	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 364 (5.22%)	26 / 362 (7.18%)	
occurrences (all)	22	31	
Back pain			
subjects affected / exposed	21 / 364 (5.77%)	20 / 362 (5.52%)	
occurrences (all)	22	20	
Pain in extremity			
subjects affected / exposed	26 / 364 (7.14%)	21 / 362 (5.80%)	
occurrences (all)	28	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	52 / 364 (14.29%)	51 / 362 (14.09%)	
occurrences (all)	52	55	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	- Add safety assessments (additional chemistry labs) at baseline, dosing visits, Weeks 12 and 24, and at End of Treatment visit and to clarify the assessments of adverse events at the End of Treatment visit - Add the BMS Medical Monitor
25 September 2012	- Removes the general instructions for dilution and administration of ipilimumab from the protocol and refer sites to the Dose Preparation guidelines - Provides specific guidance on confirmation of progressive disease at Week 36 or later - Updates sections to include BMS required language for women of child bearing potential, results of the immune mediated adverse reaction (imAR) adjudication process, and ipilimumab program language for adverse events of interest
24 June 2013	- Removes the interim analysis - Clarifies response and progression requirements for re-induction - Includes response tables for subjects with no index lesions at baseline - Updates sections to incorporate BMS protocol model document language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported