



Clinical trial results:

An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN) Summary

EudraCT number	2013-003622-86
Trial protocol	IT GB ES DE NL FR
Global end of trial date	10 September 2021

Results information

Result version number	v1 (current)
This version publication date	22 September 2022
First version publication date	22 September 2022

Trial information

Trial identification

Sponsor protocol code	CA209-141
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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	19 October 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare OS of Nivolumab to Investigator's Choice in subjects who have tumor progression within 6 months of last dose of platinum therapy in the primary, recurrent, or metastatic setting.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2014
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: 4
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Japan: 27
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	United States: 139
Worldwide total number of subjects	361
EEA total number of subjects	130

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)	248
From 65 to 84 years	113
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

361 participants randomized and 347 treated

Period 1

Period 1 title	Pre-Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 3mg/kg

Arm description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

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

Dosage and administration details:

3mg/kg every 2 weeks

Arm title	Investigators Choice
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Arm description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m²) for the first dose followed that a doses of 250 mg/m² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30mg/m² weekly

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

Dosage and administration details:

400mg/m² once then 250mg/m² weekly

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

Dosage and administration details:

40mg/m² weekly, may be increased to 60mg/m² if tolerated

Number of subjects in period 1	Nivolumab 3mg/kg	Investigators Choice
Started	240	121
Completed	236	111
Not completed	4	10
Participant withdrew consent	-	6
Participant no longer meets study criteria	2	2
Disease Progression	1	-
Participant request to discontinue study treatment	1	2

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 3mg/kg

Arm description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

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

Dosage and administration details:

3mg/kg every 2 weeks

Arm title	Investigators Choice
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Arm description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m²) for the first dose followed that a doses of 250 mg/m² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a

dose of 30 or 40 mg/m² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30mg/m² weekly

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

Dosage and administration details:

40mg/m² weekly, may be increased to 60mg/m² if tolerated

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

Dosage and administration details:

400mg/m² once then 250mg/m² weekly

Number of subjects in period 2	Nivolumab 3mg/kg	Investigators Choice
Started	236	111
Completed	1	0
Not completed	235	111
Participant withdrew consent	5	1
Maximum Clinical Benefit	1	3
Adverse event unrelated to study drug	19	3
Participant no longer meets study criteria	1	-
Other reasons	1	-
Poor/Non-compliance	-	1
Study Drug Toxicity	14	10
Lost to follow-up	1	-
Disease Progression	185	87
Participant request to discontinue study treatment	8	6

Baseline characteristics

Reporting groups

Reporting group title	Nivolumab 3mg/kg
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Reporting group description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

Reporting group title	Investigators Choice
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Reporting group description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m²) for the first dose followed that a doses of 250 mg/m² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

Reporting group values	Nivolumab 3mg/kg	Investigators Choice	Total
Number of subjects	240	121	361
Age Categorical Units: Participants			
< 65 years	172	76	248
>=65 and <75 years	56	39	95
>=75 years	12	6	18
Age Continuous Units: years			
arithmetic mean	59.0	59.4	
standard deviation	± 10.15	± 11.00	-
Sex: Female, Male Units:			
Female	43	18	61
Male	197	103	300
Race/Ethnicity, Customized Units: Subjects			
White	196	104	300
Black or African American	10	3	13
Asian	29	14	43
Other	5	0	5
Race/Ethnicity, Customized Units: Subjects			
Hispanic/Latino	9	4	13
Not Hispanic/Latino	132	60	192
Not Reported	99	57	156

End points

End points reporting groups

Reporting group title	Nivolumab 3mg/kg
Reporting group description: Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.	
Reporting group title	Investigators Choice
Reporting group description: Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m ²) for the first dose followed that a doses of 250 mg/m ² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m ² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m ² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice	
Reporting group title	Nivolumab 3mg/kg
Reporting group description: Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.	
Reporting group title	Investigators Choice
Reporting group description: Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m ²) for the first dose followed that a doses of 250 mg/m ² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m ² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m ² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. Median OS time was calculated using Kaplan-Meier (KM) method.	
End point type	Primary
End point timeframe: From date of randomization to date of death (Up to approximately 18 months)	

End point values	Nivolumab 3mg/kg	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	121		
Units: Months				
median (confidence interval 95%)	7.49 (5.49 to 9.10)	5.06 (4.04 to 6.05)		

Statistical analyses

Statistical analysis title	OS HR
Statistical analysis description: Stratified Cox proportional hazard model. HR = Nivolumab over investigator's choice therapy (Cetuximab, Methotrexate, or Docetaxel)	
Comparison groups	Nivolumab 3mg/kg v Investigators Choice
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0101 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.92

Notes:

[1] - Log-rank Test stratified by prior treatment with cetuximab (yes, no) as entered into the Interactive Voice Response System (IVRS). For OS the boundary for statistical significance requires the p-value to be less than 0.0227.

Secondary: Investigator-Assessed Progression-Free Survival (PFS)

End point title	Investigator-Assessed Progression-Free Survival (PFS)
End point description: PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator (as per Response Evaluation Criteria In Solid Tumors (RECIST1.1)), or death due to any cause, whichever occurs first. Progressive Disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must demonstrate an absolute increase of at least 5mm. Participants who: <ul style="list-style-type: none"> - Die without a reported progression were considered to have progressed on the date of their death. - Did not progress or die were censored on the date of their last evaluable tumor assessment. - Without any on study tumor assessments and did not die were censored on their date of randomization. - Received subsequent systemic anti-cancer therapy prior to documented progression were censored at the date of the last tumor assessment prior to the initiation of the new therapy. 	
End point type	Secondary
End point timeframe: From date of randomization to date of disease progression or death, whichever occurs first (Up to approximately 87 months)	

End point values	Nivolumab 3mg/kg	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	121		
Units: Months				
median (confidence interval 95%)	2.04 (1.91 to 2.14)	2.33 (1.94 to 3.06)		

Statistical analyses

Statistical analysis title	PFS HR
Comparison groups	Nivolumab 3mg/kg v Investigators Choice
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.1

Secondary: Investigator-Assessed Objective Response Rate (ORR)

End point title	Investigator-Assessed Objective Response Rate (ORR)
End point description:	
ORR was defined as the percentage of randomized participants who achieved a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria as per investigator assessment. Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions.	
End point type	Secondary
End point timeframe:	
From date of randomization to date of disease progression or study drug is discontinued, whichever occurs first (Up to approximately 87 months)	

End point values	Nivolumab 3mg/kg	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	121		
Units: Percentage of Participants				
number (confidence interval 95%)	13.3 (9.3 to 18.3)	5.8 (2.4 to 11.6)		

Statistical analyses

Statistical analysis title	Difference in ORR
Comparison groups	Nivolumab 3mg/kg v Investigators Choice
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in ORR
Point estimate	7.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	13.6

Statistical analysis title	ORR Odds Ratio
Comparison groups	Nivolumab 3mg/kg v Investigators Choice
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	CMH Estimate of Common Odds Ratio
Point estimate	2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	5.82

Post-hoc: Overall Survival (OS) - Extended Collection

End point title	Overall Survival (OS) - Extended Collection
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End point description:

OS was defined as the time from randomization to the date of death from any cause. Participants were censored at the date they were last known to be alive and at the date of randomization if they were randomized but had no follow-up. Median OS time was calculated using Kaplan-Meier (KM) method. Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date. (Assessments were made until 10-Sep-2021)

End point type	Post-hoc
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End point timeframe:

From date of randomization to date of death (Up to approximately 87 months)

End point values	Nivolumab 3mg/kg	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	121		
Units: Months				
median (confidence interval 95%)	7.72 (5.68 to 8.74)	5.06 (4.04 to 6.24)		

Statistical analyses

Statistical analysis title	OS HR
Comparison groups	Nivolumab 3mg/kg v Investigators Choice
Number of subjects included in analysis	361
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.85

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were monitored from first dose to 100 days post last dose (Up to a max of approximately 70 months). Participants were assessed for Deaths (all causes) from their date of first treatment until study completion (up to approximately 87 months)

Adverse event reporting additional description:

Total number of subjects exposed represents all participants that received at least 1 dose of study medication. Of the randomized population that did not receive any study medication, 1 participant randomized in Nivolumab arm died and 9 participants randomized in Investigator's Choice arm died.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Investigators Choice
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Reporting group description:

Participants were provided a dose of Cetuximab intravenous (IV) solution for injection at a dose of 400 milligrams per square meter (mg/m²) for the first dose followed that a doses of 250 mg/m² weekly until disease progression OR a Methotrexate intravenous (IV) solution for Injection at a dose of 40 or 60 mg/m² weekly until disease progression OR a Docetaxel intravenous (IV) solution for Injection at a dose of 30 or 40 mg/m² weekly until disease progression. The decision regarding which treatment the participant received was at the discretion of the investigator and referred to as Investigators Choice

Reporting group title	Nivolumab 3mg/kg
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Reporting group description:

Nivolumab was provided at a dose of 3 milligrams/kilogram (mg/kg) using an intravenous (IV) solution for Injection every 2 weeks until disease progression.

Serious adverse events	Investigators Choice	Nivolumab 3mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 111 (78.38%)	165 / 236 (69.92%)	
number of deaths (all causes)	110	219	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cancer pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Head and neck cancer			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	55 / 111 (49.55%)	94 / 236 (39.83%)	
occurrences causally related to treatment / all	0 / 57	0 / 96	
deaths causally related to treatment / all	0 / 55	0 / 92	
Malignant pleural effusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	3 / 111 (2.70%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Tumour pain			
subjects affected / exposed	4 / 111 (3.60%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive urgency			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superior vena cava syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous thrombosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 111 (1.80%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Face oedema			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 111 (0.90%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	2 / 111 (1.80%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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	4 / 111 (3.60%)	5 / 236 (2.12%)	
occurrences causally related to treatment / all	2 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic granulomatosis with polyangiitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 111 (0.90%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cough			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 111 (1.80%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Emphysema			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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	2 / 111 (1.80%)	11 / 236 (4.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal oedema			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 111 (2.70%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	4 / 111 (3.60%)	10 / 236 (4.24%)	
occurrences causally related to treatment / all	0 / 4	1 / 10	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax spontaneous			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	3 / 111 (2.70%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 111 (0.90%)	5 / 236 (2.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stridor			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agoraphobia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Suicide attempt			

subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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			
Humerus fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 111 (0.90%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Procedural haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm ruptured			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	3 / 111 (2.70%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular disorder			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			

subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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 / 111 (1.80%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal dyscognitive seizures			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuralgia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Radiculopathy			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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			
Anaemia			
subjects affected / exposed	4 / 111 (3.60%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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	3 / 111 (2.70%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 111 (2.70%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
subjects affected / exposed	3 / 111 (2.70%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	

Gastric disorder			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland haemorrhage			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (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 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatomyositis			

subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin mass			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Secondary hypothyroidism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 111 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Localised infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 111 (2.70%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 111 (4.50%)	17 / 236 (7.20%)	
occurrences causally related to treatment / all	2 / 5	0 / 21	
deaths causally related to treatment / all	2 / 2	0 / 3	
Pneumonia bacterial			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purulent discharge			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
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	1 / 111 (0.90%)	5 / 236 (2.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	4 / 111 (3.60%)	6 / 236 (2.54%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	1 / 111 (0.90%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 111 (0.00%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular device infection			

subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 111 (1.80%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 111 (0.90%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 111 (0.90%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 111 (0.90%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperamylasaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 111 (0.90%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hyponatraemia			
subjects affected / exposed	1 / 111 (0.90%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 111 (0.00%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypophosphataemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Investigators Choice	Nivolumab 3mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 111 (97.30%)	210 / 236 (88.98%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	8 / 111 (7.21%)	13 / 236 (5.51%)	
occurrences (all)	10	16	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 5	16 / 236 (6.78%) 27	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	24 / 111 (21.62%) 32	27 / 236 (11.44%) 32	
Face oedema subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 10	11 / 236 (4.66%) 11	
Fatigue subjects affected / exposed occurrences (all)	37 / 111 (33.33%) 43	67 / 236 (28.39%) 73	
Mucosal inflammation subjects affected / exposed occurrences (all)	19 / 111 (17.12%) 24	11 / 236 (4.66%) 11	
Oedema peripheral subjects affected / exposed occurrences (all)	5 / 111 (4.50%) 6	19 / 236 (8.05%) 26	
Pyrexia subjects affected / exposed occurrences (all)	16 / 111 (14.41%) 23	37 / 236 (15.68%) 46	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	12 / 111 (10.81%) 14	32 / 236 (13.56%) 36	
Cough subjects affected / exposed occurrences (all)	13 / 111 (11.71%) 16	37 / 236 (15.68%) 47	
Epistaxis subjects affected / exposed occurrences (all)	11 / 111 (9.91%) 11	5 / 236 (2.12%) 7	
Pleural effusion subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 7	5 / 236 (2.12%) 5	
Productive cough			

subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2	14 / 236 (5.93%) 15	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 111 (8.11%)	9 / 236 (3.81%)	
occurrences (all)	9	9	
Insomnia			
subjects affected / exposed	7 / 111 (6.31%)	13 / 236 (5.51%)	
occurrences (all)	7	13	
Depression			
subjects affected / exposed	3 / 111 (2.70%)	12 / 236 (5.08%)	
occurrences (all)	3	13	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 111 (5.41%)	9 / 236 (3.81%)	
occurrences (all)	9	9	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 111 (5.41%)	14 / 236 (5.93%)	
occurrences (all)	9	17	
Lipase increased			
subjects affected / exposed	2 / 111 (1.80%)	13 / 236 (5.51%)	
occurrences (all)	2	20	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 111 (2.70%)	18 / 236 (7.63%)	
occurrences (all)	3	20	
Lymphocyte count decreased			
subjects affected / exposed	6 / 111 (5.41%)	8 / 236 (3.39%)	
occurrences (all)	7	20	
Weight decreased			
subjects affected / exposed	19 / 111 (17.12%)	35 / 236 (14.83%)	
occurrences (all)	22	38	
White blood cell count decreased			
subjects affected / exposed	8 / 111 (7.21%)	3 / 236 (1.27%)	
occurrences (all)	11	3	
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 7	7 / 236 (2.97%) 7	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 9	9 / 236 (3.81%) 12	
Neuropathy peripheral subjects affected / exposed occurrences (all)	9 / 111 (8.11%) 9	6 / 236 (2.54%) 6	
Headache subjects affected / exposed occurrences (all)	4 / 111 (3.60%) 5	23 / 236 (9.75%) 35	
Paraesthesia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	4 / 236 (1.69%) 4	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	42 / 111 (37.84%) 52	53 / 236 (22.46%) 63	
Neutropenia subjects affected / exposed occurrences (all)	9 / 111 (8.11%) 18	2 / 236 (0.85%) 2	
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 9	4 / 236 (1.69%) 5	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6	1 / 236 (0.42%) 1	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	27 / 111 (24.32%) 40	47 / 236 (19.92%) 65	
Constipation subjects affected / exposed occurrences (all)	21 / 111 (18.92%) 23	43 / 236 (18.22%) 48	

Dry mouth			
subjects affected / exposed	8 / 111 (7.21%)	8 / 236 (3.39%)	
occurrences (all)	8	9	
Dysphagia			
subjects affected / exposed	17 / 111 (15.32%)	30 / 236 (12.71%)	
occurrences (all)	18	32	
Dyspepsia			
subjects affected / exposed	6 / 111 (5.41%)	7 / 236 (2.97%)	
occurrences (all)	7	9	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 111 (7.21%)	3 / 236 (1.27%)	
occurrences (all)	8	3	
Stomatitis			
subjects affected / exposed	12 / 111 (10.81%)	14 / 236 (5.93%)	
occurrences (all)	18	16	
Nausea			
subjects affected / exposed	37 / 111 (33.33%)	55 / 236 (23.31%)	
occurrences (all)	53	75	
Vomiting			
subjects affected / exposed	16 / 111 (14.41%)	28 / 236 (11.86%)	
occurrences (all)	23	43	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	16 / 111 (14.41%)	4 / 236 (1.69%)	
occurrences (all)	16	4	
Erythema			
subjects affected / exposed	6 / 111 (5.41%)	3 / 236 (1.27%)	
occurrences (all)	6	3	
Dry skin			
subjects affected / exposed	12 / 111 (10.81%)	14 / 236 (5.93%)	
occurrences (all)	12	14	
Pruritus			
subjects affected / exposed	1 / 111 (0.90%)	23 / 236 (9.75%)	
occurrences (all)	1	24	
Rash			

subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 7	22 / 236 (9.32%) 29	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 10	21 / 236 (8.90%) 22	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	2 / 111 (1.80%) 2 0 / 111 (0.00%) 0 9 / 111 (8.11%) 9	19 / 236 (8.05%) 22 17 / 236 (7.20%) 17 17 / 236 (7.20%) 18	
Infections and infestations Oral candidiasis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	6 / 111 (5.41%) 6 6 / 111 (5.41%) 7 5 / 111 (4.50%) 5	11 / 236 (4.66%) 11 6 / 236 (2.54%) 8 16 / 236 (6.78%) 16	
Metabolism and nutrition disorders Hypercalcaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 8 21 / 111 (18.92%) 23 9 / 111 (8.11%) 9	17 / 236 (7.20%) 23 46 / 236 (19.49%) 54 16 / 236 (6.78%) 36	

Hypoalbuminaemia			
subjects affected / exposed	4 / 111 (3.60%)	12 / 236 (5.08%)	
occurrences (all)	4	16	
Hypokalaemia			
subjects affected / exposed	7 / 111 (6.31%)	11 / 236 (4.66%)	
occurrences (all)	9	12	
Hyponatraemia			
subjects affected / exposed	15 / 111 (13.51%)	25 / 236 (10.59%)	
occurrences (all)	19	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2014	Update to investigational product description
30 January 2015	Update to Endpoints
09 June 2015	Update to OS interim analysis trigger
11 February 2016	Update to Study Design
03 November 2016	Update to the treatment management algorithms and study treatment dose options

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported