Clinical trial results:
A Randomized, Multi-center Phase III Study of Nivolumab Versus Sorafenib as First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma (CheckMate 459: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 459)

Summary

EudraCT number	2015-002740-13
Trial protocol	DE AT CZ GB SE FR ES PL IT
Global end of trial date	07 February 2024

Results information

Result version number	v1 (current)
This version publication date	09 February 2025
First version publication date	09 February 2025

Trial information

Trial identification

Sponsor protocol code	CA209-459

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576509
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium,
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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	14 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine if nivolumab or sorafenib is more effective in the treatment of Advanced Hepatocellular Carcinoma.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 22
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	France: 112
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Hong Kong: 42
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Japan: 107
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Singapore: 20
Country: Number of subjects enrolled	Korea, Republic of: 75
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 7

Country: Number of subjects enrolled	Switzerland: 13
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	743
EEA total number of subjects	279

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)	361
From 65 to 84 years	377
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled in 22 countries.

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 240 mg

Arm description:

Nivolumab 240 mg IV 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	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 mg every 2 weeks

Arm title	Sorafenib 400 mg

Arm description:

Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg PO twice a day

Number of subjects in period 1	Nivolumab 240 mg	Sorafenib 400 mg
Started	371	372
Completed	367	363
Not completed	4	9
Participant withdrew consent	1	5
Participant no longer meets criteria	3	2
Participant request to stop therapy	-	2

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 240 mg

Arm description:

Nivolumab 240 mg IV 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	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

240 mg every 2 weeks

Arm title	Sorafenib 400 mg

Arm description:

Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg PO twice a day

Number of subjects in period 2	Nivolumab 240 mg	Sorafenib 400 mg
Started	367	363
Completed	0	0
Not completed	367	363
Adverse event, serious fatal	1	1

Disease progression	263	244
Participant request to stop treatment	8	18
Participant withdrew consent	3	7
Maximum clinical benefit	1	-
Other reason	12	8
Participant no longer meets criteria	1	-
Study drug toxicity	37	41
NOT REPORTED	1	-
Adverse event unrelated to study drug	39	41
Lost to follow-up	-	1
Poor/non-compliance	1	1
Administrative reason by sponsor	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab 240 mg
Reporting group description:	
Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Sorafenib 400 mg
Reporting group description:	
Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity	

Reporting group values	Nivolumab 240 mg	Sorafenib 400 mg	Total
Number of subjects	371	372	743
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	185	176	361
>=65 years	186	196	382
Age Continuous Units: years			
arithmetic mean	63.9	64.5	
standard deviation	± 10.61	± 10.91	-
Sex: Female, Male Units: Participants			
Female	57	55	112
Male	314	317	631
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	165	167	332
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	5
White	199	196	395
More than one race	0	0	0
Unknown or Not Reported	4	6	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	10	15
Not Hispanic or Latino	180	170	350
Unknown or Not Reported	186	192	378

End points

End points reporting groups

Reporting group title	Nivolumab 240 mg
Reporting group description:	
Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Sorafenib 400 mg
Reporting group description:	
Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity	
Reporting group title	Nivolumab 240 mg
Reporting group description:	
Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity	
Reporting group title	Sorafenib 400 mg
Reporting group description:	
Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time from the date of randomization to the date of death due to any cause in all randomized participants. Participants who are alive will be censored at the last known alive dates. Based on Kaplan-Meier Estimates.	
End point type	Primary
End point timeframe:	
time from the date of randomization to the date of death due to any cause, assessed up to June 2019 (approximately 41 months)	

End point values	Nivolumab 240 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	372		
Units: Months				
median (confidence interval 95%)	16.39 (13.93 to 18.37)	14.69 (11.89 to 17.22)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0752 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.02

Notes:

[1] - A priori threshold for statistical significance is 0.0419

Secondary: Objective Response Rate (ORR) per BICR RECIST 1.1

End point title	Objective Response Rate (ORR) per BICR RECIST 1.1

End point description:

ORR is defined as the proportion of participants whose best overall response (BOR) is either a complete response (CR) or partial response (PR). BOR is defined as the best response designation, as determined based on BICR-assessed tumor response according to RECIST 1.1, recorded between the date of randomization and the
date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For participants without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

Estimate of (Nivolumab - Sorafenib) is based on CMH method of weighting, stratified by stratification factors

End point type	Secondary

End point timeframe:

the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first, assessed up to May 2019 (approximately 40 months)

End point values	Nivolumab 240 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	372		
Units: Percentage of participants				
number (confidence interval 95%)	15.4 (11.8 to 19.4)	7.0 (4.6 to 10.1)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 2
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	3.92

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of ORRs
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.9
upper limit	12.7

Secondary: Efficacy based on PD-L1 expression - OS and PFS

End point title	Efficacy based on PD-L1 expression - OS and PFS

End point description:

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per Dako PD-L1 IHC assay unless otherwise specified. This is referred as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classifies as:

Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling.

Not evaluable: Tumor biopsy specimen was not optimally collected or prepared (e.g. PD-L1 expression is neither quantifiable nor indeterminate).

PD-L1 status is a dichotomized variable using an X% cut-off for quantifiable PD-L1 expression:
• PD-L1 > X %: ≥ X % PD-L1 expression
• PD-L1 < X %: < X % PD-L1 expression
where X% denotes the PD-L1 expression cut-off of 1%. Additional cut off values may also be explored.

Confidence interval based on the Clopper and Pearson method.

End point type	Secondary

End point timeframe:

the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first, assessed up to May 2019 (approximately 40 months)

End point values	Nivolumab 240 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	372		
Units: Months				
median (confidence interval 95%)				
>=1%, OS	16.07 (8.41 to 22.34)	8.62 (5.72 to 16.30)		
>=1%, PFS	3.84 (2.10 to 7.62)	3.58 (1.97 to 5.36)		
<1%, OS	16.72 (13.93 to 18.56)	15.24 (12.58 to 18.10)		
<1%, PFS	3.61 (2.43 to 3.81)	3.75 (3.71 to 5.32)		
without PD-L1 quantifiable, OS	16.23 (5.82 to 99999)	22.05 (1.77 to 99999)		
without PD-L1 quantifiable, PFS	2.00 (1.87 to 99999)	6.13 (1.08 to 11.17)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.19

Statistical analysis title	Statisitical Analysis 2
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.03

Statistical analysis title	Statisitical Analysis 3
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.02

Statistical analysis title	Statisitical Analysis 4
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.17

Statistical analysis title	Statisitical Analysis 5
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	4.74

Statistical analysis title	Statisitical Analysis 5
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	3.52

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by BICR according to RECIST 1.1 or death due to any cause in all randomized participants. Participants who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last tumor assessment. Participants who did not have baseline tumor assessment will be censored on the date they were randomized. Participants who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to subsequent anti-cancer therapy.

End point type	Secondary

End point timeframe:

time from the date of randomization to the date of the first objectively documented tumor progression or death, assessed up to May 2019 (approximately 40 months)

End point values	Nivolumab 240 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	372		
Units: Months				
median (confidence interval 95%)	3.68 (3.06 to 3.88)	3.75 (3.71 to 4.47)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.1

Secondary: Efficacy based on PD-L1 expression - ORR

End point title	Efficacy based on PD-L1 expression - ORR

End point description:

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per Dako PD-L1 IHC assay unless otherwise specified. This is referred as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classifies as:

Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling.

Not evaluable: Tumor biopsy specimen was not optimally collected or prepared (e.g. PD-L1 expression is neither quantifiable nor indeterminate).

PD-L1 status is a dichotomized variable using an X% cut-off for quantifiable PD-L1 expression:
• PD-L1 > X %: ≥ X % PD-L1 expression
• PD-L1 < X %: < X % PD-L1 expression
where X% denotes the PD-L1 expression cut-off of 1%. Additional cut off values may also be explored.

Confidence interval based on the Clopper and Pearson method.

End point type	Secondary

End point timeframe:

the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first, assessed up to May 2019 (approximately 40 months)

End point values	Nivolumab 240 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	372		
Units: Percentage of participants				
number (confidence interval 95%)				
>=1%, ORR	28.2 (18.1 to 40.1)	9.4 (3.5 to 19.3)		
<1%, ORR	12.2 (8.7 to 16.5)	6.7 (4.1 to 10.1)		
without PD-L1 quantifiable, ORR	20.0 (0.5 to 71.6)	0.0 (0.0 to 36.9)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 2
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.45

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Nivolumab 240 mg v Sorafenib 400 mg
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	10.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non-serious adverse events were collected from first dose till 100 days after last dose of study therapy (up to approximately 95 months).

Adverse event reporting additional description:

All cause mortality, serious and non serious adverse events were collected for all participants who received at least one dose of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Sorafenib 400 mg

Reporting group description:

Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity

Reporting group title	Nivolumab 240 mg

Reporting group description:

Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity

Serious adverse events	Sorafenib 400 mg	Nivolumab 240 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	216 / 363 (59.50%)	216 / 367 (58.86%)	
number of deaths (all causes)	329	319	
number of deaths resulting from adverse events	105	99	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostate cancer			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma ruptured			
subjects affected / exposed	2 / 363 (0.55%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	70 / 363 (19.28%)	69 / 367 (18.80%)	
occurrences causally related to treatment / all	0 / 71	2 / 70	
deaths causally related to treatment / all	0 / 64	0 / 55	
Neoplasm malignant			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spinal cord			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	4 / 363 (1.10%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour thrombosis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aneurysm ruptured			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Assisted suicide			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 363 (0.83%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Catheter site related reaction			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

General physical health deterioration			
subjects affected / exposed	14 / 363 (3.86%)	8 / 367 (2.18%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 11	0 / 5	
Fatigue			
subjects affected / exposed	4 / 363 (1.10%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pyrexia			
subjects affected / exposed	7 / 363 (1.93%)	8 / 367 (2.18%)	
occurrences causally related to treatment / all	3 / 8	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 363 (0.28%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal ulcer			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agonal respiration			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 363 (0.55%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 363 (0.83%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 363 (0.00%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleurisy			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			

subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult blood positive			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Exposure to communicable disease			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic rupture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haemorrhage			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper limb fracture			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 363 (0.00%)	5 / 367 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			

subjects affected / exposed	1 / 363 (0.28%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 363 (0.83%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Headache			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	4 / 363 (1.10%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cognitive disorder			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	6 / 363 (1.65%)	6 / 367 (1.63%)	
occurrences causally related to treatment / all	1 / 6	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 2	
Hypoglycaemic coma			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Middle cerebral artery stroke			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuritis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant spinal cord compression			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Transient ischaemic attack			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 363 (1.65%)	8 / 367 (2.18%)	
occurrences causally related to treatment / all	2 / 6	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid function disorder			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vascular disorder			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	11 / 363 (3.03%)	7 / 367 (1.91%)	
occurrences causally related to treatment / all	1 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain lower			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	5 / 363 (1.38%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	1 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	7 / 363 (1.93%)	9 / 367 (2.45%)	
occurrences causally related to treatment / all	0 / 9	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			

subjects affected / exposed	0 / 363 (0.00%)	5 / 367 (1.36%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 363 (0.28%)	5 / 367 (1.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis haemorrhagic			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	6 / 363 (1.65%)	7 / 367 (1.91%)	
occurrences causally related to treatment / all	2 / 8	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 2	
Gastrointestinal disorder			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			

subjects affected / exposed	8 / 363 (2.20%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	1 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 363 (0.28%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 363 (0.83%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	2 / 363 (0.55%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	6 / 363 (1.65%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Stomatitis			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangitis			
subjects affected / exposed	4 / 363 (1.10%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic failure			
subjects affected / exposed	7 / 363 (1.93%)	10 / 367 (2.72%)	
occurrences causally related to treatment / all	2 / 7	2 / 11	
deaths causally related to treatment / all	1 / 6	2 / 6	
Hepatic cirrhosis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune-mediated hepatic disorder			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic lesion			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	3 / 363 (0.83%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Hepatotoxicity			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 363 (0.55%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jaundice cholestatic			
subjects affected / exposed	1 / 363 (0.28%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver injury			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoplakia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkeratosis			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			

subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 363 (0.55%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 363 (1.38%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Biliary tract infection			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 363 (0.00%)	3 / 367 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 363 (1.10%)	6 / 367 (1.63%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 363 (0.55%)	7 / 367 (1.91%)	
occurrences causally related to treatment / all	1 / 2	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 6	
Tooth abscess			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 363 (0.28%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 363 (0.55%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Virologic failure			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cell death			
subjects affected / exposed	1 / 363 (0.28%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	4 / 363 (1.10%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 363 (0.55%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Failure to thrive			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 363 (0.00%)	4 / 367 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipasaemia			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 363 (0.00%)	2 / 367 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	1 / 363 (0.28%)	0 / 367 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 363 (0.00%)	1 / 367 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sorafenib 400 mg	Nivolumab 240 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	351 / 363 (96.69%)	339 / 367 (92.37%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	85 / 363 (23.42%)	33 / 367 (8.99%)	
occurrences (all)	97	37	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 363 (11.85%)	40 / 367 (10.90%)	
occurrences (all)	63	52	
Fatigue			
subjects affected / exposed	117 / 363 (32.23%)	103 / 367 (28.07%)	
occurrences (all)	134	131	
Pyrexia			
subjects affected / exposed	58 / 363 (15.98%)	71 / 367 (19.35%)	
occurrences (all)	71	90	
Oedema peripheral			
subjects affected / exposed	41 / 363 (11.29%)	43 / 367 (11.72%)	
occurrences (all)	45	49	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	47 / 363 (12.95%)	45 / 367 (12.26%)	
occurrences (all)	53	63	
Dyspnoea			
subjects affected / exposed	23 / 363 (6.34%)	27 / 367 (7.36%)	
occurrences (all)	24	32	
Dysphonia			

subjects affected / exposed	49 / 363 (13.50%)	11 / 367 (3.00%)	
occurrences (all)	55	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 363 (8.54%)	32 / 367 (8.72%)	
occurrences (all)	31	35	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 363 (4.68%)	19 / 367 (5.18%)	
occurrences (all)	21	20	
Aspartate aminotransferase increased			
subjects affected / exposed	60 / 363 (16.53%)	84 / 367 (22.89%)	
occurrences (all)	74	108	
Amylase increased			
subjects affected / exposed	14 / 363 (3.86%)	26 / 367 (7.08%)	
occurrences (all)	23	65	
Alanine aminotransferase increased			
subjects affected / exposed	38 / 363 (10.47%)	51 / 367 (13.90%)	
occurrences (all)	51	57	
Blood bilirubin increased			
subjects affected / exposed	48 / 363 (13.22%)	41 / 367 (11.17%)	
occurrences (all)	62	53	
Lipase increased			
subjects affected / exposed	27 / 363 (7.44%)	38 / 367 (10.35%)	
occurrences (all)	36	80	
Weight decreased			
subjects affected / exposed	68 / 363 (18.73%)	34 / 367 (9.26%)	
occurrences (all)	78	38	
Platelet count decreased			
subjects affected / exposed	28 / 363 (7.71%)	17 / 367 (4.63%)	
occurrences (all)	42	19	
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 363 (3.86%)	23 / 367 (6.27%)	
occurrences (all)	14	25	
Headache			

subjects affected / exposed	33 / 363 (9.09%)	24 / 367 (6.54%)	
occurrences (all)	39	30	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	30 / 363 (8.26%)	35 / 367 (9.54%)	
occurrences (all)	37	36	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	22 / 363 (6.06%)	15 / 367 (4.09%)	
occurrences (all)	26	15	
Abdominal pain			
subjects affected / exposed	82 / 363 (22.59%)	69 / 367 (18.80%)	
occurrences (all)	97	86	
Abdominal pain upper			
subjects affected / exposed	50 / 363 (13.77%)	42 / 367 (11.44%)	
occurrences (all)	57	46	
Ascites			
subjects affected / exposed	44 / 363 (12.12%)	46 / 367 (12.53%)	
occurrences (all)	55	51	
Constipation			
subjects affected / exposed	52 / 363 (14.33%)	50 / 367 (13.62%)	
occurrences (all)	68	58	
Diarrhoea			
subjects affected / exposed	191 / 363 (52.62%)	100 / 367 (27.25%)	
occurrences (all)	363	140	
Stomatitis			
subjects affected / exposed	25 / 363 (6.89%)	16 / 367 (4.36%)	
occurrences (all)	29	21	
Nausea			
subjects affected / exposed	70 / 363 (19.28%)	62 / 367 (16.89%)	
occurrences (all)	90	78	
Vomiting			
subjects affected / exposed	40 / 363 (11.02%)	36 / 367 (9.81%)	
occurrences (all)	51	41	
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	21 / 363 (5.79%)	16 / 367 (4.36%)	
occurrences (all)	23	17	
Alopecia			
subjects affected / exposed	71 / 363 (19.56%)	6 / 367 (1.63%)	
occurrences (all)	72	7	
Rash			
subjects affected / exposed	59 / 363 (16.25%)	75 / 367 (20.44%)	
occurrences (all)	70	98	
Erythema			
subjects affected / exposed	31 / 363 (8.54%)	5 / 367 (1.36%)	
occurrences (all)	37	5	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	181 / 363 (49.86%)	29 / 367 (7.90%)	
occurrences (all)	236	30	
Pruritus			
subjects affected / exposed	51 / 363 (14.05%)	88 / 367 (23.98%)	
occurrences (all)	54	115	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	12 / 363 (3.31%)	29 / 367 (7.90%)	
occurrences (all)	12	42	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 363 (9.92%)	54 / 367 (14.71%)	
occurrences (all)	38	64	
Back pain			
subjects affected / exposed	33 / 363 (9.09%)	38 / 367 (10.35%)	
occurrences (all)	34	95	
Muscle spasms			
subjects affected / exposed	29 / 363 (7.99%)	16 / 367 (4.36%)	
occurrences (all)	37	18	
Myalgia			
subjects affected / exposed	12 / 363 (3.31%)	19 / 367 (5.18%)	
occurrences (all)	12	22	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	23 / 363 (6.34%)	33 / 367 (8.99%)	
occurrences (all)	25	48	
Upper respiratory tract infection			
subjects affected / exposed	15 / 363 (4.13%)	29 / 367 (7.90%)	
occurrences (all)	20	42	
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	31 / 363 (8.54%)	19 / 367 (5.18%)	
occurrences (all)	38	20	
Hyperglycaemia			
subjects affected / exposed	8 / 363 (2.20%)	21 / 367 (5.72%)	
occurrences (all)	8	23	
Decreased appetite			
subjects affected / exposed	135 / 363 (37.19%)	77 / 367 (20.98%)	
occurrences (all)	167	88	
Hypokalaemia			
subjects affected / exposed	21 / 363 (5.79%)	13 / 367 (3.54%)	
occurrences (all)	42	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2015	Addition of collection of peripheral blood mononuclear cells (PBMCs) and myeloid derived suppressor cells (MDSCs) collected from subjects at baseline from selected sites, reduction of frequency of HCV RNA testing for HCV infected subjects, clarification of locoregional therapy inclusion criteria
24 August 2016	Updated Study Director/Medical Monitor information; Co-primary endpoint and objective changed from time to progression (TTP) to objective response rate (ORR); Added requirement for confirmatory scan to be performed for CR/PR assessment of best overall response (BOR); Management algorithms updated per revised nivolumab IB
15 August 2017	The purpose of this amendment is to change Overall Response Rate (ORR) from a co-primary objective to a secondary objective of the study. Overall Survival (OS) will be the sole Primary Endpoint of the study.
15 January 2019	The primary reason for this amendment is to update several protocol sections to reflect the most recent guidance for treating study participants with nivolumab. In addition, an exploratory objective evaluating the correlation of tumor inflammation with efficacy based on recent preliminary data has been added. Several minor inconsistencies in study objectives and endpoints and minor administrative changes are also addressed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported