



Clinical trial results:

A Randomized, Multicenter, Double-Blind Phase 3 Trial Comparing the Efficacy of Ipilimumab in Addition to Paclitaxel and Carboplatin versus Placebo in Addition to Paclitaxel and Carboplatin in Subjects with Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2009-017396-19
Trial protocol	HU SE DE BE GB AT NL DK CZ PT IE ES IT
Global end of trial date	22 August 2017

Results information

Result version number	v1 (current)
This version publication date	07 September 2018
First version publication date	07 September 2018

Trial information

Trial identification

Sponsor protocol code	CA184-104
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare overall survival (OS) of ipilimumab + paclitaxel/carboplatin to placebo + paclitaxel/carboplatin in subjects with stage IV or recurrent non-small cell lung cancer (NSCLC) of squamous histology who received at least one dose of blinded study therapy.

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	22 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 29
Country: Number of subjects enrolled	China: 72
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 102
Country: Number of subjects enrolled	Hungary: 71
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Italy: 61
Country: Number of subjects enrolled	Japan: 84
Country: Number of subjects enrolled	Korea, Republic of: 98

Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Romania: 66
Country: Number of subjects enrolled	Russian Federation: 103
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 47
Country: Number of subjects enrolled	Thailand: 35
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	1289
EEA total number of subjects	576

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)	670
From 65 to 84 years	616
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1289 participants were enrolled and 956 were randomized (479 Ipilimumab, 477 Placebo). 948 were treated (475 Ipilimumab, 473 Placebo). Reasons for non-treatment is 4 no longer met study criteria, 2 adverse events unrelated to study drug, 1 participant request to discontinue, and 1 other .

Period 1

Period 1 title	Randomized
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab with Paclitaxel/Carboplatin

Arm description:

Ipilimumab + Active Chemotherapy Backbone The blinded therapy (Ipilimumab) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Ipilimumab: IV solution, intravenous (IV), 10 mg/kg, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemo Backbone: Paclitaxel: IV solution, IV, 175 mg/m², 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses

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

Dosage and administration details:

Injection, 200 mg/vial

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 50 mg/vial

Investigational medicinal product name	Taxol (for IV infusion)
Investigational medicinal product code	
Other name	Paclitaxel
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The prescribed dose of TAXOL should be diluted in 500 mL of 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection. A concentration of 1.2 mg/mL should not be exceeded.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25 C).

Arm title	Placebo with Paclitaxel/Carboplatin
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Arm description:

Placebo + Active Chemotherapy Backbone The blinded therapy (Placebo) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Placebo: IV solution, IV, 0.9% sodium chloride or 5% dextrose, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemotherapy Backbone: Paclitaxel: IV solution, IV, 175 mg/m², 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses

Arm type	Placebo
Investigational medicinal product name	Placebo of Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 200 mg/vial

Investigational medicinal product name	Taxol (for IV infusion)
Investigational medicinal product code	
Other name	Paclitaxel
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The prescribed dose of TAXOL should be diluted in 500 mL of 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection. A concentration of 1.2 mg/mL should not be exceeded.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25 C).

Investigational medicinal product name	Placebo of Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 50 mg/vial

Number of subjects in period 1	Ipilimumab with Paclitaxel/Carboplatin	Placebo with Paclitaxel/Carboplatin
Started	479	477
Treated with Chemotherapy (1st dose)	475	473
Completed	388	361
Not completed	91	116
Adverse event, serious fatal	5	7
Consent withdrawn by subject	8	11
Undisclosed Reasons	1	-
Progressive Disease	41	61
Subject No Longer Met Study Criteria	1	1
Adverse Event Unrelated to Study Drug	18	18
Randomized but not Treated	4	4
Study Drug Toxicity	13	14

Period 2

Period 2 title	Treated with Blinded Therapy
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab with Paclitaxel/Carboplatin

Arm description:

Ipilimumab + Active Chemotherapy Backbone The blinded therapy (Ipilimumab) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Ipilimumab: IV solution, intravenous (IV), 10 mg/kg, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemo Backbone: Paclitaxel: IV solution, IV, 175 mg/m², 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses

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

Dosage and administration details:

Injection, 200 mg/vial

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 50 mg/vial

Investigational medicinal product name	Taxol (for IV infusion)
Investigational medicinal product code	
Other name	Paclitaxel
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The prescribed dose of TAXOL should be diluted in 500 mL of 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection. A concentration of 1.2 mg/mL should not be exceeded.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25 C).

Arm title	Placebo with Paclitaxel/Carboplatin
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Arm description:

Placebo + Active Chemotherapy Backbone The blinded therapy (Placebo) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Placebo: IV solution, IV, 0.9% sodium chloride or 5% dextrose, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemotherapy Backbone: Paclitaxel: IV solution, IV, 175 mg/m², 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses

Arm type	Placebo
Investigational medicinal product name	Placebo of Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 200 mg/vial

Investigational medicinal product name	Taxol (for IV infusion)
Investigational medicinal product code	
Other name	Paclitaxel
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The prescribed dose of TAXOL should be diluted in 500 mL of 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection. A concentration of 1.2 mg/mL should not be exceeded.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	PARAPLATIN

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25 C).

Investigational medicinal product name	Placebo of Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Injection, 50 mg/vial

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline period for this study covers only subjects that have been treated with blinded therapy.

Number of subjects in period 2^[2]	Ipilimumab with Paclitaxel/Carboplatin	Placebo with Paclitaxel/Carboplatin
Started	388	361
Completed	1	2
Not completed	387	359
Adverse event, serious fatal	11	3
Poor/Non-Compliance	1	2
Not Reported	-	2
Physician and subject decision	1	3
Maximum Clinical Benefit	2	4
Subject refused participation	1	-
Subject hospitalized	1	-
Study Drug Toxicity	87	14
Worsening of general condition	-	1
Consent withdrawn by subject	20	7
Progressive Disease	223	305
Subject No Longer Met Study Criteria	1	-
Adverse Event Unrelated to Study Drug	36	14
PI decision to discontinue	-	1
Subject started radiotherapy	1	-
Administrative Reason by Sponsor	1	3
Investigator assessment	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial as out of 1289 subjects who were enrolled only 956 were

randomised and 948 were treated. Reasons for no treatment after randomisation include: 4 no longer met study criteria, 2 adverse events unrelated to study drug, 1 participant request to discontinue, and 1 other .

Baseline characteristics

Reporting groups

Reporting group title	Treated with Blinded Therapy
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Reporting group description: -

Reporting group values	Treated with Blinded Therapy	Total	
Number of subjects	749	749	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	380	380	
From 65-84 years	368	368	
85 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	63.7		
standard deviation	± 8.47	-	
Sex: Female, Male Units: Subjects			
Female	114	114	
Male	635	635	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	214	214	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	6	6	
White	519	519	
More than one race	0	0	
Unknown or Not Reported	9	9	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG Performance Status is a 6-item scale used to assess disease progression, daily functioning, appropriate treatment, and prognosis. Performance status is scored on a scale ranging from 0-5, with (best score) 0=fully active and able to carry on all pre-disease performance without restriction and (worst score) 5=death.			
Units: Subjects			
baseline ECOG = 0	259	259	
baseline ECOG = 1	485	485	
baseline ECOG = 2	4	4	
baseline ECOG = 3	1	1	
Disease Stage at Study Entry			

Non-Small Cell Lung Cancer is categorized in 4 Stages (I-IV). I: Cancer located only in lungs and has not spread to any lymph nodes. II: Cancer in the lung and nearby lymph nodes. III: Cancer in the lung and lymph nodes in the middle of the chest. Stage III has two subtypes, IIIA (cancer has spread only to lymph nodes on the same side of the chest where the cancer started) and IIIB (cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone). IV: Cancer has spread to both lungs, to fluid in the area around the lungs, or to another part of the body.

Units: Subjects			
Stage IV	700	700	
Recurrent	49	49	

End points

End points reporting groups

Reporting group title	Ipilimumab with Paclitaxel/Carboplatin
Reporting group description:	
Ipilimumab + Active Chemotherapy Backbone The blinded therapy (Ipilimumab) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Ipilimumab: IV solution, intravenous (IV), 10 mg/kg, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemo Backbone: Paclitaxel: IV solution, IV, 175 mg/m ² , 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses	
Reporting group title	Placebo with Paclitaxel/Carboplatin
Reporting group description:	
Placebo + Active Chemotherapy Backbone The blinded therapy (Placebo) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Placebo: IV solution, IV, 0.9% sodium chloride or 5% dextrose, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemotherapy Backbone: Paclitaxel: IV solution, IV, 175 mg/m ² , 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses	
Reporting group title	Ipilimumab with Paclitaxel/Carboplatin
Reporting group description:	
Ipilimumab + Active Chemotherapy Backbone The blinded therapy (Ipilimumab) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Ipilimumab: IV solution, intravenous (IV), 10 mg/kg, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemo Backbone: Paclitaxel: IV solution, IV, 175 mg/m ² , 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses	
Reporting group title	Placebo with Paclitaxel/Carboplatin
Reporting group description:	
Placebo + Active Chemotherapy Backbone The blinded therapy (Placebo) started at the 3rd dose of active chemotherapy backbone (Paclitaxel/Carboplatin). Placebo: IV solution, IV, 0.9% sodium chloride or 5% dextrose, 90 minute infusion, Once every 3 weeks for 4 doses and then every 12 weeks until disease progression (for a maximum treatment period of 3 years from the first dose) Active Chemotherapy Backbone: Paclitaxel: IV solution, IV, 175 mg/m ² , 3 hour infusion, Once every 3 weeks for 6 doses Carboplatin: IV solution, IV, Area Under the Curve (AUC) = 6, 30 minute infusion, Once every 3 weeks for 6 doses	

Primary: Overall Survival (OS) in Participants who received at least one dose of blinded study therapy at Primary Endpoint

End point title	Overall Survival (OS) in Participants who received at least one dose of blinded study therapy at Primary Endpoint
End point description:	
Overall Survival (OS) was defined as the time from randomization to the date of death. Participants that had not died were censored at last known date alive. Median OS time was calculated using Kaplan-Meier Estimates. Interim analysis for the Primary Endpoint occurred when the following 2 conditions were both met: (1) 518 deaths were observed in randomized participants treated with at least one dose of blinded study therapy and (2) 705 deaths were observed in all randomized participants.	
End point type	Primary
End point timeframe:	
Randomization until 518 deaths, up to June 2015 (approximately 48 months post study start)	

End point values	Ipilimumab with Paclitaxel/Carboplatin	Placebo with Paclitaxel/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	361		
Units: months				
median (confidence interval 95%)	13.37 (11.76 to 14.78)	12.42 (11.60 to 13.63)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Hazard ratio = Ipilimumab with Paclitaxel/Carboplatin over Placebo with Paclitaxel/Carboplatin	
Comparison groups	Ipilimumab with Paclitaxel/Carboplatin v Placebo with Paclitaxel/Carboplatin
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2517
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.907
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.767
upper limit	1.072

Secondary: Overall Survival (OS) in all Randomized Participants at Primary Endpoint

End point title	Overall Survival (OS) in all Randomized Participants at Primary Endpoint
End point description:	
Overall Survival (OS) was defined as the time from randomization to the date of death. Participants that had not died were censored at last known date alive. Median OS time was calculated using Kaplan-Meier Estimates. Interim analysis for the Primary Endpoint occurred when the following 2 conditions were both met: (1) 518 deaths were observed in randomized participants treated with at least one dose of blinded study therapy and (2) 705 deaths were observed in all randomized participants.	
End point type	Secondary
End point timeframe:	
Randomization until 705 deaths, up to June 2015 (approximately 48 months post study start)	

End point values	Ipilimumab with Paclitaxel/Carboplatin	Placebo with Paclitaxel/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	479	477		
Units: months				
median (confidence interval 95%)	10.94 (9.56 to 12.02)	10.74 (9.66 to 11.73)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Hazard ratio = Ipilimumab with Paclitaxel/Carboplatin over Placebo with Paclitaxel/Carboplatin	
Comparison groups	Ipilimumab with Paclitaxel/Carboplatin v Placebo with Paclitaxel/Carboplatin
Number of subjects included in analysis	956
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2421 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.792
upper limit	1.061

Notes:

[1] - p-value based on stratified 2-sided log-rank test

Secondary: Median Number of Months with Progression Free Survival (PFS) per mWHO in participants who have received at least one dose of blinded study therapy at Primary Endpoint

End point title	Median Number of Months with Progression Free Survival (PFS) per mWHO in participants who have received at least one dose of blinded study therapy at Primary Endpoint
End point description:	
Progression-free survival (PFS) is defined as the time between the date of randomization and the date of tumor progression per Modified World Health Organization (mWHO) criteria or death, whichever occurs first. A participant who died without reported progression per mWHO criteria were considered to have progressed on the date of death. For participants who remain alive and have not progressed, PFS was censored on the date of last evaluable tumor assessment. For participants who remain alive and have no recorded post-baseline tumor assessment, PFS was censored on the day of randomization.	
End point type	Secondary
End point timeframe:	
Randomization until 518 deaths, up to June 2015 (approximately 48 months post study start)	

End point values	Ipilimumab with Paclitaxel/Carboplatin	Placebo with Paclitaxel/Carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	361		
Units: months				
median (confidence interval 95%)	5.55 (5.36 to 5.85)	5.59 (5.52 to 5.72)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Hazard ratio = Ipilimumab with Paclitaxel/Carboplatin over Placebo with Paclitaxel/Carboplatin	
Comparison groups	Ipilimumab with Paclitaxel/Carboplatin v Placebo with Paclitaxel/Carboplatin
Number of subjects included in analysis	749
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0678
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.869
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.749
upper limit	1.009

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study therapy and within 90 days of the last dose

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Ipilimumab + Paclitaxel/Carboplatin
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Reporting group description:

Subjects received Ipilimumab 10 milligram per kilogram (mg/kg) intravenous (IV) 90 minute infusion once every 3 weeks (q 3 weeks) for up to 4 doses starting at Cycle 3/week 7, then every 12 weeks for a maximum treatment period of 3 years from the first dose; Paclitaxel 175 milligram per meter square (mg/m²) IV q 3 weeks for up to 6 doses starting at randomization; Carboplatin area under the curve (AUC) equal to (=) 6 IV q 3 weeks for up to 6 doses starting at randomization.

Reporting group title	Placebo + Paclitaxel/ Carboplatin
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Reporting group description:

Subjects received Placebo IV q 3 weeks for up to 4 doses starting at Cycle 3/week 7 then q 12 weeks for a maximum treatment period of 3 years from the first dose; Paclitaxel 175 mg/m² IV q 3 weeks for up to 6 doses starting at randomization; Carboplatin AUC = 6 IV q 3 weeks for up to 6 doses starting at randomization.

Serious adverse events	Ipilimumab + Paclitaxel/Carboplatin	Placebo + Paclitaxel/ Carboplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	300 / 475 (63.16%)	235 / 473 (49.68%)	
number of deaths (all causes)	359	371	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung cancer metastatic			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colorectal cancer			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 475 (0.63%)	8 / 473 (1.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 8	
Malignant neoplasm progression			
subjects affected / exposed	35 / 475 (7.37%)	37 / 473 (7.82%)	
occurrences causally related to treatment / all	0 / 37	0 / 38	
deaths causally related to treatment / all	0 / 35	0 / 36	
Metastases to central nervous system			
subjects affected / exposed	3 / 475 (0.63%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma metastatic			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Neoplasm progression			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small cell lung cancer			
subjects affected / exposed	2 / 475 (0.42%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Tumour perforation			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour compression			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 475 (0.42%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis superficial			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 475 (1.05%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	5 / 6	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 475 (0.21%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	10 / 475 (2.11%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 10	0 / 7	
Device occlusion			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	4 / 475 (0.84%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 4	
Extravasation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 475 (1.47%)	10 / 473 (2.11%)	
occurrences causally related to treatment / all	2 / 8	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	8 / 475 (1.68%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	4 / 8	5 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	1 / 3	1 / 1	
Pain			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Performance status decreased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	21 / 475 (4.42%)	14 / 473 (2.96%)	
occurrences causally related to treatment / all	8 / 24	2 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 475 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial disorder			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 475 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 475 (0.84%)	8 / 473 (1.69%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchostenosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	9 / 475 (1.89%)	10 / 473 (2.11%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 2	
Dyspnoea			
subjects affected / exposed	17 / 475 (3.58%)	16 / 473 (3.38%)	
occurrences causally related to treatment / all	2 / 17	2 / 22	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hiccups			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 475 (0.42%)	6 / 473 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	4 / 475 (0.84%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	4 / 475 (0.84%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	1 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery stenosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	11 / 475 (2.32%)	10 / 473 (2.11%)	
occurrences causally related to treatment / all	2 / 11	2 / 11	
deaths causally related to treatment / all	0 / 1	1 / 2	
Pulmonary haemorrhage			
subjects affected / exposed	4 / 475 (0.84%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 2	
Pulmonary infarction			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 475 (1.26%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 2	
Tachypnoea			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (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	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	5 / 475 (1.05%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
C-Reactive protein increased			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 475 (0.21%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count decreased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asbestosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain herniation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fall			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart injury			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (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	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Overdose			
subjects affected / exposed	1 / 475 (0.21%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxicity to various agents			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 475 (1.05%)	8 / 473 (1.69%)	
occurrences causally related to treatment / all	1 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (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	2 / 475 (0.42%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 2	
Atrial flutter			

subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 475 (0.21%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-Respiratory arrest			
subjects affected / exposed	5 / 475 (1.05%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	1 / 5	0 / 2	
Cardiogenic shock			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 475 (0.63%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Migraine			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord paralysis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	21 / 475 (4.42%)	10 / 473 (2.11%)	
occurrences causally related to treatment / all	19 / 23	8 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	20 / 475 (4.21%)	11 / 473 (2.33%)	
occurrences causally related to treatment / all	23 / 23	9 / 11	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bone marrow failure			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 475 (0.63%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	16 / 475 (3.37%)	9 / 473 (1.90%)	
occurrences causally related to treatment / all	16 / 17	12 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	7 / 475 (1.47%)	11 / 473 (2.33%)	
occurrences causally related to treatment / all	7 / 7	10 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Pupils unequal			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	14 / 475 (2.95%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	17 / 18	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	37 / 475 (7.79%)	10 / 473 (2.11%)	
occurrences causally related to treatment / all	42 / 46	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 475 (0.00%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	6 / 475 (1.26%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	3 / 6	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced liver injury			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative rash			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perivascular dermatitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	6 / 475 (1.26%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 475 (0.63%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 475 (0.84%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			

subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothalamo-Pituitary disorder			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 475 (0.00%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 475 (0.63%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 475 (0.21%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 475 (0.63%)	4 / 473 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 475 (0.63%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	9 / 475 (1.89%)	5 / 473 (1.06%)	
occurrences causally related to treatment / all	1 / 11	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	3 / 475 (0.63%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 475 (0.21%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Necrotising fasciitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (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	37 / 475 (7.79%)	34 / 473 (7.19%)	
occurrences causally related to treatment / all	11 / 41	7 / 45	
deaths causally related to treatment / all	1 / 3	1 / 6	
Pneumonia bacterial			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	7 / 475 (1.47%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	2 / 8	3 / 8	
deaths causally related to treatment / all	0 / 0	2 / 2	
Staphylococcal infection			

subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 475 (0.63%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 475 (0.21%)	3 / 473 (0.63%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cachexia			

subjects affected / exposed	2 / 475 (0.42%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	8 / 475 (1.68%)	7 / 473 (1.48%)	
occurrences causally related to treatment / all	4 / 9	3 / 7	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	1 / 475 (0.21%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 475 (0.63%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 475 (0.42%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	1 / 475 (0.21%)	2 / 473 (0.42%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 475 (0.00%)	1 / 473 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 475 (0.63%)	0 / 473 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab + Paclitaxel/Carboplatin	Placebo + Paclitaxel/ Carboplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	437 / 475 (92.00%)	428 / 473 (90.49%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	37 / 475 (7.79%)	26 / 473 (5.50%)	
occurrences (all)	45	29	
Neutrophil count decreased			
subjects affected / exposed	31 / 475 (6.53%)	31 / 473 (6.55%)	
occurrences (all)	55	66	
Aspartate aminotransferase increased			
subjects affected / exposed	34 / 475 (7.16%)	20 / 473 (4.23%)	
occurrences (all)	45	24	
Platelet count decreased			

subjects affected / exposed occurrences (all)	47 / 475 (9.89%) 70	32 / 473 (6.77%) 52	
Haemoglobin decreased subjects affected / exposed occurrences (all)	38 / 475 (8.00%) 55	30 / 473 (6.34%) 51	
White blood cell count decreased subjects affected / exposed occurrences (all)	25 / 475 (5.26%) 43	31 / 473 (6.55%) 80	
Weight decreased subjects affected / exposed occurrences (all)	44 / 475 (9.26%) 45	27 / 473 (5.71%) 29	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	35 / 475 (7.37%) 40	58 / 473 (12.26%) 63	
Headache subjects affected / exposed occurrences (all)	30 / 475 (6.32%) 30	22 / 473 (4.65%) 24	
Neuropathy peripheral subjects affected / exposed occurrences (all)	61 / 475 (12.84%) 73	57 / 473 (12.05%) 65	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	71 / 475 (14.95%) 79	98 / 473 (20.72%) 111	
Paraesthesia subjects affected / exposed occurrences (all)	20 / 475 (4.21%) 23	28 / 473 (5.92%) 31	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	171 / 475 (36.00%) 232	157 / 473 (33.19%) 205	
Neutropenia subjects affected / exposed occurrences (all)	107 / 475 (22.53%) 207	102 / 473 (21.56%) 214	
Leukopenia			

subjects affected / exposed	44 / 475 (9.26%)	54 / 473 (11.42%)	
occurrences (all)	106	122	
Thrombocytopenia			
subjects affected / exposed	77 / 475 (16.21%)	70 / 473 (14.80%)	
occurrences (all)	123	102	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	80 / 475 (16.84%)	55 / 473 (11.63%)	
occurrences (all)	112	70	
Chest pain			
subjects affected / exposed	26 / 475 (5.47%)	45 / 473 (9.51%)	
occurrences (all)	30	49	
Oedema peripheral			
subjects affected / exposed	25 / 475 (5.26%)	31 / 473 (6.55%)	
occurrences (all)	28	35	
Fatigue			
subjects affected / exposed	142 / 475 (29.89%)	140 / 473 (29.60%)	
occurrences (all)	185	190	
Mucosal inflammation			
subjects affected / exposed	10 / 475 (2.11%)	27 / 473 (5.71%)	
occurrences (all)	12	32	
Pyrexia			
subjects affected / exposed	91 / 475 (19.16%)	70 / 473 (14.80%)	
occurrences (all)	144	94	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 475 (5.26%)	26 / 473 (5.50%)	
occurrences (all)	30	29	
Constipation			
subjects affected / exposed	117 / 475 (24.63%)	103 / 473 (21.78%)	
occurrences (all)	147	137	
Abdominal pain upper			
subjects affected / exposed	24 / 475 (5.05%)	23 / 473 (4.86%)	
occurrences (all)	26	26	
Diarrhoea			

subjects affected / exposed occurrences (all)	145 / 475 (30.53%) 235	89 / 473 (18.82%) 124	
Nausea subjects affected / exposed occurrences (all)	152 / 475 (32.00%) 254	151 / 473 (31.92%) 238	
Vomiting subjects affected / exposed occurrences (all)	89 / 475 (18.74%) 134	68 / 473 (14.38%) 91	
Stomatitis subjects affected / exposed occurrences (all)	27 / 475 (5.68%) 33	24 / 473 (5.07%) 29	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	94 / 475 (19.79%) 111	97 / 473 (20.51%) 114	
Haemoptysis subjects affected / exposed occurrences (all)	34 / 475 (7.16%) 38	41 / 473 (8.67%) 46	
Cough subjects affected / exposed occurrences (all)	82 / 475 (17.26%) 92	85 / 473 (17.97%) 104	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	181 / 475 (38.11%) 188	175 / 473 (37.00%) 177	
Pruritus subjects affected / exposed occurrences (all)	78 / 475 (16.42%) 92	27 / 473 (5.71%) 33	
Rash subjects affected / exposed occurrences (all)	87 / 475 (18.32%) 115	45 / 473 (9.51%) 55	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	61 / 475 (12.84%) 65	49 / 473 (10.36%) 51	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	77 / 475 (16.21%)	58 / 473 (12.26%)	
occurrences (all)	107	95	
Musculoskeletal pain			
subjects affected / exposed	20 / 475 (4.21%)	24 / 473 (5.07%)	
occurrences (all)	24	28	
Bone pain			
subjects affected / exposed	32 / 475 (6.74%)	26 / 473 (5.50%)	
occurrences (all)	49	43	
Back pain			
subjects affected / exposed	34 / 475 (7.16%)	38 / 473 (8.03%)	
occurrences (all)	39	42	
Myalgia			
subjects affected / exposed	66 / 475 (13.89%)	61 / 473 (12.90%)	
occurrences (all)	107	105	
Pain in extremity			
subjects affected / exposed	43 / 475 (9.05%)	43 / 473 (9.09%)	
occurrences (all)	56	54	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	145 / 475 (30.53%)	116 / 473 (24.52%)	
occurrences (all)	189	154	
Dehydration			
subjects affected / exposed	24 / 475 (5.05%)	7 / 473 (1.48%)	
occurrences (all)	27	8	
Hypomagnesaemia			
subjects affected / exposed	27 / 475 (5.68%)	15 / 473 (3.17%)	
occurrences (all)	33	15	
Hypokalaemia			
subjects affected / exposed	51 / 475 (10.74%)	31 / 473 (6.55%)	
occurrences (all)	68	36	
Hyponatraemia			
subjects affected / exposed	37 / 475 (7.79%)	11 / 473 (2.33%)	
occurrences (all)	46	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2010	Grammatical and typographical errors corrected. Deleted optional re-induction sections, changed patient population to squamous only changed irRC to exploratory and patient management using mWHO criteria.
25 April 2011	Adds pre-dose TSH testing to the protocol in order to ensure consistency with the FDA approved label for ipilimumab.
15 July 2011	Moves randomization to Day 1 and removes the Lead-in Phase. Sample size changed to 920 randomized. CA184041 efficacy results updated. Added in secondary objective for OS in all blinded therapy treated subjects and moved outcomes objective to exploratory.
21 August 2011	Changes placebo to IMP.
04 October 2012	Updates to WOCBP language, informed consent and follow up after study treatment discontinuation, imAR and irAE language, inclusion and exclusion criteria modifications.
25 April 2014	Updates study endpoints, adds 3-year dosing limit, updates the Global Medical Monitor, and makes other miscellaneous clarifications and corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported