Clinical trial results:
Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, doubleblind Phase 3 trial of the EORTC Melanoma Group

Summary

EudraCT number	2007-001974-10
Trial protocol	GB BE IT SE FI CZ DK DE ES FR AT NL
Global end of trial date	26 November 2018

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	CA184-029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00636168
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	26 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to determine whether post-operative adjuvant therapy with ipilimumab improves recurrence-free survival (RFS) as compared to placebo

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	24 June 2008
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	Australia: 51
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Denmark: 70
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 178
Country: Number of subjects enrolled	Germany: 101
Country: Number of subjects enrolled	Italy: 168
Country: Number of subjects enrolled	Norway: 17
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Switzerland: 51
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	United Kingdom: 46
Country: Number of subjects enrolled	United States: 285

Worldwide total number of subjects	1211
EEA total number of subjects	716

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)	968
From 65 to 84 years	243
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Protocol definition of Enrolled population: All 1211 participants who signed the Informed Consent Form; 951 were randomized to treatment and 945 were treated. Reasons for not being randomized: 193 were ineligible; 42 participants refused; 19 could not be randomized within 12 weeks after complete lymph node dissection; 6 due to other reasons.

Period 1

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

Arms

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

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-73016, MDX-010
Other name	human Anti-human CTL4(CD152) mAb
Pharmaceutical forms	Solution for infusion, Solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm title	Placebo

Arm description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

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

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Number of subjects in period 1[1]	Ipilimumab 10mg/kg	Placebo
Started	475	476
Completed	471	474
Not completed	4	2
Consent withdrawn by subject	2	2
Adverse event, non-fatal	1	-
No longer meets study criteria	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: 1211 participants were enrolled.Baseline characteristics were collected for the 951 randomized participants.

Period 2

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

Arms

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

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-73016, MDX-010
Other name	human Anti-human CTL4(CD152) mAb
Pharmaceutical forms	Solution for infusion, Solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning

at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm title	Placebo

Arm description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

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

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Number of subjects in period 2	Ipilimumab 10mg/kg	Placebo
Started	471	474
Completed	63	143
Not completed	408	331
Adverse event, serious fatal	3	-
Recurrence of disease	135	282
Participant withdrew consent	16	21
Adverse event, non-fatal	250	22
Pregnancy	1	-
Other reason	1	3
No longer meets study criteria	1	-
Poor/non-compliance	1	3

Period 3	
Period 3 title	Long Term Follow-Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator

Arms

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

Arm description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-73016, MDX-010
Other name	human Anti-human CTL4(CD152) mAb
Pharmaceutical forms	Solution for infusion, Solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Arm title	Placebo

Arm description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

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

Dosage and administration details:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Number of subjects in period 3	Ipilimumab 10mg/kg	Placebo
Started	63	143
Completed	130	129
Not completed	11	14
Adverse event, serious fatal	8	9
Participant withdrew consent	-	2

Lost to follow-up	3	3
Joined	78	0
Randomized, consented to participate in LTFU	78	-

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab 10mg/kg
Reporting group description:	
Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).	
Reporting group title	Placebo
Reporting group description:	
Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).	

Reporting group values	Ipilimumab 10mg/kg	Placebo	Total
Number of subjects	475	476	951
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	395	389	784
From 65-84 years	80	87	167
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.7	51.5	
standard deviation	± 12.9	± 12.82	-
Sex: Female, Male Units:			
Female	179	183	362
Male	296	293	589
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	0	0
White	470	476	946
More than one race	0	0	0
Unknown or Not Reported	3	0	3

End points

End points reporting groups

Reporting group title	Ipilimumab 10mg/kg

Reporting group description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Reporting group title	Placebo

Reporting group description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Reporting group title	Ipilimumab 10mg/kg

Reporting group description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Reporting group title	Placebo

Reporting group description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Reporting group title	Ipilimumab 10mg/kg

Reporting group description:

Ipilimumab (10 mg/kg) as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (every 21 days in the Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, Ipilimumab was administered at a dose of 10 mg/kg, by IV infusion, every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Reporting group title	Placebo

Reporting group description:

Placebo as a single dose via a 90 minute intravenous (IV) infusion (not as bolus or IV push) during Days 1, 22, 43 and 64 (Induction Phase) for a total of four separate doses, until disease recurrence, unacceptable toxicity or withdrawal of consent. During the maintenance phase, placebo was administered by IV infusion every 12 weeks, beginning at Week 24, until disease recurrence, unacceptable toxicity or withdrawal of consent, for a maximum of 3 years (Week 156).

Primary: Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point title	Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point description:

Recurrence free survival (RFS) was programmatically determined based on the disease recurrence data provided by the IRC and was defined as the time between the date of randomization and the date of first recurrence or death (whatever the cause), whichever occurred first. A participant who died without

reported recurrence was considered to have recurrence on the date of death. For those participants who remained alive and recurrence-free, RFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment, RFS was censored on the day of randomization. Participants with disease at baseline were considered to have an event on the day of randomization. The primary analysis was event-driven and planned when at least 512 RFS events assessed per IRC were collected. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Primary

End point timeframe:

Date of randomization to first date of recurrence or death or last available disease assessment with RFS data up to 5 years. Median follow-up was 2.7 years.

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: months				
median (confidence interval 95%)				
RFS per IRC in ITT	26.09 (19.32 to 39.26)	17.05 (13.40 to 21.62)		

Statistical analyses

Statistical analysis title	Statistical Analysis for RFS per IRC in ITT

Statistical analysis description:

Hazard ratio, and its 95 % confidence interval estimated using a Cox proportional hazards model, stratified by stage (IIIa vs. IIIb vs. IIIc with 1-3 positive lymph-nodes vs. IIIc with >= 4 positive lymph-nodes) as indicated at randomization, with treatment as the single covariate. 2-sided, 95% confidence intervals for median RFS computed by the Brookmeyer and Crowley method using log-log transformation. P-value was based on stratified 2-sided log-rank test.

Comparison groups	Placebo v Ipilimumab 10mg/kg
Number of subjects included in analysis	951
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	0.9

Primary: Number of participants with recurrence or death as per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point title	Number of participants with recurrence or death as per Independent Review Committee (IRC) in the Intent to Treat

	(ITT) Population[1]

End point description:

Recurrence was defined as appearance of one or more new melanoma lesions: local, regional or distant metastasis. Computerized tomography (CT) and magnetic resonance imaging (MRI) were mandatory to establish recurrence. A participant who died without reported recurrence was considered to have recurred on the date of death. Disease was assessed at randomization and every 12 weeks (±2 weeks) for 3 years, then every 24 weeks until documented distant progression. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Primary

End point timeframe:

Date of randomization to first date of recurrence or death or last available disease assessment with RFS data upto 5 years. Median follow-up was 2.7 years.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint is the same as that for previous endpoint: Recurrence free survival (RFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Participants				
No. of participants with recurrence or death	234	294		

Statistical analyses

No statistical analyses for this end point

Primary: Recurrence-Free Survival (RFS) Rates per IRC at 1 year, 2 years, and 3 years in the ITT Population

End point title	Recurrence-Free Survival (RFS) Rates per IRC at 1 year, 2 years, and 3 years in the ITT Population[2]

End point description:

Yearly recurrence-free survival rates, eg. at 1 year, defined as the probability that a participant was recurrence-free at 1 year following randomization, were estimated for each treatment group using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals. RFS was defined as the time between the date of randomization and the date of first recurrence or death (whatever the cause), whichever occurred first. A participant who died without reported recurrence was considered to have recurrence on the date of death. For those who remained alive and had no recorded post-randomization tumor assessment, RFS was censored on the day of randomization. Participants with disease at baseline were considered to have an event on the day of randomization. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Primary

End point timeframe:

At years 1, 2, and 3

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Percentage				
number (confidence interval 95%)				
RFS Rate at 1 Year	63.50 (58.89 to 67.74)	56.13 (51.52 to 60.47)		
RFS Rate at 2 Years	51.45 (46.69 to 56.00)	43.83 (39.27 to 48.28)		
RFS Rate at 3 Years	46.48 (41.46 to 51.34)	34.79 (30.12 to 39.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point title	Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point description:

Distant Metastasis-Free Survival (DMFS) was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. Participants with disease at baseline were considered to have an event on the day of randomization. Disease was assessed at baseline (randomization) and every 12 weeks (±2 weeks) for 3 years, then every 24 weeks until documented distant progression. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Secondary

End point timeframe:

From June 2008 to January 2016 (approximately 90 months)

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Months				
median (confidence interval 95%)				
DMFS per IRC in ITT	48.30 (35.45 to 71.56)	27.47 (21.91 to 34.79)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DMFS per IRC in ITT

Statistical analysis description:

Medians and associated 2-sided 95% confidence intervals are calculated using the method of Brookmeyer and Crowley. Analysis was stratified for stage (IIIa vs. IIIb vs. IIIc with 1-3 positive lymph-nodes vs. IIIc with >= 4 positive lymph-nodes) as recorded at randomization. P-value was based on stratified 2-sided log-rank test. Hazard of 10 mg/kg Ipilimumab over hazard of Placebo, with 2-sided 95.8% confidence interval are based on a stratified Cox proportional hazards model

Comparison groups	Ipilimumab 10mg/kg v Placebo
Number of subjects included in analysis	951
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0024
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95.8 %
sides	2-sided
lower limit	0.64
upper limit	0.92

Secondary: Number of participants with Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point title	Number of participants with Distant Metastasis-Free Survival (DMFS) per Independent Review Committee (IRC) in the Intent to Treat (ITT) Population

End point description:

DMFS was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment, DMFS was censored on the day of randomization. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Secondary

End point timeframe:

From June 2008 to January 2016 (approximately 90 months)

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Participants				
No. of participants with DMFS per IRC	227	279		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastasis-Free Survival (DMFS) Rates per IRC at 1 year, 2 years, 3 years, 4 years and 5 years in the ITT Population

End point title	Distant Metastasis-Free Survival (DMFS) Rates per IRC at 1 year, 2 years, 3 years, 4 years and 5 years in the ITT Population

End point description:

Yearly distant metastasis-free survival rates, e.g. at 1 year, defined as the probability that a participant was alive at 1 year following randomization, were estimated via the Kaplan-Meier method. Distant Metastasis-Free Survival (DMFS) was programmatically determined based on the first date of distant metastasis provided by the IRC and was defined as the time between the date of randomization and the date of first distant metastasis or death (whatever the cause), whichever occurred first. A participant who died without reported disease distant metastasis was considered to have distant metastasis on the date of death. For those who remained alive and metastasis-free, DMFS was censored on the date of last evaluable post-randomization tumor assessment. For those who remained alive and had no recorded post-randomization tumor assessment. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Secondary

End point timeframe:

At years 1, 2, 3, 4 and 5

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Percentage				
number (confidence interval 95%)				
DMFS Rate at 1 Year	74.27 (69.98 to 78.04)	65.77 (61.27 to 69.88)		
DMFS Rate at 2 Years	61.48 (56.75 to 65.85)	53.26 (48.58 to 57.70)		
DMFS Rate at 3 Years	53.90 (49.04 to 58.50)	45.17 (40.53 to 49.70)		
DMFS Rate at 4 Years	50.19 (45.30 to 54.87)	41.48 (36.87 to 46.02)		
DMFS Rate at 5 Years	48.29 (43.36 to 53.04)	38.90 (34.29 to 43.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in the Intent to Treat (ITT) Population

End point title	Overall Survival in the Intent to Treat (ITT) Population

End point description:

OS was defined as the time from the date of randomization to the date of death. For those participants who had not died, OS was censored at the recorded last non-missing date of contact for which the participant was known to be alive. Here'99999' signifies data not available as the upper limit or median was not reached. Intent-to-treat population: All randomized participants, analyzed in the arm to which they were allocated by randomization

End point type	Secondary

End point timeframe:

From June 2008 to January 2016 (approximately 90 months)

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Months				
median (confidence interval 95%)				
OS in ITT	86.60 (86.60 to 99999)	99999 (59.30 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS in ITT

Statistical analysis description:

Medians and associated 2-sided 95% confidence intervals are calculated using the method of Brookmeyer and Crowley. Analysis was stratified for stage (IIIa vs. IIIb vs. IIIc with 1-3 positive lymph-nodes vs. IIIc with >= 4 positive lymph-nodes) as recorded at randomization. P-value was based on stratified 2-sided log-rank test. Hazard of 10 mg/kg Ipilimumab over hazard of Placebo, with 2-sided 95.1% confidence interval are based on a stratified Cox proportional hazards model

Comparison groups	Ipilimumab 10mg/kg v Placebo
Number of subjects included in analysis	951
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	0.58
upper limit	0.88

Secondary: Rate of Overall Survival (OS)

End point title	Rate of Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death. For those participants who had not died, OS was censored at the recorded last non-missing date of contact for which the participant was known to be alive.Yearly survival rates, e.g. at 3 years, defined as the probability that a participant was alive at 3 years following randomization, were estimated via the Kaplan-Meier method. Intent to Treat Population: All randomized participants,analyzed in the arm to which they were allocated by randomization

End point type	Secondary

End point timeframe:

From date of randomization to date of death, assessed up to 9 years

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	476		
Units: Percentage of participants				
number (confidence interval 95%)				
OS Rate at 1 year	93.53 (90.88 to 95.43)	87.72 (84.40 to 90.37)		
OS Rate at 2 years	82.55 (78.76 to 85.73)	75.27 (71.10 to 78.92)		
OS Rate at 3 years	74.20 (69.90 to 77.98)	65.43 (60.91 to 69.56)		
OS Rate at 4 years	67.79 (63.24 to 71.90)	60.34 (55.72 to 64.64)		
OS Rate at 5 years	65.42 (60.80 to 69.64)	54.43 (49.71 to 58.89)		
OS Rate at 7 years	60.0 (55.0 to 64.7)	51.3 (46.5 to 55.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with On-Study Adverse Events (AEs) Leading to Discontinuation of Treatment, Serious AEs (SAEs), Drug-Related SAEs, Immune-related AEs (irAEs), Immune-mediated adverse reactions (imARs), Deaths in Treated Population

End point title	Number of Participants with On-Study Adverse Events (AEs) Leading to Discontinuation of Treatment, Serious AEs (SAEs), Drug-Related SAEs, Immune-related AEs (irAEs), Immune-mediated adverse reactions (imARs), Deaths in Treated Population

End point description:

AEs: Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. irAEs=unknown etiology consistent with an immune phenomenon, considered as causally related to drug. imARs=based on investigator's assessment of immune-mediated etiology. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Drug-related (D-R)=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling, Gr 5=Death. Safety population: All randomized participants who received at least 1 dose of study therapy

End point type	Secondary

End point timeframe:

Day 1 up to 70 days after last dose; up to 5 years

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	474		
Units: Participants				
On-study AE leading to Discontinuation (Any Grade)	247	43		
On-study SAE (At least 5%, Any Grade)	257	128		
On-study D-R SAE (Any Grade)	217	10		
On-study irAE (Any Grade)	426	188		
On-study gastrointestinal irAE (Any Grade)	217	85		
On-study endocrine irAE (Any Grade)	178	38		
On-study liver irAE (Any Grade)	115	20		
On-study skin irAE (Any Grade)	298	99		
On-study neurological irAE (Any Grade)	21	9		
On-study other irAE (Any Grade)	111	23		
On-study imAR (Grade 3-4)	194	16		
On-study imAR (Grade 5)	1	0		
On-study enterocolitis imAR (Grade 5)	1	0		
On-study enterocolitis imAR (Grade 3-4)	76	4		
On-study endocrinopathy imAR (Grade 3-4)	39	1		
On-study hepatitis imAR (Grade 3-4)	51	1		
On-study dermatitis imAR (Grade 3-4)	19	2		
On-study neuropathy imAR (Grade 3-4)	10	0		
On-study other imAR (Grade 3-4)	30	9		
Any Death	162	214		
Death within 70 days of last dose study drug	6	6		
Death within 30 days of last dose study drug	1	0		
Drug-related Deaths	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serious Adverse Events (SAEs), Non-serious AEs (NSAEs) and number of Deaths: Overall study

End point title	Number of Participants with Serious Adverse Events (SAEs), Non-serious AEs (NSAEs) and number of Deaths: Overall study

End point description:

AEs: Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Safety population: All randomized participants who received at least 1 dose of study therapy

End point type	Secondary

End point timeframe:

SAEs and NSAEs: Day 1 up to 70 days after last dose(safety window). Deaths: All deaths regardless of 70 day safety window.Up to 10 years

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	474		
Units: Participants				
No. of deaths	173	223		
No. of participants with SAEs	257	128		
No of participants with NSAEs (freq. >= 5%)	441	382		

Statistical analyses

No statistical analyses for this end point

Secondary: Exposure Adjusted Incidence Rate of Adverse Events Including Multiple Occurrences of Unique Events

End point title	Exposure Adjusted Incidence Rate of Adverse Events Including Multiple Occurrences of Unique Events

End point description:

P-Y = person-years of exposure. Incidence rate per 100 person-years of exposure (IR/100 P-Y) was calculated as event count * 100 /person-years of exposure. MedDRA Version: 19. Duplicate AEs have been eliminated and overlapping and contiguous occurrences of the same event have been collapsed. All participants who received at least one dose of ipilimumab or placebo, adjusted for person-years (P-Y) of exposure; P-Y=467.4; P-Y=781.7 for ipilimumab and placebo, respectively.

End point type	Secondary

End point timeframe:

Day 1 up to 70 days after last dose; up to 5 years

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	474		
Units: Events per 100 person-years of exposure				
number (not applicable)				
Exp. adj. incidence rate of AEs	1171.8	465.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Global Health Status Scores at Each Assessment Timepoint

End point title	Mean Change from Baseline in Global Health Status Scores at Each Assessment Timepoint

End point description:

Global health status was measured using European Organization for Research and Treatment of Cancer (EORTC) Quality Life Questionnaire (QLQ) C-30. This health related quality of life (HRQoL) questionnaire was comprised of 15 questions on functional scales, 13 questions on symptom scales and 2 on global health status scale. Global Health Status used a 7 point Likert-type scale of 1 (Very poor) to 7 (Excellent). All scales linearly transformed to 0-100 scales. Higher scores for Global Health Status indicate better HRQoL. An increase from baseline indicates improvement in HRQoL compared to baseline. All randomized participants (ITT) analyzed in the arm to which they were allocated by randomization were analyzed. At timepoint level, all randomized participants (ITT) with a measurement at the timepoint were analyzed.

End point type	Secondary

End point timeframe:

Baseline up to 2 years from randomization

End point values	Ipilimumab 10mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	421		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4 Day 22	-2.29 (± 15.96)	1.33 (± 14.02)		
Week 7, Day 43 (360, 412)	-6.64 (± 20.44)	-0.10 (± 16.75)		
Week 10 Day 64 (356, 405)	-9.06 (± 23.56)	-0.23 (± 16.18)		
Week 24 Day 162 (300, 347)	-4.33 (± 21.55)	1.37 (± 17.00)		
Week 36 Day 246 (290, 307)	-5.09 (± 21.32)	1.52 (± 18.52)		
Week 48 Day 330 (275, 276)	-3.67 (± 20.17)	1.54 (± 18.87)		
Week 60 Day 414 (242, 255)	-5.30 (± 21.34)	2.84 (± 17.05)		
Week 72 day 498 (217, 248)	-4.07 (± 23.19)	1.18 (± 17.46)		
Week 84 Day 582 (205, 227)	-3.90 (± 22.06)	1.84 (± 17.08)		
Week 96 Day 666 (199, 214)	-4.48 (± 21.71)	1.36 (± 18.67)		
Week 108 Day 750 (162,177)	-4.27 (± 20.35)	2.45 (± 16.72)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time frame for AE reporting	
Adverse event reporting additional description:	
Adverse Events were collected for the safety population which included all 945 randomized subjects who received at least 1 dose of study therapy (471 in the ipilimumab group and 474 in the placebo group)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	PLACEBO
Reporting group description:	
PLACEBO	
Reporting group title	IPILIMUMAB 10 MG/KG
Reporting group description:	
IPILIMUMAB 10 MG/KG	

Serious adverse events	PLACEBO	IPILIMUMAB 10 MG/KG	
Total subjects affected by serious adverse events			
subjects affected / exposed	128 / 474 (27.00%)	257 / 471 (54.56%)	
number of deaths (all causes)	223	173	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	3 / 474 (0.63%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	4 / 474 (0.84%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous			

system			
subjects affected / exposed	2 / 474 (0.42%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer stage 0			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal adenoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to skin			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	6 / 474 (1.27%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposarcoma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	6 / 474 (1.27%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 9	2 / 5	
deaths causally related to treatment / all	0 / 6	2 / 4	
Malignant pleural effusion			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Melanocytic naevus			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic malignant melanoma			
subjects affected / exposed	11 / 474 (2.32%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 12	1 / 2	
deaths causally related to treatment / all	0 / 8	1 / 2	
Neoplasm progression			
subjects affected / exposed	2 / 474 (0.42%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melanoma recurrent			
subjects affected / exposed	7 / 474 (1.48%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Metastases to lymph nodes			

subjects affected / exposed	2 / 474 (0.42%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastasis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Benign lung neoplasm			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endobronchial lipoma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	12 / 474 (2.53%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	2 / 13	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Malignant melanoma			
subjects affected / exposed	9 / 474 (1.90%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 10	1 / 1	
deaths causally related to treatment / all	0 / 4	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system melanoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Oncocytoma			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 474 (0.00%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	3 / 3	
Haematoma			
subjects affected / exposed	2 / 474 (0.42%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Withdrawal hypertension			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			

Disease progression			
subjects affected / exposed	4 / 474 (0.84%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 474 (0.21%)	18 / 471 (3.82%)	
occurrences causally related to treatment / all	0 / 1	17 / 20	
deaths causally related to treatment / all	0 / 1	6 / 8	
Asthenia			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Fatigue			
subjects affected / exposed	1 / 474 (0.21%)	5 / 471 (1.06%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 1	3 / 3	
Disease recurrence			
subjects affected / exposed	3 / 474 (0.63%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chest pain			
subjects affected / exposed	2 / 474 (0.42%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Retention cyst			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (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			
Drug hypersensitivity			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Autoimmune disorder			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactoid reaction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 474 (0.21%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ovarian cyst			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 474 (0.42%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eosinophilic pneumonia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mental status changes			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Substance-Induced psychotic disorder			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 474 (0.00%)	17 / 471 (3.61%)	
occurrences causally related to treatment / all	0 / 0	30 / 31	
deaths causally related to treatment / all	0 / 0	15 / 16	

Thyroid function test abnormal			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Ejection fraction decreased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lymph nodes scan abnormal			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 474 (0.00%)	15 / 471 (3.18%)	
occurrences causally related to treatment / all	0 / 0	20 / 21	
deaths causally related to treatment / all	0 / 0	10 / 11	
Lipase increased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood corticotrophin decreased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood creatinine increased			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver function test increased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza a virus test positive			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract procedural complication			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Coronary artery disease			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 474 (0.21%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Bifascicular block			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Presyncope			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve disorder			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningoradiculitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Ataxia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Trigeminal nerve disorder			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axonal neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Spinal cord compression			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Autoimmune neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Carotid artery stenosis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 474 (0.42%)	6 / 471 (1.27%)	
occurrences causally related to treatment / all	1 / 2	6 / 6	
deaths causally related to treatment / all	1 / 2	2 / 2	
Seizure			
subjects affected / exposed	2 / 474 (0.42%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	3 / 474 (0.63%)	5 / 471 (1.06%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 2	
Lymphoid tissue hyperplasia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness unilateral			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Episcleritis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune uveitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 474 (0.21%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	1 / 1	1 / 1	
Colitis ulcerative			
subjects affected / exposed	1 / 474 (0.21%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	4 / 4	
Haemorrhoids			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 474 (0.21%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pancreatitis			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatitis acute			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 474 (0.21%)	51 / 471 (10.83%)	
occurrences causally related to treatment / all	1 / 1	62 / 63	
deaths causally related to treatment / all	1 / 1	25 / 26	
Duodenal ulcer			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	1 / 474 (0.21%)	8 / 471 (1.70%)	
occurrences causally related to treatment / all	1 / 1	7 / 8	
deaths causally related to treatment / all	0 / 0	4 / 4	
Abdominal hernia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 474 (1.27%)	36 / 471 (7.64%)	
occurrences causally related to treatment / all	4 / 6	43 / 43	
deaths causally related to treatment / all	3 / 3	19 / 19	
Intestinal perforation			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastritis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dysphagia			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 474 (0.42%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 474 (0.00%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatotoxicity			

subjects affected / exposed	0 / 474 (0.00%)	5 / 471 (1.06%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	6 / 6	
Hepatitis			
subjects affected / exposed	0 / 474 (0.00%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	2 / 2	
Autoimmune hepatitis			
subjects affected / exposed	1 / 474 (0.21%)	12 / 471 (2.55%)	
occurrences causally related to treatment / all	1 / 1	12 / 12	
deaths causally related to treatment / all	1 / 1	5 / 5	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pruritus			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Angioedema			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin exfoliation			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Exfoliative rash			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Actinic keratosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Urinary tract obstruction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Hyperadrenocorticism			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypophysitis			
subjects affected / exposed	0 / 474 (0.00%)	37 / 471 (7.86%)	
occurrences causally related to treatment / all	0 / 0	38 / 38	
deaths causally related to treatment / all	0 / 0	15 / 15	
Hypopituitarism			
subjects affected / exposed	0 / 474 (0.00%)	10 / 471 (2.12%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	4 / 4	
Adrenal insufficiency			
subjects affected / exposed	0 / 474 (0.00%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
Hypothyroidism			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
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	0 / 474 (0.00%)	5 / 471 (1.06%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck mass			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 474 (0.42%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Osteoarthritis			
subjects affected / exposed	3 / 474 (0.63%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (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			
Bronchitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	4 / 474 (0.84%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroborreliosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Perirectal abscess			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis			
subjects affected / exposed	0 / 474 (0.00%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Herpes zoster			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			

subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Viral infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (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 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic embolus			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Meningitis aseptic			

subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Erysipelas			
subjects affected / exposed	7 / 474 (1.48%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	1 / 8	1 / 2	
deaths causally related to treatment / all	0 / 4	0 / 0	
Localised infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Staphylococcal infection			
subjects affected / exposed	0 / 474 (0.00%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Otitis externa			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteomyelitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Appendicitis			
subjects affected / exposed	1 / 474 (0.21%)	3 / 471 (0.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	3 / 474 (0.63%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Beta haemolytic streptococcal infection			

subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Groin infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 474 (0.21%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	1 / 1	0 / 1	
Herpes ophthalmic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 474 (0.00%)	4 / 471 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	2 / 5	
Hypoglycaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 471 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 474 (0.21%)	2 / 471 (0.42%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperglycaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 471 (0.21%)	
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	PLACEBO	IPILIMUMAB 10 MG/KG	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	382 / 474 (80.59%)	441 / 471 (93.63%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 474 (5.49%)	95 / 471 (20.17%)	
occurrences (all)	41	115	
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 474 (2.53%)	33 / 471 (7.01%)	
occurrences (all)	15	38	
Blood testosterone decreased			
subjects affected / exposed	8 / 474 (1.69%)	29 / 471 (6.16%)	
occurrences (all)	10	32	
Aspartate aminotransferase increased			
subjects affected / exposed	26 / 474 (5.49%)	72 / 471 (15.29%)	
occurrences (all)	36	85	
Lipase increased			
subjects affected / exposed	30 / 474 (6.33%)	42 / 471 (8.92%)	
occurrences (all)	41	53	
Weight decreased			

subjects affected / exposed	42 / 474 (8.86%)	149 / 471 (31.63%)	
occurrences (all)	54	167	
Weight increased			
subjects affected / exposed	114 / 474 (24.05%)	71 / 471 (15.07%)	
occurrences (all)	163	90	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 474 (3.80%)	29 / 471 (6.16%)	
occurrences (all)	26	34	
Headache			
subjects affected / exposed	85 / 474 (17.93%)	150 / 471 (31.85%)	
occurrences (all)	122	205	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	30 / 474 (6.33%)	35 / 471 (7.43%)	
occurrences (all)	50	45	
Oedema peripheral			
subjects affected / exposed	27 / 474 (5.70%)	21 / 471 (4.46%)	
occurrences (all)	28	23	
Pyrexia			
subjects affected / exposed	22 / 474 (4.64%)	73 / 471 (15.50%)	
occurrences (all)	33	100	
Asthenia			
subjects affected / exposed	38 / 474 (8.02%)	29 / 471 (6.16%)	
occurrences (all)	49	43	
Fatigue			
subjects affected / exposed	143 / 474 (30.17%)	188 / 471 (39.92%)	
occurrences (all)	207	242	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	44 / 474 (9.28%)	64 / 471 (13.59%)	
occurrences (all)	48	86	
Nausea			
subjects affected / exposed	82 / 474 (17.30%)	117 / 471 (24.84%)	
occurrences (all)	120	144	
Colitis			

subjects affected / exposed	5 / 474 (1.05%)	43 / 471 (9.13%)	
occurrences (all)	6	54	
Vomiting			
subjects affected / exposed	27 / 474 (5.70%)	61 / 471 (12.95%)	
occurrences (all)	34	65	
Constipation			
subjects affected / exposed	30 / 474 (6.33%)	31 / 471 (6.58%)	
occurrences (all)	31	33	
Diarrhoea			
subjects affected / exposed	141 / 474 (29.75%)	229 / 471 (48.62%)	
occurrences (all)	245	381	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	16 / 474 (3.38%)	31 / 471 (6.58%)	
occurrences (all)	17	33	
Cough			
subjects affected / exposed	48 / 474 (10.13%)	68 / 471 (14.44%)	
occurrences (all)	57	78	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	80 / 474 (16.88%)	186 / 471 (39.49%)	
occurrences (all)	116	274	
Pruritus			
subjects affected / exposed	70 / 474 (14.77%)	203 / 471 (43.10%)	
occurrences (all)	100	290	
Dermatitis acneiform			
subjects affected / exposed	6 / 474 (1.27%)	26 / 471 (5.52%)	
occurrences (all)	7	29	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	25 / 474 (5.27%)	21 / 471 (4.46%)	
occurrences (all)	26	23	
Insomnia			
subjects affected / exposed	21 / 474 (4.43%)	45 / 471 (9.55%)	
occurrences (all)	21	49	
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	2 / 474 (0.42%)	56 / 471 (11.89%)	
occurrences (all)	2	65	
Hypothyroidism			
subjects affected / exposed	7 / 474 (1.48%)	47 / 471 (9.98%)	
occurrences (all)	9	54	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	26 / 474 (5.49%)	16 / 471 (3.40%)	
occurrences (all)	29	19	
Pain in extremity			
subjects affected / exposed	36 / 474 (7.59%)	21 / 471 (4.46%)	
occurrences (all)	43	21	
Arthralgia			
subjects affected / exposed	45 / 474 (9.49%)	34 / 471 (7.22%)	
occurrences (all)	50	39	
Back pain			
subjects affected / exposed	41 / 474 (8.65%)	29 / 471 (6.16%)	
occurrences (all)	49	31	
Myalgia			
subjects affected / exposed	24 / 474 (5.06%)	21 / 471 (4.46%)	
occurrences (all)	28	25	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	31 / 474 (6.54%)	21 / 471 (4.46%)	
occurrences (all)	36	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 474 (3.38%)	65 / 471 (13.80%)	
occurrences (all)	17	75	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2009	After careful review of a Serious Adverse Event (Grade 3 toxic epidermal necrolysis [TEN] with subsequent Grade 5 Sepsis) by the Data Monitoring Committee that has been established for the ipilimumab program, the dose skipping criteria for ipilimumab is being modified in order to make it more conservative. Because this is a safety amendment that is intended to avoid potentially life threatening events, all sites are asked to implement this amendment immediately (prior to IRB / IEC / HA review and approval). This revision applies to all subjects that are currently receiving ipilimumab therapy.
29 April 2011	In accordance with the FDA approved label, BMS now requires that all the patients participating in clinical studies with ipilimumab, regardless of the dose used, have their TSH level assessed at baseline and before each dose. Results do not have to be known at the time of dosing with ipilimumab as treatment modifications should be based on signs and symptoms related to endocrinopathies consistent with existing guidelines within the investigator brochure and protocol. If a subject has thyroid dysfunction and concomitant symptoms (i.e. fatigue), the subject should be monitored more frequently and be treated as per standard medical practice. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented.
13 May 2015	The main protocol is amended to follow the NCCN guidelines and Swiss guidelines, which describe that routine radiologic imaging to screen for asymptomatic recurrence/metastatic disease is not recommended after 5 years by NCCN and recommend to only perform a physical examination in recurrence-free patients after 5 years. [Ref. NCCN guidelines version 4, 2014, J Natl Compr Canc Netw. 2014 May;12(5):621-9); Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Swiss Med Wkly. 2011 Dec 15;141: w13320. doi: 10.4414/smw.2011.13320]. This amendment also includes updated background information as well as updated clinical safety data on the study medication and a new section of Adverse Event of Interest This amendment also includes update of contact details and some administrative updates and a change in nomenclature for HAHA into ADA
25 January 2016	With the change in treatment landscape of melanoma subjects, OS might be affected due to treatment with subsequent therapy and hence the potential treatment effect might be attenuated. Therefore, the final OS analysis will be performed at the time of the final DMFS analysis, recognizing the drop in power for OS (75% power anticipated). The applicable statistical sections have been updated accordingly. In addition, the protocol is being amended to include a long term follow-up phase. The main protocol is also amended to describe the end of activities of the several CROs (responsible for the on-site monitoring, medical monitoring/SAE contacts and Independent Review Committee) involved in the study, which will occur at the time of the DFMS/OS analyses. After the database lock for the DMFS/OS final analyses, the SAE contacts will change from the current CRO to BMS. Lastly, this amendment also includes update of contact details and some administrative updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported