Clinical trial results:
An Open-Label, Randomized, Phase 3 Trial of Nivolumab versus Investigator Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer

Summary

EudraCT number	2012-004502-93
Trial protocol	ES DE BE AT GB SE FI CZ HU IT FR NL RO PL GR
Global end of trial date	27 May 2022

Results information

Result version number	v1 (current)
This version publication date	22 February 2023
First version publication date	22 February 2023

Trial information

Trial identification

Sponsor protocol code	CA209-026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02041533
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, Bristol-Myers Squibb International, 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	25 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the PFS, based on IRRC assessment, of nivolumab monotherapy with investigator choice chemotherapy in subjects with stage IV or recurrent NSCLC with strongly PD-L1+ tumor expression.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study subjects were the most important consideration and prevailed over the interests of science and society.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 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: 9
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Czechia: 18
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 7
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Netherlands: 29
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Spain: 35

Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Switzerland: 16
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 175
Worldwide total number of subjects	541
EEA total number of subjects	233

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)	281
From 65 to 84 years	256
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

541 participants were randomized, 530 participants were treated. Participants in the Investigator Choice Arm who progressed on or after chemotherapy could be eligible to receive optional crossover nivolumab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab

Arm description:

Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity

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:

Nivolumab (3 mg/kg) as an IV infusion, every 2 weeks until disease progression or unacceptable toxicity

Arm title	Investigator Choice of Chemotherapy

Arm description:

Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). Participants who progressed on or after chemotherapy could be eligible to receive optional crossover nivolumab 3 mg/kg is administered every 2 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure.

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1250 mg/m2) as a 30-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin (75 mg/m2) as a 30 to 120-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1000 mg/m2) as a 30-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed (500 mg/m2) as a 10-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Paclitaxel (200 mg/m2) as a 180-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Carboplatin (AUC 6) as a 30 to 60-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Carboplatin (AUC 5) as a 30 to 60-minute IV infusion for up to 6-cycles

Number of subjects in period 1	Nivolumab	Investigator Choice of Chemotherapy
Started	271	270
Completed	267	263
Not completed	4	7
Participant no Longer Meets Study Criteria	3	1
Participant Withdrew Consent	-	5
Disease Progression	1	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab

Arm description:

Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity

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:

Nivolumab (3 mg/kg) as an IV infusion, every 2 weeks until disease progression or unacceptable toxicity

Arm title	Investigator Choice of Chemotherapy

Arm description:

Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total).

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1000 mg/m2) as a 30-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin (75 mg/m2) as a 30 to 120-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine (1250 mg/m2) as a 30-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Carboplatin (AUC 6) as a 30 to 60-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Paclitaxel (200 mg/m2) as a 180-minute IV infusion for up to 6-cycles

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed (500 mg/m2) as a 10-minute IV infusion for up to 6-cycles

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

Dosage and administration details:

Carboplatin (AUC 5) as a 30 to 60-minute IV infusion for up to 6-cycles

Number of subjects in period 2	Nivolumab	Investigator Choice of Chemotherapy
Started	267	263
Received optional Nivolumab	0	159
Completed	0	28
Not completed	267	235
Study drug toxicity	30	34
Death	1	-
Not reported	-	1
Maximum clinical benefit	-	18
Adverse event unrelated to study drug	22	23
Poor/Non-compliance	1	-
Other reasons	9	2
Participant Withdrew Consent	2	2
Disease Progression	189	146

Participant request to discontinue study treatment	12	9
Administrative reason by sponsor	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Investigator Choice of Chemotherapy
Reporting group description:	
Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). Participants who progressed on or after chemotherapy could be eligible to receive optional crossover nivolumab 3 mg/kg is administered every 2 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure.	

Reporting group values	Nivolumab	Investigator Choice of Chemotherapy	Total
Number of subjects	271	270	541
Age categorical Units: Subjects			
Adults (18-64 years)	148	133	281
From 65-84 years	120	136	256
85 years and over	3	1	4
Age Continuous Units: years			
arithmetic mean	62.8	63.4	
standard deviation	± 10.25	± 9.63	-
Sex: Female, Male Units: Subjects			
Female	87	122	209
Male	184	148	332
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	30	17	47
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	10	16
White	228	242	470
Other	6	1	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	141	139	280
Unknown or Not Reported	126	128	254

End points

End points reporting groups

Reporting group title	Nivolumab
Reporting group description:	
Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Investigator Choice of Chemotherapy
Reporting group description:	
Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). Participants who progressed on or after chemotherapy could be eligible to receive optional crossover nivolumab 3 mg/kg is administered every 2 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure.	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Investigator Choice of Chemotherapy
Reporting group description:	
Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total).	

Primary: Progression-Free Survival in participants with PD-L1 expression >= 5%

End point title	Progression-Free Survival in participants with PD-L1 expression >= 5%
End point description:	
Progression-Free Survival (PFS) was defined as the time between the date of randomization and the first date of documented tumor progression, as determined by the Independent Radiology Review Committee (IRRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause, whichever occurs first. Participants who die without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or die were censored on the date of their last evaluable tumor assessment. Participants who did not have any on-study tumor assessments and did not die were censored on the day they were randomized. Participants who received subsequent anti-cancer therapy prior to documented progression were censored at the last evaluable tumor assessment prior to the initiation of new therapy.	
End point type	Primary
End point timeframe:	
From date of randomization until date of documented tumor progression (assessed up to August 2016, approximately 28 months)	

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	212		
Units: Months				
median (confidence interval 95%)	4.21 (2.96 to 5.55)	5.88 (5.42 to 6.93)		

Statistical analyses

Statistical analysis title	PFS in participants with PD-L1 expression >= 5%
Comparison groups	Nivolumab v Investigator Choice of Chemotherapy
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2511
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.45

Secondary: Progression-Free Survival in all randomized participants

End point title	Progression-Free Survival in all randomized participants

End point description:

Progression-Free Survival (PFS) was defined as the time between the date of randomization and the first date of documented tumor progression, as determined by the Independent Radiology Review Committee (IRRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause, whichever occurs first. Participants who die without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or die were censored on the date of their last evaluable tumor assessment. Participants who did not have any on-study tumor assessments and did not die were censored on the day they were randomized. Participants who received subsequent anti-cancer therapy prior to documented progression were censored at the last evaluable tumor assessment prior to the initiation of new therapy.

End point type	Secondary

End point timeframe:

From date of randomization until date of documented tumor progression (assessed up to August 2016, approximately 28 months)

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	270		
Units: Months				
median (confidence interval 95%)	4.21 (3.06 to 5.52)	5.82 (5.42 to 6.90)		

Statistical analyses

Statistical analysis title	PFS in all randomized participants
Comparison groups	Nivolumab v Investigator Choice of Chemotherapy
Number of subjects included in analysis	541
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.43

Secondary: Overall Survival in participants with PD-L1 expression >= 5%

End point title	Overall Survival in participants with PD-L1 expression >= 5%

End point description:

Overall Survival (OS) was defined as the time from randomization to the date of death. A participant who had not died was censored at the last known alive date. OS was censored at the date of randomization for participants who were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

From date of randomization to date of death (up to approximately 89 months)

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	212		
Units: Months				
median (confidence interval 95%)	14.36 (11.66 to 17.08)	13.21 (10.81 to 17.28)		

Statistical analyses

Statistical analysis title	OS in participants with PD-L1 expression >= 5%
Comparison groups	Nivolumab v Investigator Choice of Chemotherapy
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.2

Secondary: Overall Survival in all randomized participants

End point title	Overall Survival in all randomized participants
End point description:	
Overall Survival (OS) was defined as the time from randomization to the date of death. A participant who had not died was censored at the last known alive date. OS was censored at the date of randomization for participants who were randomized but had no follow-up.	
End point type	Secondary
End point timeframe:	
From date of randomization to date of death (up to approximately 89 months)	

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	270		
Units: Months				
median (confidence interval 95%)	13.73 (11.76 to 15.41)	13.80 (11.01 to 16.99)		

Statistical analyses

Statistical analysis title	OS in all randomized participants
Comparison groups	Nivolumab v Investigator Choice of Chemotherapy
Number of subjects included in analysis	541
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.24

Secondary: Objective Response Rate (ORR) in participants with PD-L1 expression >= 5%

End point title	Objective Response Rate (ORR) in participants with PD-L1 expression >= 5%

End point description:

ORR was defined as the proportion of randomized participants who achieved a Best Overall Response (BOR) of CR or PR using the RECIST v1.1 criteria per Independent Radiology Review Committee (IRRC) assessment. BOR was defined as the best response designation recorded between the date of randomization and the date of objectively documented progression or start of subsequent anti-cancer therapy, whichever occurred first. For participants without documented progression or subsequent therapy, all available response designations contributed to the BOR assessment. For participants who continued treatment beyond progression, BOR was determined from response designations recorded up to the time of initial progression. CR= Disappearance of all evidence of disease, confirmed by PET scan; PR= Regression of measureable disease and no new sites; Stable Disease (SD)= Failure to attain CR/PR or PD; Progressive Disease (PD)= Any new lesion or increase by >=50% of previously involved sites from nadir.

End point type	Secondary

End point timeframe:

From date of randomization until date of documented tumor progression or subsequent anti-cancer therapy, whichever occurs first (assessed up to August 2016, approximately 28 months)

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	212		
Units: Percentage of participants				
number (confidence interval 95%)	26.1 (20.3 to 32.5)	33.5 (27.2 to 40.3)		

Statistical analyses

Statistical analysis title	ORR in participants with PD-L1 expression >= 5%
Comparison groups	Nivolumab v Investigator Choice of Chemotherapy
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.06

Secondary: Disease-related symptom improvement rate by Week 12

End point title	Disease-related symptom improvement rate by Week 12

End point description:

The Lung Cancer Symptom Score (LCSS) is a validated instrument designed to assess the impact of treatment on disease-related symptoms. It consists of 6 symptom-specific questions related to dyspnea, cough, fatigue, pain, hemoptysis and anorexia plus 3 summary items: symptom distress, interference with activity, and global HRQoL. The degree of impairment was recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score. Disease-related symptom improvement rate by Week 12 is defined as the proportion of all randomized (all PD-L1+) participants who had 10 points or more decrease from baseline in average symptom burden index score at any time between randomization and Week 12.

End point type	Secondary

End point timeframe:

From date of randomization to week 12

End point values	Nivolumab	Investigator Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	270		
Units: Percentage of participants				
number (confidence interval 95%)	35.4 (29.7 to 41.4)	33.7 (28.1 to 39.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for All-Cause Mortality from randomization until study completion (up to approximately 89 months).
SAEs and NSAEs were assessed from first dose to 100 days following last dose (up to approximately 89 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Nivolumab

Reporting group description:

Nivolumab 3mg/kg IV infusion, every 2 weeks until disease progression or unacceptable toxicity.

Reporting group title	Post Chemotherapy Optional Nivolumab

Reporting group description:

Participants in the Investigator Choice Arm who progressed on or after chemotherapy transitioned to nivolumab at 3 mg/kg administered every 2 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or study closure.

Reporting group title	Investigator's Choice of Chemotherapy

Reporting group description:

Administered in 3-week cycles for up to 6 cycles: Squamous: -gemcitabine (1250 mg/mg2) with cisplatin (75 mg/m2); or -gemcitabine (1000 mg/m2) with carboplatin (AUC 5); or -paclitaxel (200 mg/m2) with carboplatin (AUC 6) Non-Squamous: -pemetrexed (500 mg/m2) with cisplatin (75 mg/m2); or -pemetrexed (500 mg/m2) with carboplatin (AUC 6) Subjects who discontinued cisplatin could be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total).

Serious adverse events	Nivolumab	Post Chemotherapy Optional Nivolumab	Investigator's Choice of Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	195 / 267 (73.03%)	110 / 159 (69.18%)	203 / 263 (77.19%)
number of deaths (all causes)	233	136	92
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal metastasis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic myeloid leukaemia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular lymphoma			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioblastoma			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	8 / 267 (3.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 267 (0.00%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Malignant melanoma			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	69 / 267 (25.84%)	55 / 159 (34.59%)	95 / 263 (36.12%)
occurrences causally related to treatment / all	0 / 76	0 / 65	0 / 105
deaths causally related to treatment / all	0 / 48	0 / 51	0 / 89
Metastases to meninges			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesothelioma malignant			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	2 / 267 (0.75%)	6 / 159 (3.77%)	8 / 263 (3.04%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to liver			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	4 / 267 (1.50%)	3 / 159 (1.89%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	3 / 267 (1.12%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Non-small cell lung cancer			

subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tumour associated fever			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	4 / 267 (1.50%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion malignant			
subjects affected / exposed	5 / 267 (1.87%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Air embolism			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Deep vein thrombosis			

subjects affected / exposed	3 / 267 (1.12%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Extremity necrosis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leriche syndrome			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vein disorder			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular occlusion			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			

subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Illness			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	4 / 267 (1.50%)	4 / 159 (2.52%)	6 / 263 (2.28%)
occurrences causally related to treatment / all	0 / 4	0 / 5	3 / 8
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 1
Fatigue			
subjects affected / exposed	2 / 267 (0.75%)	3 / 159 (1.89%)	8 / 263 (3.04%)
occurrences causally related to treatment / all	1 / 2	1 / 3	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	7 / 267 (2.62%)	6 / 159 (3.77%)	9 / 263 (3.42%)
occurrences causally related to treatment / all	2 / 7	1 / 6	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 267 (1.12%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspiration			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Asthma			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 267 (1.12%)	1 / 159 (0.63%)	7 / 263 (2.66%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	6 / 267 (2.25%)	5 / 159 (3.14%)	9 / 263 (3.42%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Interstitial lung disease			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Eosinophilic pneumonia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Haemothorax			

subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal disorder			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	9 / 267 (3.37%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	10 / 10	1 / 1	1 / 2
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	4 / 267 (1.50%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	8 / 267 (3.00%)	5 / 159 (3.14%)	11 / 263 (4.18%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 4
Pleural effusion			
subjects affected / exposed	8 / 267 (3.00%)	3 / 159 (1.89%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 11	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary microemboli			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	4 / 267 (1.50%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	3 / 267 (1.12%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organic brain syndrome			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			

Device occlusion			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 267 (1.87%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	5 / 5	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 267 (2.25%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	6 / 6	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fall			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compression fracture			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kyphosis postoperative			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pneumothorax			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation necrosis			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular procedure complication			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tornwaldt cyst			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 267 (0.37%)	3 / 159 (1.89%)	6 / 263 (2.28%)
occurrences causally related to treatment / all	0 / 1	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	3 / 267 (1.12%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Atrial flutter			
subjects affected / exposed	0 / 267 (0.00%)	2 / 159 (1.26%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 267 (0.75%)	3 / 159 (1.89%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cardiac arrest			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Atrial tachycardia			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 267 (0.00%)	4 / 159 (2.52%)	7 / 263 (2.66%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Cardiovascular disorder			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac tamponade			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Aphasia			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cubital tunnel syndrome			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant spinal cord compression			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IIIrd nerve paresis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Loss of consciousness			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasticity			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	4 / 267 (1.50%)	0 / 159 (0.00%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paresis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	4 / 267 (1.50%)	1 / 159 (0.63%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	3 / 267 (1.12%)	1 / 159 (0.63%)	7 / 263 (2.66%)
occurrences causally related to treatment / all	0 / 3	0 / 1	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 2
Anaemia of malignant disease			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 267 (0.37%)	2 / 159 (1.26%)	16 / 263 (6.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	12 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	6 / 263 (2.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic nerve disorder			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic vein thrombosis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			

subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exophthalmos			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	4 / 267 (1.50%)	3 / 159 (1.89%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	3 / 4	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 267 (2.62%)	4 / 159 (2.52%)	6 / 263 (2.28%)
occurrences causally related to treatment / all	4 / 7	1 / 4	2 / 6
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Large intestine perforation			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	4 / 267 (1.50%)	1 / 159 (0.63%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 4	0 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	4 / 267 (1.50%)	1 / 159 (0.63%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 4	0 / 1	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cholelithiasis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 267 (0.00%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	4 / 267 (1.50%)	2 / 159 (1.26%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	5 / 6	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Pain in extremity			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	2 / 267 (0.75%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Cellulitis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 267 (0.75%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	21 / 267 (7.87%)	8 / 159 (5.03%)	26 / 263 (9.89%)
occurrences causally related to treatment / all	2 / 25	0 / 9	5 / 35
deaths causally related to treatment / all	0 / 4	0 / 1	0 / 4
Peritonitis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Norovirus infection			

subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	5 / 267 (1.87%)	3 / 159 (1.89%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 5	0 / 3	1 / 5
deaths causally related to treatment / all	0 / 3	0 / 1	1 / 3
Respiratory tract infection			

subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Pulmonary sepsis			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural infection			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 267 (1.12%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 267 (1.50%)	3 / 159 (1.89%)	5 / 263 (1.90%)
occurrences causally related to treatment / all	0 / 5	0 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	5 / 267 (1.87%)	2 / 159 (1.26%)	4 / 263 (1.52%)
occurrences causally related to treatment / all	1 / 5	1 / 2	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	3 / 267 (1.12%)	3 / 159 (1.89%)	3 / 263 (1.14%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 267 (0.75%)	2 / 159 (1.26%)	2 / 263 (0.76%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 267 (0.37%)	0 / 159 (0.00%)	0 / 263 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 267 (0.00%)	0 / 159 (0.00%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 267 (0.00%)	1 / 159 (0.63%)	1 / 263 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Nivolumab	Post Chemotherapy Optional Nivolumab	Investigator's Choice of Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	245 / 267 (91.76%)	137 / 159 (86.16%)	252 / 263 (95.82%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 267 (6.74%)	8 / 159 (5.03%)	19 / 263 (7.22%)
occurrences (all)	19	12	30
Hypotension			
subjects affected / exposed	9 / 267 (3.37%)	8 / 159 (5.03%)	14 / 263 (5.32%)
occurrences (all)	11	11	19
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	9 / 267 (3.37%)	9 / 159 (5.66%)	25 / 263 (9.51%)
occurrences (all)	10	10	27
Asthenia			
subjects affected / exposed	26 / 267 (9.74%)	13 / 159 (8.18%)	41 / 263 (15.59%)
occurrences (all)	28	28	74
Chills			
subjects affected / exposed	18 / 267 (6.74%)	6 / 159 (3.77%)	18 / 263 (6.84%)
occurrences (all)	21	6	20
Pyrexia			
subjects affected / exposed	37 / 267 (13.86%)	22 / 159 (13.84%)	55 / 263 (20.91%)
occurrences (all)	56	31	97
Pain			
subjects affected / exposed	14 / 267 (5.24%)	9 / 159 (5.66%)	12 / 263 (4.56%)
occurrences (all)	17	10	14
Oedema peripheral			
subjects affected / exposed	35 / 267 (13.11%)	21 / 159 (13.21%)	67 / 263 (25.48%)
occurrences (all)	39	22	78
Non-cardiac chest pain			
subjects affected / exposed	25 / 267 (9.36%)	11 / 159 (6.92%)	21 / 263 (7.98%)
occurrences (all)	30	13	26
Mucosal inflammation			
subjects affected / exposed	7 / 267 (2.62%)	3 / 159 (1.89%)	23 / 263 (8.75%)
occurrences (all)	9	3	28
Malaise			

subjects affected / exposed	15 / 267 (5.62%)	5 / 159 (3.14%)	14 / 263 (5.32%)
occurrences (all)	20	7	28
Fatigue			
subjects affected / exposed	108 / 267 (40.45%)	47 / 159 (29.56%)	134 / 263 (50.95%)
occurrences (all)	130	57	194
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	17 / 267 (6.37%)	8 / 159 (5.03%)	20 / 263 (7.60%)
occurrences (all)	25	11	29
Epistaxis			
subjects affected / exposed	8 / 267 (3.00%)	4 / 159 (2.52%)	22 / 263 (8.37%)
occurrences (all)	8	8	36
Dyspnoea			
subjects affected / exposed	69 / 267 (25.84%)	38 / 159 (23.90%)	75 / 263 (28.52%)
occurrences (all)	81	57	108
Dysphonia			
subjects affected / exposed	12 / 267 (4.49%)	3 / 159 (1.89%)	21 / 263 (7.98%)
occurrences (all)	12	3	21
Cough			
subjects affected / exposed	77 / 267 (28.84%)	37 / 159 (23.27%)	79 / 263 (30.04%)
occurrences (all)	99	53	115
Oropharyngeal pain			
subjects affected / exposed	8 / 267 (3.00%)	5 / 159 (3.14%)	15 / 263 (5.70%)
occurrences (all)	11	7	17
Pleural effusion			
subjects affected / exposed	8 / 267 (3.00%)	9 / 159 (5.66%)	16 / 263 (6.08%)
occurrences (all)	10	11	21
Pneumonitis			
subjects affected / exposed	12 / 267 (4.49%)	15 / 159 (9.43%)	17 / 263 (6.46%)
occurrences (all)	13	18	20
Productive cough			
subjects affected / exposed	30 / 267 (11.24%)	8 / 159 (5.03%)	25 / 263 (9.51%)
occurrences (all)	36	13	33
Psychiatric disorders			

Anxiety			
subjects affected / exposed	17 / 267 (6.37%)	12 / 159 (7.55%)	18 / 263 (6.84%)
occurrences (all)	19	12	20
Depression			
subjects affected / exposed	14 / 267 (5.24%)	4 / 159 (2.52%)	13 / 263 (4.94%)
occurrences (all)	15	4	13
Insomnia			
subjects affected / exposed	24 / 267 (8.99%)	18 / 159 (11.32%)	40 / 263 (15.21%)
occurrences (all)	27	18	46
Investigations			
Blood creatinine increased			
subjects affected / exposed	13 / 267 (4.87%)	17 / 159 (10.69%)	34 / 263 (12.93%)
occurrences (all)	28	20	54
Blood alkaline phosphatase increased			
subjects affected / exposed	22 / 267 (8.24%)	7 / 159 (4.40%)	18 / 263 (6.84%)
occurrences (all)	29	9	30
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 267 (3.75%)	4 / 159 (2.52%)	14 / 263 (5.32%)
occurrences (all)	11	4	16
Alanine aminotransferase increased			
subjects affected / exposed	31 / 267 (11.61%)	13 / 159 (8.18%)	30 / 263 (11.41%)
occurrences (all)	34	19	47
Aspartate aminotransferase increased			
subjects affected / exposed	39 / 267 (14.61%)	10 / 159 (6.29%)	28 / 263 (10.65%)
occurrences (all)	53	19	48
Lymphocyte count decreased			
subjects affected / exposed	18 / 267 (6.74%)	5 / 159 (3.14%)	18 / 263 (6.84%)
occurrences (all)	38	20	49
Neutrophil count decreased			
subjects affected / exposed	9 / 267 (3.37%)	4 / 159 (2.52%)	43 / 263 (16.35%)
occurrences (all)	21	5	70
Platelet count decreased			
subjects affected / exposed	12 / 267 (4.49%)	1 / 159 (0.63%)	38 / 263 (14.45%)
occurrences (all)	24	1	60
Weight decreased			

subjects affected / exposed	42 / 267 (15.73%)	12 / 159 (7.55%)	37 / 263 (14.07%)
occurrences (all)	47	13	39
White blood cell count decreased			
subjects affected / exposed	7 / 267 (2.62%)	6 / 159 (3.77%)	33 / 263 (12.55%)
occurrences (all)	15	8	47
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	15 / 267 (5.62%)	5 / 159 (3.14%)	11 / 263 (4.18%)
occurrences (all)	17	7	16
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	14 / 267 (5.24%)	7 / 159 (4.40%)	25 / 263 (9.51%)
occurrences (all)	17	7	30
Dizziness			
subjects affected / exposed	30 / 267 (11.24%)	21 / 159 (13.21%)	41 / 263 (15.59%)
occurrences (all)	36	27	63
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 267 (2.62%)	7 / 159 (4.40%)	24 / 263 (9.13%)
occurrences (all)	9	7	27
Neuropathy peripheral			
subjects affected / exposed	5 / 267 (1.87%)	8 / 159 (5.03%)	15 / 263 (5.70%)
occurrences (all)	5	8	15
Headache			
subjects affected / exposed	30 / 267 (11.24%)	19 / 159 (11.95%)	50 / 263 (19.01%)
occurrences (all)	37	31	70
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 267 (0.37%)	1 / 159 (0.63%)	17 / 263 (6.46%)
occurrences (all)	1	1	25
Anaemia			
subjects affected / exposed	54 / 267 (20.22%)	38 / 159 (23.90%)	142 / 263 (53.99%)
occurrences (all)	84	54	235
Neutropenia			
subjects affected / exposed	5 / 267 (1.87%)	4 / 159 (2.52%)	54 / 263 (20.53%)
occurrences (all)	5	5	101
Thrombocytopenia			

subjects affected / exposed	5 / 267 (1.87%)	4 / 159 (2.52%)	40 / 263 (15.21%)
occurrences (all)	7	9	66
Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 267 (1.12%)	1 / 159 (0.63%)	21 / 263 (7.98%)
occurrences (all)	7	1	21
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	86 / 267 (32.21%)	36 / 159 (22.64%)	149 / 263 (56.65%)
occurrences (all)	126	41	270
Abdominal pain upper			
subjects affected / exposed	11 / 267 (4.12%)	9 / 159 (5.66%)	23 / 263 (8.75%)
occurrences (all)	11	11	27
Constipation			
subjects affected / exposed	65 / 267 (24.34%)	24 / 159 (15.09%)	84 / 263 (31.94%)
occurrences (all)	73	30	123
Diarrhoea			
subjects affected / exposed	84 / 267 (31.46%)	29 / 159 (18.24%)	82 / 263 (31.18%)
occurrences (all)	124	42	119
Dry mouth			
subjects affected / exposed	13 / 267 (4.87%)	8 / 159 (5.03%)	12 / 263 (4.56%)
occurrences (all)	13	8	13
Dyspepsia			
subjects affected / exposed	19 / 267 (7.12%)	2 / 159 (1.26%)	13 / 263 (4.94%)
occurrences (all)	20	3	15
Abdominal pain			
subjects affected / exposed	35 / 267 (13.11%)	12 / 159 (7.55%)	32 / 263 (12.17%)
occurrences (all)	41	14	38
Vomiting			
subjects affected / exposed	59 / 267 (22.10%)	16 / 159 (10.06%)	77 / 263 (29.28%)
occurrences (all)	87	18	126
Stomatitis			
subjects affected / exposed	13 / 267 (4.87%)	5 / 159 (3.14%)	20 / 263 (7.60%)
occurrences (all)	14	5	29
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	39 / 267 (14.61%)	20 / 159 (12.58%)	37 / 263 (14.07%)
occurrences (all)	58	24	46
Pruritus			
subjects affected / exposed	39 / 267 (14.61%)	17 / 159 (10.69%)	31 / 263 (11.79%)
occurrences (all)	59	26	42
Dry skin			
subjects affected / exposed	22 / 267 (8.24%)	14 / 159 (8.81%)	26 / 263 (9.89%)
occurrences (all)	28	15	29
Alopecia			
subjects affected / exposed	9 / 267 (3.37%)	3 / 159 (1.89%)	26 / 263 (9.89%)
occurrences (all)	9	3	26
Rash maculo-papular			
subjects affected / exposed	18 / 267 (6.74%)	6 / 159 (3.77%)	12 / 263 (4.56%)
occurrences (all)	24	8	16
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	23 / 267 (8.61%)	14 / 159 (8.81%)	23 / 263 (8.75%)
occurrences (all)	28	14	24
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	53 / 267 (19.85%)	29 / 159 (18.24%)	47 / 263 (17.87%)
occurrences (all)	63	43	67
Back pain			
subjects affected / exposed	42 / 267 (15.73%)	23 / 159 (14.47%)	62 / 263 (23.57%)
occurrences (all)	51	24	67
Muscular weakness			
subjects affected / exposed	17 / 267 (6.37%)	9 / 159 (5.66%)	26 / 263 (9.89%)
occurrences (all)	18	17	38
Musculoskeletal chest pain			
subjects affected / exposed	18 / 267 (6.74%)	5 / 159 (3.14%)	13 / 263 (4.94%)
occurrences (all)	19	5	14
Myalgia			
subjects affected / exposed	28 / 267 (10.49%)	10 / 159 (6.29%)	28 / 263 (10.65%)
occurrences (all)	31	12	31
Pain in extremity			

subjects affected / exposed	23 / 267 (8.61%)	11 / 159 (6.92%)	31 / 263 (11.79%)
occurrences (all)	27	12	32
Muscle spasms			
subjects affected / exposed	9 / 267 (3.37%)	10 / 159 (6.29%)	14 / 263 (5.32%)
occurrences (all)	10	12	17
Infections and infestations			
Bronchitis			
subjects affected / exposed	13 / 267 (4.87%)	10 / 159 (6.29%)	19 / 263 (7.22%)
occurrences (all)	16	11	24
Nasopharyngitis			
subjects affected / exposed	19 / 267 (7.12%)	10 / 159 (6.29%)	20 / 263 (7.60%)
occurrences (all)	42	18	39
Pneumonia			
subjects affected / exposed	25 / 267 (9.36%)	9 / 159 (5.66%)	23 / 263 (8.75%)
occurrences (all)	29	10	27
Urinary tract infection			
subjects affected / exposed	14 / 267 (5.24%)	4 / 159 (2.52%)	13 / 263 (4.94%)
occurrences (all)	16	6	19
Upper respiratory tract infection			
subjects affected / exposed	24 / 267 (8.99%)	9 / 159 (5.66%)	24 / 263 (9.13%)
occurrences (all)	34	9	25
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	91 / 267 (34.08%)	37 / 159 (23.27%)	102 / 263 (38.78%)
occurrences (all)	112	40	171
Dehydration			
subjects affected / exposed	10 / 267 (3.75%)	7 / 159 (4.40%)	19 / 263 (7.22%)
occurrences (all)	12	7	23
Hyperglycaemia			
subjects affected / exposed	19 / 267 (7.12%)	10 / 159 (6.29%)	18 / 263 (6.84%)
occurrences (all)	35	19	37
Hyperkalaemia			
subjects affected / exposed	15 / 267 (5.62%)	11 / 159 (6.92%)	19 / 263 (7.22%)
occurrences (all)	25	32	53
Hypoalbuminaemia			

subjects affected / exposed	28 / 267 (10.49%)	11 / 159 (6.92%)	27 / 263 (10.27%)
occurrences (all)	35	14	37
Hypokalaemia			
subjects affected / exposed	24 / 267 (8.99%)	13 / 159 (8.18%)	31 / 263 (11.79%)
occurrences (all)	27	18	47
Hypophosphataemia			
subjects affected / exposed	6 / 267 (2.25%)	6 / 159 (3.77%)	17 / 263 (6.46%)
occurrences (all)	7	16	43
Hyponatraemia			
subjects affected / exposed	28 / 267 (10.49%)	13 / 159 (8.18%)	37 / 263 (14.07%)
occurrences (all)	57	23	65
Hypomagnesaemia			
subjects affected / exposed	16 / 267 (5.99%)	19 / 159 (11.95%)	49 / 263 (18.63%)
occurrences (all)	21	33	78

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2014	Updated guidelines for use of palliative local therapy, Best Overall Response was added to the Efficacy Assessments section, and the Inclusion Criteria were updated.
08 September 2014	The requirements for submission of tumor tissue slides during the Screening Phase of the study were modified. Additional updates to the eligibility criteria were also made.
12 February 2015	Clarifications as to the sample size and timing of the primary analysis were added. The order of the first two secondary objectives were also changed. Additional changes included a clarification of the tumor assessment submission duration, an update of tissue requirements for PDL1 testing, and that survival data collection may be requested outside the protocol defined 3-month window.
09 December 2015	The timing of the final analysis of PFS based on external data was updated. In addition, an interim analysis of PFS was included. OS was moved ahead of ORR in the hierarchical testing of secondary efficacy endpoints.
31 May 2016	The interim analysis for superiority was removed. An additional secondary objective of comparing overall survival associated with nivolumab monotherapy and investigator’s choice chemotherapy in subjects with any PD-L1+ tumor expression was specified.
24 August 2016	Study-related procedures were updated after the final analysis data base lock on 02-Aug-2016 demonstrated that the study did not meet its primary endpoint of PFS as assessed by the IRRC among subjects with strongly PD-L1+ tumor expression. Changes from the updated nivolumab IB Version 15 and Erratum 01, including those related to the use of contraceptives were also incorporated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported