Clinical trial results:
Trial in Extensive-Disease Small Cell Lung Cancer (ED-SCLC) Subjects Comparing Ipilimumab Plus Etoposide and Platinum Therapy to Etoposide and Platinum Therapy Alone

Summary

EudraCT number	2011-000850-48
Trial protocol	BE FI IT SE DE CZ AT GB PT HU ES NL IE FR
Global end of trial date	17 May 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2018
First version publication date	02 June 2018

Trial information

Trial identification

Sponsor protocol code	CA184-156

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01450761
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	BMS Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 May 2017
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to determine whether the addition of Ipilimumab to Etoposide and Platinum therapy will extend the lives of patients with Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) more than Etoposide and Platinum therapy alone.

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	31 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	China: 113
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Germany: 120
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 104
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 96

Country: Number of subjects enrolled	Korea, Republic of: 72
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Poland: 109
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Russian Federation: 188
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 274
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Switzerland: 8
Worldwide total number of subjects	1414
EEA total number of subjects	586

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)	841
From 65 to 84 years	572
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 1414 enrolled participants, 566 participants each were randomized to Ipilimumab and placebo arms. The remaining 282 participants were not randomized, the most frequently reported reason being that the participants no longer met study criteria.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide
Started	566	566
Completed	562	561
Not completed	4	5
Consent withdrawn by subject	2	-
Disease progression	-	2
Adverse event unrelated to study drug	1	-
Unspecified	-	1
Subject no longer meets study criteria	1	2

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

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

Dosage and administration details:

ipilimumab (10 mg/kg IV) every 3 weeks

Arm title	Placebo and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

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

Dosage and administration details:

Placebo administered by IV every 3 weeks

Number of subjects in period 2	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide
Started	562	561
Completed	478	476
Not completed	84	85
Adverse event, serious fatal	3	3
Consent withdrawn by subject	14	12
Disease progression	33	32
Study drug toxicity	6	10
Adverse event unrelated to study drug	21	19
No longer meets study criteria	3	7
Unspecified	2	2
Lost to follow-up	2	-

Period 3

Period 3 title	Treatment with blinded study therapy
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

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

Dosage and administration details:

ipilimumab (10 mg/kg IV) every 12 weeks

Arm title	Placebo and platinum/etoposide

Arm description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

Arm type	Placebo

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

Dosage and administration details:

Placebo administered by IV every 12 weeks

Notes:

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

Justification: Baseline statistics were calculated for subjects that received at least one dose of blinded study therapy.

Number of subjects in period 3[2]	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide
Started	478	476
Completed	0	0
Not completed	478	476
Subject request to discontinue treatment	15	8
Disease progression	318	415
Other/Unspecified	5	4
Maximum clinical benefit	1	2
No longer meets study criteria	1	2
Consent withdrawn by subject	12	5
Study drug toxicity	87	9
Death	5	6
Not reported	2	2
Adverse event unrelated to study drug	27	19
Lost to follow-up	2	1
Poor/non-compliance	1	-
Administrative reason by sponsor	2	3

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: Of the 1414 enrolled subjects, 566 participants each were randomized to Ipilimumab and placebo arms. The remaining 282 subjects were not randomized, the most frequently reported reason being that the subjects no longer met study criteria.

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab and platinum/etoposide
Reporting group description:	
During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.	
Reporting group title	Placebo and platinum/etoposide
Reporting group description:	
During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.	

Reporting group values	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide	Total
Number of subjects	478	476	954
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	299	277	576
From 65-84 years	178	199	377
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	61.3	62.6	
standard deviation	± 8.90	± 8.61	-
Sex: Female, Male Units: Subjects			
Female	161	150	311
Male	317	326	643

End points

End points reporting groups

Reporting group title	Ipilimumab and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

Reporting group title	Placebo and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

Reporting group title	Ipilimumab and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

Reporting group title	Placebo and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

Reporting group title	Ipilimumab and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with ipilimumab (10 mg/kg IV) every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, ipilimumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

Reporting group title	Placebo and platinum/etoposide

Reporting group description:

During the lead-in chemotherapy (induction) phase, participants received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles, with placebo every 3 weeks for cycles 3-6. During the treatment with blinded study therapy phase, placebo was administered every 12 weeks, beginning 9-12 weeks after the last induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

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

End point title	Overall Survival (OS) in participants who received at least one dose of blinded study therapy

End point description:

Overall Survival was defined as the time from the date of randomization until the date of death from any cause. For participants without documentation of death, OS was censored on the last date the participant was known to be alive.

End point type	Primary

End point timeframe:

Randomization until date of death, up to March 2015, approximately 38 months

End point values	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	10.97 (10.45 to 11.33)	10.94 (10.02 to 11.50)		

Statistical analyses

Statistical analysis title	Comparison of Overall Survival

Statistical analysis description:

Comparison of Overall Survival Between Treatment Groups
in Randomized Subjects who Received At Least One Dose of Blinded Study Therapy

Comparison groups	Ipilimumab and platinum/etoposide v Placebo and platinum/etoposide
Number of subjects included in analysis	954
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3775
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.936
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.807
upper limit	1.085

Secondary: Overall Survival in all Randomized Participants

End point title	Overall Survival in all Randomized Participants

End point description:

Overall Survival was defined as the time from the date of randomization until the date of death from any cause. For participants without documentation of death, OS was censored on the last date the participant was known to be alive.

End point type	Secondary

End point timeframe:

From randomization until date of death, up to March 2015, approximately 38 months

End point values	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	566	566		
Units: months				
median (confidence interval 95%)	10.22 (9.59 to 10.81)	9.95 (9.33 to 10.94)		

Statistical analyses

Statistical analysis title	Comparison of Overall Survival
Statistical analysis description:	
Comparison of Overall Survival Between Treatment Groups in All Randomized Subjects	
Comparison groups	Ipilimumab and platinum/etoposide v Placebo and platinum/etoposide
Number of subjects included in analysis	1132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5678
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.961
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.838
upper limit	1.102

Secondary: Progression Free Survival (PFS) time in participants who have received at least one dose of blinded study therapy

End point title	Progression Free Survival (PFS) time in participants who have received at least one dose of blinded study therapy
End point description:	
Progression-Free Survival was defined as the time from the date of randomization to the date of progression per modified World Health Organization (mWHO) criteria or death, whichever occured first. A participant who died without reported progression per mWHO criteria was considered progressed on the date of death. For those participants who remained alive and did not progress, PFS was censored on the date of last evaluable tumor assessment. For those participants who remained alive and had no recorded post-baseline tumor assessment, PFS was censored on the day of randomization.	
End point type	Secondary
End point timeframe:	
From randomization until disease progression, up to March 2015, approximately 38 months	

End point values	Ipilimumab and platinum/etoposide	Placebo and platinum/etoposide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	4.63 (4.50 to 4.99)	4.44 (4.37 to 4.63)		

Statistical analyses

Statistical analysis title	Comparison of Progression-Free Survival
Statistical analysis description:	
Comparison of Progression-Free Survival Between Treatment Groups in Randomized Subjects who Received At Least one Dose of Blinded Study Therapy	
Comparison groups	Ipilimumab and platinum/etoposide v Placebo and platinum/etoposide
Number of subjects included in analysis	954
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0161
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	0.971

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to last dose plus 90 days, through study completion (May 2017)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	10 MG/KG IPILIMUMAB + PLATINUM/ETOPOSIDE

Reporting group description:

Subjects received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles with Ipilimumab 10 milligram per kilogram (mg/kg) was administered intravenously (IV) every 3 weeks from cycles 3 - 6 of the induction phase . During the Maintenance phase ipilimiumab (10 mg/kg IV) was administered every 12 weeks, beginning 9-12 weeks after the last Induction dose, for a maximum treatment period of 3 years from the first dose of ipilimumab.

Reporting group title	PLACEBO + PLATINUM/ETOPOSIDE

Reporting group description:

Subjects received platinum/etoposide (investigator's choice of platinum) every 3 weeks for 4 cycles with placebo every 3 weeks from cycle 3-6 during the Induction phase. During the Maintenance phase placebo was administered every 12 weeks, beginning 9-12 weeks after the last Induction dose, for a maximum treatment period of 3 years from the first dose of placebo.

Serious adverse events	10 MG/KG IPILIMUMAB + PLATINUM/ETOPOSIDE	PLACEBO + PLATINUM/ETOPOSIDE	
Total subjects affected by serious adverse events			
subjects affected / exposed	316 / 562 (56.23%)	278 / 561 (49.55%)	
number of deaths (all causes)	91	118	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	36 / 562 (6.41%)	43 / 561 (7.66%)	
occurrences causally related to treatment / all	0 / 39	0 / 45	
deaths causally related to treatment / all	0 / 30	0 / 38	
Metastases to central nervous system			
subjects affected / exposed	3 / 562 (0.53%)	8 / 561 (1.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Metastases to meninges			
subjects affected / exposed	3 / 562 (0.53%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Small cell lung cancer			

subjects affected / exposed	9 / 562 (1.60%)	13 / 561 (2.32%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 8	0 / 12	
Tumour embolism			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	0 / 562 (0.00%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 562 (0.18%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Deep vein thrombosis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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	0 / 562 (0.00%)	7 / 561 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 562 (0.71%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	5 / 562 (0.89%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	4 / 562 (0.71%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Disease progression			
subjects affected / exposed	6 / 562 (1.07%)	9 / 561 (1.60%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 9	
Euthanasia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	4 / 562 (0.71%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	13 / 562 (2.31%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	3 / 16	1 / 5	
deaths causally related to treatment / all	0 / 3	1 / 2	
Influenza like illness			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 562 (0.18%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			

subjects affected / exposed	0 / 562 (0.00%)	6 / 561 (1.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 5	
Non-Cardiac chest pain			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 562 (0.18%)	4 / 561 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 562 (1.25%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	1 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 562 (0.18%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Apnoea			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	4 / 562 (0.71%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	13 / 562 (2.31%)	16 / 561 (2.85%)	
occurrences causally related to treatment / all	1 / 13	2 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	4 / 562 (0.71%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 562 (1.07%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 6	2 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 562 (0.36%)	4 / 561 (0.71%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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	9 / 562 (1.60%)	4 / 561 (0.71%)	
occurrences causally related to treatment / all	2 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 562 (0.18%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	9 / 562 (1.60%)	14 / 561 (2.50%)	
occurrences causally related to treatment / all	1 / 9	0 / 15	
deaths causally related to treatment / all	0 / 4	0 / 12	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 562 (0.18%)	4 / 561 (0.71%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	2 / 562 (0.36%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 562 (0.53%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Full blood count decreased			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
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	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contrast media reaction			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femoral neck fracture			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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 coronary syndrome			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 562 (0.71%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 562 (0.53%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardiac failure acute			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory distress			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 562 (0.18%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Cardiovascular insufficiency			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	3 / 562 (0.53%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	3 / 562 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 562 (0.18%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	2 / 562 (0.36%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	4 / 562 (0.71%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Iiird nerve disorder			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic neuropathy			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Memory impairment			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 562 (0.89%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord disorder			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 562 (0.71%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery occlusion			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Viith nerve paralysis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 562 (2.31%)	23 / 561 (4.10%)	
occurrences causally related to treatment / all	15 / 15	24 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	3 / 562 (0.53%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	3 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Eosinophilia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	25 / 562 (4.45%)	15 / 561 (2.67%)	
occurrences causally related to treatment / all	20 / 30	12 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocytopenia			

subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	15 / 562 (2.67%)	20 / 561 (3.57%)	
occurrences causally related to treatment / all	16 / 18	19 / 21	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancytopenia			
subjects affected / exposed	6 / 562 (1.07%)	7 / 561 (1.25%)	
occurrences causally related to treatment / all	7 / 7	5 / 8	
deaths causally related to treatment / all	1 / 1	1 / 1	
Thrombocytopenia			
subjects affected / exposed	4 / 562 (0.71%)	8 / 561 (1.43%)	
occurrences causally related to treatment / all	3 / 4	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	4 / 562 (0.71%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	24 / 562 (4.27%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	24 / 26	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	42 / 562 (7.47%)	13 / 561 (2.32%)	
occurrences causally related to treatment / all	45 / 48	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Duodenal perforation			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	12 / 562 (2.14%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	7 / 13	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 562 (1.78%)	9 / 561 (1.60%)	
occurrences causally related to treatment / all	5 / 12	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis sclerosing			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-Induced liver injury			
subjects affected / exposed	4 / 562 (0.71%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	3 / 562 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 562 (0.71%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	4 / 562 (0.71%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	3 / 562 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxoedema			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 562 (0.36%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 562 (0.00%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
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	3 / 562 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adrenalitis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	3 / 562 (0.53%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 562 (0.18%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 562 (0.36%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 562 (0.53%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 562 (0.18%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	0 / 562 (0.00%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	33 / 562 (5.87%)	16 / 561 (2.85%)	
occurrences causally related to treatment / all	7 / 34	5 / 16	
deaths causally related to treatment / all	1 / 8	0 / 5	
Pneumonia bacterial			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyomyositis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 562 (0.53%)	6 / 561 (1.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 562 (1.25%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	3 / 8	3 / 3	
deaths causally related to treatment / all	2 / 4	2 / 2	
Septic shock			

subjects affected / exposed	3 / 562 (0.53%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 1	1 / 2	
Staphylococcal infection			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
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	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 562 (0.36%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (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	3 / 562 (0.53%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	4 / 562 (0.71%)	5 / 561 (0.89%)	
occurrences causally related to treatment / all	3 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 562 (0.00%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	2 / 562 (0.36%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 562 (0.53%)	3 / 561 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 562 (0.18%)	1 / 561 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 562 (0.36%)	2 / 561 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	12 / 562 (2.14%)	13 / 561 (2.32%)	
occurrences causally related to treatment / all	3 / 16	3 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin d deficiency			
subjects affected / exposed	1 / 562 (0.18%)	0 / 561 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	10 MG/KG IPILIMUMAB + PLATINUM/ETOPOSIDE	PLACEBO + PLATINUM/ETOPOSIDE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	519 / 562 (92.35%)	520 / 561 (92.69%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	47 / 562 (8.36%)	26 / 561 (4.63%)	
occurrences (all)	65	31	
Aspartate aminotransferase increased			
subjects affected / exposed	44 / 562 (7.83%)	23 / 561 (4.10%)	
occurrences (all)	59	30	
Haemoglobin decreased			
subjects affected / exposed	38 / 562 (6.76%)	32 / 561 (5.70%)	
occurrences (all)	58	48	
Neutrophil count decreased			
subjects affected / exposed	87 / 562 (15.48%)	67 / 561 (11.94%)	
occurrences (all)	198	183	
Platelet count decreased			
subjects affected / exposed	39 / 562 (6.94%)	48 / 561 (8.56%)	
occurrences (all)	78	96	
Weight decreased			
subjects affected / exposed	46 / 562 (8.19%)	41 / 561 (7.31%)	
occurrences (all)	51	43	
White blood cell count decreased			

subjects affected / exposed	51 / 562 (9.07%)	51 / 561 (9.09%)	
occurrences (all)	126	148	
Nervous system disorders			
Dizziness			
subjects affected / exposed	52 / 562 (9.25%)	59 / 561 (10.52%)	
occurrences (all)	63	68	
Headache			
subjects affected / exposed	67 / 562 (11.92%)	56 / 561 (9.98%)	
occurrences (all)	87	60	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	171 / 562 (30.43%)	189 / 561 (33.69%)	
occurrences (all)	254	274	
Leukopenia			
subjects affected / exposed	73 / 562 (12.99%)	87 / 561 (15.51%)	
occurrences (all)	132	179	
Neutropenia			
subjects affected / exposed	234 / 562 (41.64%)	261 / 561 (46.52%)	
occurrences (all)	448	510	
Thrombocytopenia			
subjects affected / exposed	64 / 562 (11.39%)	84 / 561 (14.97%)	
occurrences (all)	109	134	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	55 / 562 (9.79%)	61 / 561 (10.87%)	
occurrences (all)	72	74	
Chest pain			
subjects affected / exposed	38 / 562 (6.76%)	45 / 561 (8.02%)	
occurrences (all)	38	55	
Fatigue			
subjects affected / exposed	180 / 562 (32.03%)	170 / 561 (30.30%)	
occurrences (all)	214	221	
Oedema peripheral			
subjects affected / exposed	38 / 562 (6.76%)	27 / 561 (4.81%)	
occurrences (all)	43	33	
Pyrexia			

subjects affected / exposed	79 / 562 (14.06%)	60 / 561 (10.70%)	
occurrences (all)	107	73	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	34 / 562 (6.05%)	33 / 561 (5.88%)	
occurrences (all)	41	36	
Abdominal pain upper			
subjects affected / exposed	30 / 562 (5.34%)	24 / 561 (4.28%)	
occurrences (all)	32	24	
Diarrhoea			
subjects affected / exposed	159 / 562 (28.29%)	116 / 561 (20.68%)	
occurrences (all)	226	150	
Constipation			
subjects affected / exposed	121 / 562 (21.53%)	99 / 561 (17.65%)	
occurrences (all)	163	135	
Nausea			
subjects affected / exposed	232 / 562 (41.28%)	209 / 561 (37.25%)	
occurrences (all)	440	357	
Vomiting			
subjects affected / exposed	115 / 562 (20.46%)	97 / 561 (17.29%)	
occurrences (all)	182	153	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	94 / 562 (16.73%)	81 / 561 (14.44%)	
occurrences (all)	109	100	
Hiccups			
subjects affected / exposed	26 / 562 (4.63%)	32 / 561 (5.70%)	
occurrences (all)	44	57	
Dyspnoea			
subjects affected / exposed	75 / 562 (13.35%)	83 / 561 (14.80%)	
occurrences (all)	90	98	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	199 / 562 (35.41%)	208 / 561 (37.08%)	
occurrences (all)	205	215	
Pruritus			

subjects affected / exposed	82 / 562 (14.59%)	15 / 561 (2.67%)	
occurrences (all)	93	17	
Rash			
subjects affected / exposed	121 / 562 (21.53%)	28 / 561 (4.99%)	
occurrences (all)	161	38	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	53 / 562 (9.43%)	62 / 561 (11.05%)	
occurrences (all)	64	70	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	37 / 562 (6.58%)	26 / 561 (4.63%)	
occurrences (all)	40	27	
Back pain			
subjects affected / exposed	43 / 562 (7.65%)	47 / 561 (8.38%)	
occurrences (all)	49	54	
Pain in extremity			
subjects affected / exposed	24 / 562 (4.27%)	36 / 561 (6.42%)	
occurrences (all)	24	38	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	169 / 562 (30.07%)	138 / 561 (24.60%)	
occurrences (all)	268	199	
Hypokalaemia			
subjects affected / exposed	47 / 562 (8.36%)	31 / 561 (5.53%)	
occurrences (all)	53	49	
Hyponatraemia			
subjects affected / exposed	53 / 562 (9.43%)	50 / 561 (8.91%)	
occurrences (all)	81	82	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2012	The original CA184156 protocol included an option for subjects who progressed > 6 months after completion of first-line chemotherapy to be re-induced with carboplatin/etoposide plus the same blinded study drug received in Induction, if the investigator felt the subjects were candidates for doublet chemotherapy, and if the subjects had not experienced any adverse events which required discontinuation of blinded study drug. This design was based on: • the current recommendation by NCCN, other international guidelines, and investigator feedback that re-induction with the original regimen may be appropriate in these cases; • preliminary data from melanoma suggesting activity and tolerability of ipilimumab in a re-induction setting; • the hypothesis that re-induction with chemotherapy might prime additional immune responses to the relapsed tumor, which could be augmented by ipilimumab. However, the EU member states involved in the review of the Clinical Trial Application (CTA) submitted through the Voluntary Harmonization Procedure (VHP), expressed concern regarding the blinded re-induction phase included in the protocol. Since there is no European consensus on a particular second line regimen, they further recommended that treatment of subjects after progression should be left open to the investigator/patient. To address this feedback, the protocol was modified to remove the Re-induction phase with ipilimumab. Thus, after discontinuation of ipilimumab in the Induction or Maintenance phases, subjects will now transition directly to Toxicity/Progression Follow Up. Second-line therapy (including potential re-induction with chemotherapy) is at discretion of the treating physician and will not include ipilimumab.
05 November 2012	The purpose of this amendment is: • To add/clarify information on the definition of Women of Childbearing Potential (WOCBP), as well as requirements for pregnancy testing and contraception • To add rationale and guidance for the collection of immune-mediated Adverse Reaction (imAR) data • Other minor changes to correct and/or clarify protocol requirements.
17 July 2014	The purpose of this amendment is to update the study Primary Endpoint, modify Secondary Endpoints, implement a dosing limit of ipilimumab in the study to 3 years, update the Global Medical Monitor, and incorporate other minor changes for consistency and clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported