Clinical trial results:
Phase 2, Randomized, Double Blinded, Study of Nivolumab (BMS-936558) in Combination with Ipilimumab vs Ipilimumab alone in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma (CheckMate 069: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 069)

Summary

EudraCT number	2013-002018-11
Trial protocol	FR
Global end of trial date	26 February 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	CA209-069

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)	
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	23 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the ORR, as determined by investigators, of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with BRAF wild type (WT) unresectable or metastatic 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 participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2013
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	France: 16
Country: Number of subjects enrolled	United States: 126
Worldwide total number of subjects	142
EEA total number of subjects	16

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)	68
From 65 to 84 years	71
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

142 participants were randomized, and 140 participants received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Ipilimumab

Arm description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

Arm type	Experimental
Investigational medicinal product name	BMS-986165
Investigational medicinal product code	
Other name	Nivolumab
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg Q3W for 4 cycles, then 3 mg/kg Q2W

Investigational medicinal product name	Placebo matching BMS-986165
Investigational medicinal product code	
Other name	0.9% Sodium Chloride
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

matching nivolumab (BMS-986165)

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

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

Arm title	Ipilimumab

Arm description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

Arm type	Experimental

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

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

Number of subjects in period 1	Nivolumab + Ipilimumab	Ipilimumab
Started	95	47
Completed	94	46
Not completed	1	1
Adverse event unrelated to study drug	-	1
Participants no longer meeting study criteria	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Ipilimumab

Arm description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

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

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

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

Dosage and administration details:

1 mg/kg Q3W for 4 cycles, then 3 mg/kg Q2W

Arm title	Ipilimumab

Arm description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

Arm type	Experimental
Investigational medicinal product name	Placebo matching BMS-986165
Investigational medicinal product code	
Other name	0.9% Sodium Chloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

matching nivolumab (BMS-986165)

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

Dosage and administration details:

3 mg/kg Q3W for 4 cycles

Number of subjects in period 2	Nivolumab + Ipilimumab	Ipilimumab
Started	94	46
Completed	0	0
Not completed	94	46
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	1
Disease progression	17	20
Not Reported	1	1
Study drug toxicity	48	10
Participant request to discontinue	12	4
Maximum Clinical Benefit	6	2
Adverse event unrelated to study drug	6	3
Other reasons	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	
Reporting group title	Ipilimumab
Reporting group description:	
Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	

Reporting group values	Nivolumab + Ipilimumab	Ipilimumab	Total
Number of subjects	95	47	142
Age Categorical Units: Participants			
Younger than 65 years	48	20	68
65 years and older to younger than 75 years	35	22	57
75 years and older	12	5	17
Age Continuous Units: years			
arithmetic mean	63.3	64.5	
standard deviation	± 11.0	± 10.2	-
Sex: Female, Male Units:			
Female	32	15	47
Male	63	32	95
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	92	47	139
More than one race	0	0	0
Unknown or Not Reported	2	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	82	43	125
Unknown or Not Reported	12	4	16

End points

End points reporting groups

Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	
Reporting group title	Ipilimumab
Reporting group description:	
Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	
Reporting group title	Ipilimumab
Reporting group description:	
Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.	

Primary: Objective Response Rate (ORR) - BRAF wild-type (WT) participants

End point title	Objective Response Rate (ORR) - BRAF wild-type (WT) participants
End point description:	
Objective Response Rate is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR), assessed by the investigator by using RECIST 1.1 criteria. CR=all target and nontarget lesions have disappeared. Lymph nodes selected must have returned to normal size (<10 mm). PR=at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.	
End point type	Primary
End point timeframe:	
From 12 weeks after Randomization, assessed every 6 weeks up to Week 49 of study treatment and then every 12 weeks until disease progression (up to approximately 76 months)	

End point values	Nivolumab + Ipilimumab	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	37		
Units: Percentage of participants				
number (confidence interval 95%)	60.3 (48.1 to 71.5)	10.8 (3.0 to 25.4)		

Statistical analyses

Statistical analysis title	ORR - BRAF WT 1
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Method	Newcombe's method
Parameter estimate	Mean difference (final values)
Point estimate	49.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.4
upper limit	61.8

Statistical analysis title	ORR - BRAF WT 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	12.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.79
upper limit	52.55

Secondary: Progression-Free Survival (PFS) - BRAF wild-type (WT) participants

End point title	Progression-Free Survival (PFS) - BRAF wild-type (WT) participants

End point description:

PFS is defined as the time between the date of randomization and the first date of documented progression, as assessed by the investigator, or death due to any cause, whichever occurs first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or died were censored on the date of their last evaluable tumor assessment.
PFS values are based on Kaplan-Meier Estimates.

End point type	Secondary

End point timeframe:

From randomization to progression or death (up to approximately 88 months)

End point values	Nivolumab + Ipilimumab	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	37		
Units: Months				
median (confidence interval 95%)	58.41 (7.23 to 99999)	4.30 (2.76 to 5.32)		

Statistical analyses

Statistical analysis title	PFS - BRAF WT
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Method	Unstratified Cox proportional hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.59

Secondary: Objective Response Rate (ORR) - BRAF mutant participants

End point title	Objective Response Rate (ORR) - BRAF mutant participants

End point description:

Objective Response Rate is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR), assessed by the investigator by using RECIST 1.1 criteria.
CR=all target and nontarget lesions have disappeared. Lymph nodes selected must have returned to normal size (<10 mm).
PR=at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

End point type	Secondary

End point timeframe:

From 12 weeks after Randomization, assessed every 6 weeks up to Week 49 of study treatment and then every 12 weeks until disease progression (up to approximately 76 months)

End point values	Nivolumab + Ipilimumab	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	10		
Units: Percentage of participants				
number (confidence interval 95%)	54.5 (32.2 to 75.6)	10.0 (0.3 to 44.5)		

Statistical analyses

Statistical analysis title	ORR - BRAF Mutant 1
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Method	Newcombe's method
Parameter estimate	Mean difference (final values)
Point estimate	44.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.2
upper limit	64.8

Statistical analysis title	ORR - BRAF Mutant 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	10.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	511.89

Secondary: Progression-Free Survival (PFS) - BRAF mutant participants	
End point title	Progression-Free Survival (PFS) - BRAF mutant participants

End point description:

PFS is defined as the time between the date of randomization and the first date of documented progression, as assessed by the investigator, or death due to any cause, whichever occurs first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or died were censored on the date of their last evaluable tumor assessment.
PFS values are based on Kaplan-Meier Estimates.

End point type	Secondary

End point timeframe:

From randomization to progression or death (up to approximately 88 months)

End point values	Nivolumab + Ipilimumab	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	10		
Units: Months				
median (confidence interval 95%)	8.61 (2.79 to 99999)	2.73 (0.99 to 5.42)		

Statistical analyses

Statistical analysis title	PFS - BRAF Mutant
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
Method	Unstratified Cox proportional hazard
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.97

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Overall Quality of Life (QOL) C30 Score

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Overall Quality of Life (QOL) C30 Score

End point description:

The EORTC QLQ-C30 version 3 is a questionnaire developed to assess the QOL of cancer patients. The questionnaire is a 30-item tool, and it comprises 6 functional subscales (physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as 9 symptom subscales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).
Scores for each subscale range from 0 to 100. For the 6 functional subscales, a higher score represents a better level of functioning/health status. For the 9 symptom subscales, a lower score represents a better outcome (low level of symptomatology).
Scores for the 15 subscales are presented individually.

End point type	Secondary

End point timeframe:

From Baseline (prior to start of study treatment) to Week 25 after first dose

End point values	Nivolumab + Ipilimumab	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Physical Functioning	2.12 (± 17.625)	1.03 (± 9.367)		
Role Functioning	-1.52 (± 22.950)	5.13 (± 21.926)		
Emotional Functioning	8.33 (± 10.603)	10.26 (± 17.063)		
Cognitive Functioning	-1.52 (± 15.352)	-2.56 (± 11.479)		
Social Functioning	2.27 (± 22.593)	0.00 (± 16.667)		
Global Health Status	3.79 (± 11.422)	-0.64 (± 29.357)		
Fatigue	-3.54 (± 21.520)	-0.85 (± 17.836)		
Nausea and Vomiting	-3.03 (± 12.211)	-2.56 (± 6.259)		
Pain	-2.27 (± 12.905)	-8.97 (± 21.099)		
Dyspnea	-9.09 (± 23.417)	-7.69 (± 27.735)		
Insomnia	-12.12 (± 31.782)	-12.82 (± 16.879)		
Appetite Loss	-13.64 (± 30.271)	-2.56 (± 16.452)		
Constipation	-3.03 (± 20.339)	0.00 (± 13.608)		
Diarrhea	-3.03 (± 14.213)	5.13 (± 12.518)		
Financial Difficulties	-3.03 (± 22.792)	-2.78 (± 22.285)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from date of first dose to study completion.
Serious Adverse events and other adverse events were assessed from date of first dose to 100 days following date of last dose.

Adverse event reporting additional description:

All treated participants

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Participants received placebo-matching nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then placebo-matching nivolumab solution intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

Reporting group title	Nivolumab + Ipilimumab

Reporting group description:

Participants received 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab solution intravenously every 3 weeks for 4 doses (4 cycles), then 3 mg/kg of nivolumab intravenously every 2 weeks until documented disease progression, toxicity, withdrawal of consent, or study completion.

Serious adverse events	Ipilimumab	Nivolumab + Ipilimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 46 (58.70%)	69 / 94 (73.40%)	
number of deaths (all causes)	29	44	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	8 / 46 (17.39%)	10 / 94 (10.64%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 8	0 / 9	
Metastatic malignant melanoma			

subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 46 (2.17%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 46 (4.35%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 46 (8.70%)	6 / 94 (6.38%)	
occurrences causally related to treatment / all	2 / 4	4 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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	1 / 46 (2.17%)	0 / 94 (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	1 / 46 (2.17%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	2 / 46 (4.35%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 46 (2.17%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pleuritic pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 46 (4.35%)	7 / 94 (7.45%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	1 / 46 (2.17%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 46 (2.17%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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	1 / 46 (2.17%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular arrhythmia			

subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoradiculitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 46 (4.35%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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			
Febrile neutropenia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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	2 / 46 (4.35%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 46 (4.35%)	13 / 94 (13.83%)	
occurrences causally related to treatment / all	3 / 3	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 46 (10.87%)	10 / 94 (10.64%)	
occurrences causally related to treatment / all	5 / 6	10 / 11	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 46 (4.35%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
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 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 46 (4.35%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 46 (2.17%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			

subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			

subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
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 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 46 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 46 (6.52%)	4 / 94 (4.26%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 46 (2.17%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 94 (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	0 / 46 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 46 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab	Nivolumab + Ipilimumab	
Total subjects affected by non-serious adverse events subjects affected / exposed	45 / 46 (97.83%)	90 / 94 (95.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 46 (8.70%)	12 / 94 (12.77%)	
occurrences (all)	4	16	
Hot flush			
subjects affected / exposed	3 / 46 (6.52%)	1 / 94 (1.06%)	
occurrences (all)	3	1	
Flushing			
subjects affected / exposed	1 / 46 (2.17%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Hypotension			
subjects affected / exposed	5 / 46 (10.87%)	11 / 94 (11.70%)	
occurrences (all)	5	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 46 (23.91%)	17 / 94 (18.09%)	
occurrences (all)	15	31	
Chills			
subjects affected / exposed	8 / 46 (17.39%)	21 / 94 (22.34%)	
occurrences (all)	11	25	
Fatigue			
subjects affected / exposed	34 / 46 (73.91%)	57 / 94 (60.64%)	
occurrences (all)	47	86	
Influenza like illness			
subjects affected / exposed	6 / 46 (13.04%)	5 / 94 (5.32%)	
occurrences (all)	7	5	
Malaise			
subjects affected / exposed	3 / 46 (6.52%)	2 / 94 (2.13%)	
occurrences (all)	3	2	
Mucosal inflammation			

subjects affected / exposed	5 / 46 (10.87%)	3 / 94 (3.19%)	
occurrences (all)	5	3	
Non-cardiac chest pain			
subjects affected / exposed	4 / 46 (8.70%)	5 / 94 (5.32%)	
occurrences (all)	4	9	
Oedema peripheral			
subjects affected / exposed	10 / 46 (21.74%)	26 / 94 (27.66%)	
occurrences (all)	11	37	
Pain			
subjects affected / exposed	10 / 46 (21.74%)	14 / 94 (14.89%)	
occurrences (all)	11	20	
Peripheral swelling			
subjects affected / exposed	3 / 46 (6.52%)	3 / 94 (3.19%)	
occurrences (all)	3	4	
Pyrexia			
subjects affected / exposed	17 / 46 (36.96%)	32 / 94 (34.04%)	
occurrences (all)	21	51	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	3 / 46 (6.52%)	0 / 94 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 46 (43.48%)	30 / 94 (31.91%)	
occurrences (all)	25	43	
Dysphonia			
subjects affected / exposed	3 / 46 (6.52%)	7 / 94 (7.45%)	
occurrences (all)	3	7	
Dyspnoea			
subjects affected / exposed	14 / 46 (30.43%)	28 / 94 (29.79%)	
occurrences (all)	14	32	
Epistaxis			
subjects affected / exposed	1 / 46 (2.17%)	5 / 94 (5.32%)	
occurrences (all)	3	5	
Nasal congestion			

subjects affected / exposed	5 / 46 (10.87%)	9 / 94 (9.57%)	
occurrences (all)	8	10	
Oropharyngeal pain			
subjects affected / exposed	5 / 46 (10.87%)	9 / 94 (9.57%)	
occurrences (all)	5	9	
Pleural effusion			
subjects affected / exposed	4 / 46 (8.70%)	5 / 94 (5.32%)	
occurrences (all)	4	6	
Productive cough			
subjects affected / exposed	4 / 46 (8.70%)	3 / 94 (3.19%)	
occurrences (all)	4	4	
Pneumonitis			
subjects affected / exposed	2 / 46 (4.35%)	5 / 94 (5.32%)	
occurrences (all)	2	6	
Rhinorrhoea			
subjects affected / exposed	3 / 46 (6.52%)	2 / 94 (2.13%)	
occurrences (all)	3	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 46 (8.70%)	7 / 94 (7.45%)	
occurrences (all)	4	7	
Insomnia			
subjects affected / exposed	11 / 46 (23.91%)	20 / 94 (21.28%)	
occurrences (all)	11	20	
Depression			
subjects affected / exposed	4 / 46 (8.70%)	4 / 94 (4.26%)	
occurrences (all)	4	4	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 46 (15.22%)	31 / 94 (32.98%)	
occurrences (all)	7	48	
Amylase increased			
subjects affected / exposed	3 / 46 (6.52%)	14 / 94 (14.89%)	
occurrences (all)	3	20	
Alanine aminotransferase increased			

subjects affected / exposed	7 / 46 (15.22%)	30 / 94 (31.91%)	
occurrences (all)	8	40	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 46 (15.22%)	13 / 94 (13.83%)	
occurrences (all)	7	16	
Blood bilirubin increased			
subjects affected / exposed	1 / 46 (2.17%)	12 / 94 (12.77%)	
occurrences (all)	1	16	
Blood creatinine increased			
subjects affected / exposed	4 / 46 (8.70%)	10 / 94 (10.64%)	
occurrences (all)	4	18	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 46 (2.17%)	7 / 94 (7.45%)	
occurrences (all)	1	7	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 46 (0.00%)	8 / 94 (8.51%)	
occurrences (all)	0	9	
Lipase increased			
subjects affected / exposed	6 / 46 (13.04%)	22 / 94 (23.40%)	
occurrences (all)	8	37	
Platelet count decreased			
subjects affected / exposed	0 / 46 (0.00%)	5 / 94 (5.32%)	
occurrences (all)	0	8	
Weight decreased			
subjects affected / exposed	2 / 46 (4.35%)	16 / 94 (17.02%)	
occurrences (all)	2	17	
Weight increased			
subjects affected / exposed	3 / 46 (6.52%)	5 / 94 (5.32%)	
occurrences (all)	3	8	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 46 (6.52%)	4 / 94 (4.26%)	
occurrences (all)	3	4	
Atrial fibrillation			

subjects affected / exposed	3 / 46 (6.52%)	6 / 94 (6.38%)	
occurrences (all)	3	9	
Tachycardia			
subjects affected / exposed	5 / 46 (10.87%)	5 / 94 (5.32%)	
occurrences (all)	5	5	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 46 (23.91%)	35 / 94 (37.23%)	
occurrences (all)	14	49	
Dysgeusia			
subjects affected / exposed	1 / 46 (2.17%)	6 / 94 (6.38%)	
occurrences (all)	1	6	
Dizziness			
subjects affected / exposed	5 / 46 (10.87%)	17 / 94 (18.09%)	
occurrences (all)	7	31	
Paraesthesia			
subjects affected / exposed	0 / 46 (0.00%)	9 / 94 (9.57%)	
occurrences (all)	0	9	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 46 (8.70%)	4 / 94 (4.26%)	
occurrences (all)	6	4	
Taste disorder			
subjects affected / exposed	0 / 46 (0.00%)	5 / 94 (5.32%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 46 (32.61%)	24 / 94 (25.53%)	
occurrences (all)	17	35	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 46 (2.17%)	5 / 94 (5.32%)	
occurrences (all)	1	7	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 46 (0.00%)	15 / 94 (15.96%)	
occurrences (all)	0	17	
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	3 / 46 (6.52%)	4 / 94 (4.26%)	
occurrences (all)	4	4	
Abdominal distension			
subjects affected / exposed	3 / 46 (6.52%)	9 / 94 (9.57%)	
occurrences (all)	4	12	
Abdominal pain upper			
subjects affected / exposed	3 / 46 (6.52%)	9 / 94 (9.57%)	
occurrences (all)	4	11	
Abdominal pain			
subjects affected / exposed	12 / 46 (26.09%)	20 / 94 (21.28%)	
occurrences (all)	20	25	
Colitis			
subjects affected / exposed	4 / 46 (8.70%)	9 / 94 (9.57%)	
occurrences (all)	4	9	
Constipation			
subjects affected / exposed	14 / 46 (30.43%)	32 / 94 (34.04%)	
occurrences (all)	15	42	
Diarrhoea			
subjects affected / exposed	24 / 46 (52.17%)	54 / 94 (57.45%)	
occurrences (all)	46	112	
Dry mouth			
subjects affected / exposed	6 / 46 (13.04%)	9 / 94 (9.57%)	
occurrences (all)	6	9	
Dyspepsia			
subjects affected / exposed	3 / 46 (6.52%)	7 / 94 (7.45%)	
occurrences (all)	3	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 46 (4.35%)	5 / 94 (5.32%)	
occurrences (all)	2	5	
Flatulence			
subjects affected / exposed	4 / 46 (8.70%)	4 / 94 (4.26%)	
occurrences (all)	4	4	
Nausea			
subjects affected / exposed	25 / 46 (54.35%)	40 / 94 (42.55%)	
occurrences (all)	29	64	

Vomiting			
subjects affected / exposed	11 / 46 (23.91%)	29 / 94 (30.85%)	
occurrences (all)	13	44	
Rectal haemorrhage			
subjects affected / exposed	4 / 46 (8.70%)	1 / 94 (1.06%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 46 (10.87%)	9 / 94 (9.57%)	
occurrences (all)	5	10	
Erythema			
subjects affected / exposed	1 / 46 (2.17%)	10 / 94 (10.64%)	
occurrences (all)	1	10	
Night sweats			
subjects affected / exposed	1 / 46 (2.17%)	8 / 94 (8.51%)	
occurrences (all)	1	8	
Rash erythematous			
subjects affected / exposed	4 / 46 (8.70%)	2 / 94 (2.13%)	
occurrences (all)	5	2	
Rash			
subjects affected / exposed	17 / 46 (36.96%)	45 / 94 (47.87%)	
occurrences (all)	24	73	
Pruritus			
subjects affected / exposed	17 / 46 (36.96%)	47 / 94 (50.00%)	
occurrences (all)	25	65	
Rash maculo-papular			
subjects affected / exposed	8 / 46 (17.39%)	16 / 94 (17.02%)	
occurrences (all)	10	20	
Rash pruritic			
subjects affected / exposed	4 / 46 (8.70%)	3 / 94 (3.19%)	
occurrences (all)	4	3	
Skin hypopigmentation			
subjects affected / exposed	0 / 46 (0.00%)	5 / 94 (5.32%)	
occurrences (all)	0	5	
Vitiligo			

subjects affected / exposed	4 / 46 (8.70%)	11 / 94 (11.70%)	
occurrences (all)	4	11	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 46 (2.17%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	2 / 46 (4.35%)	10 / 94 (10.64%)	
occurrences (all)	2	10	
Adrenal insufficiency			
subjects affected / exposed	3 / 46 (6.52%)	7 / 94 (7.45%)	
occurrences (all)	3	8	
Hypothyroidism			
subjects affected / exposed	7 / 46 (15.22%)	18 / 94 (19.15%)	
occurrences (all)	7	18	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 46 (15.22%)	19 / 94 (20.21%)	
occurrences (all)	10	25	
Arthralgia			
subjects affected / exposed	11 / 46 (23.91%)	26 / 94 (27.66%)	
occurrences (all)	12	40	
Muscular weakness			
subjects affected / exposed	2 / 46 (4.35%)	12 / 94 (12.77%)	
occurrences (all)	2	12	
Muscle spasms			
subjects affected / exposed	2 / 46 (4.35%)	6 / 94 (6.38%)	
occurrences (all)	3	7	
Myalgia			
subjects affected / exposed	13 / 46 (28.26%)	14 / 94 (14.89%)	
occurrences (all)	13	19	
Pain in extremity			
subjects affected / exposed	9 / 46 (19.57%)	10 / 94 (10.64%)	
occurrences (all)	9	11	
Infections and infestations			

Pneumonia			
subjects affected / exposed	5 / 46 (10.87%)	2 / 94 (2.13%)	
occurrences (all)	5	2	
Upper respiratory tract infection			
subjects affected / exposed	5 / 46 (10.87%)	7 / 94 (7.45%)	
occurrences (all)	5	8	
Urinary tract infection			
subjects affected / exposed	2 / 46 (4.35%)	9 / 94 (9.57%)	
occurrences (all)	2	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 46 (36.96%)	26 / 94 (27.66%)	
occurrences (all)	21	28	
Dehydration			
subjects affected / exposed	4 / 46 (8.70%)	22 / 94 (23.40%)	
occurrences (all)	6	28	
Hyperglycaemia			
subjects affected / exposed	3 / 46 (6.52%)	13 / 94 (13.83%)	
occurrences (all)	3	16	
Hyperkalaemia			
subjects affected / exposed	2 / 46 (4.35%)	8 / 94 (8.51%)	
occurrences (all)	4	12	
Hypoalbuminaemia			
subjects affected / exposed	6 / 46 (13.04%)	11 / 94 (11.70%)	
occurrences (all)	6	14	
Hypocalcaemia			
subjects affected / exposed	2 / 46 (4.35%)	5 / 94 (5.32%)	
occurrences (all)	2	9	
Hypokalaemia			
subjects affected / exposed	5 / 46 (10.87%)	15 / 94 (15.96%)	
occurrences (all)	6	22	
Hypomagnesaemia			
subjects affected / exposed	3 / 46 (6.52%)	11 / 94 (11.70%)	
occurrences (all)	3	13	
Hyponatraemia			

subjects affected / exposed occurrences (all)	6 / 46 (13.04%) 7	22 / 94 (23.40%) 38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2013	Updated Study Design and Statistical Analysis Design
07 October 2013	Updated Clinical Lab evaluations section
17 December 2014	Provided instructions for unblinding participants
30 August 2016	Updated frequency of assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported