Clinical trial results:
A Randomized, Open-Label, Phase 3 Study of Nivolumab (BMS-936558) vs Everolimus in Subjects with Advanced or Metastatic Clear-Cell Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy

Summary

EudraCT number	2011-005132-26
Trial protocol	IE SE GB FI BE DE IT AT HU CZ DK ES NO GR
Global end of trial date	19 July 2021

Results information

Result version number	v1 (current)
This version publication date	03 August 2022
First version publication date	03 August 2022

Trial information

Trial identification

Sponsor protocol code	CA209-025

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Overall Survival (OS) is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known alive date.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 35
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Japan: 63
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Russian Federation: 9

Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	United States: 320
Worldwide total number of subjects	821
EEA total number of subjects	290

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)	497
From 65 to 84 years	318
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

803 Participants Treated

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab

Arm description:

Nivolumab at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Arm type	Experimental
Investigational medicinal product name	BMS-936558
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

3mg/kg IV Q2 weeks or 480mg IV Q4 weeks

Arm title	Everolimus

Arm description:

Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Arm type	Active comparator
Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

5mg PO QD

Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

10mg PO QD

Number of subjects in period 1	Nivolumab	Everolimus
Started	410	411
Completed	406	397
Not completed	4	14
No Longer Meets Study Criteria	2	1
Poor/Non-Compliance	1	-
Consent withdrawn by subject	1	8
participant treated a local facility	-	1
Request to Discontinue Study Treatment	-	3
Disease Progression	-	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 at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Arm type	Experimental
Investigational medicinal product name	BMS 936-558
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

3mg/kg IV Q2 weeks or 480mg IV Q4 weeks

Arm title	Everolimus

Arm description:

Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Arm type	Active comparator
Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

5mg PO QD

Investigational medicinal product name	everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

10mg PO QD

Number of subjects in period 2	Nivolumab	Everolimus
Started	406	397
Completed	0	0
Not completed	406	397
Adverse event, serious fatal	1	1
Consent withdrawn by subject	5	3
Not Specified	2	8
Adverse Event Unrelated to Study Drug	14	14
Study Drug Toxicity	46	53
Maximal Clinical Benefit	3	3
Request to Discontinue Study Treatment	14	21
Disease Progression	316	293
Administrative Reason by Sponsor	5	1

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	
Reporting group title	Everolimus
Reporting group description:	
Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	

Reporting group values	Nivolumab	Everolimus	Total
Number of subjects	410	411	821
Age categorical Units: Subjects			
Adults (18-64 years)	257	240	497
From 65-84 years	149	169	318
85 years and over	4	2	6
Age Continuous Units: years			
arithmetic mean	60.6	61.9	
standard deviation	± 10.87	± 10.43	-
Sex: Female, Male Units:			
Female	95	107	202
Male	315	304	619
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	42	32	74
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	1	4	5
White	353	367	720
More than one race	0	0	0
Unknown or Not Reported	13	7	20

End points

End points reporting groups

Reporting group title	Nivolumab
Reporting group description:	
Nivolumab at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	
Reporting group title	Everolimus
Reporting group description:	
Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	
Reporting group title	Everolimus
Reporting group description:	
Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.	

Primary: Overall Survival (OS) at Primary Endpoint

End point title	Overall Survival (OS) at Primary Endpoint
End point description:	
Overall Survival (OS) was defined as the time from randomization to the date of death. Participants that had not died were censored at last known date alive. Median OS time was calculated using Kaplan-Meier Estimates. Interim analysis for the Primary Endpoint occurred after 398 deaths (70% of the total OS events needed for final analysis). At that time the data monitoring committee noted that the pre-specified boundary for OS (nominal significance level $p < 0.0148$) was crossed while no new safety signals that would affect continuation of the study were found. The study was stopped early by the Sponsor, Bristol-Myers Squibb (BMS) and the interim analysis became the final analysis. As a result, participants in the everolimus groups could be assessed for a crossover to nivolumab treatment if they met all inclusion criteria. 99999 represent NA	
End point type	Primary
End point timeframe:	
Randomization until 398 deaths, up to May 2015 (approximately 30 months)	

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: months				
median (confidence interval 95%)	25.00 (21.75 to 99999)	19.55 (17.64 to 23.06)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
Comparison groups	Nivolumab v Everolimus
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0018 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	Other: 98.52 %
sides	2-sided
lower limit	0.57
upper limit	0.93

Notes:

[1] - The boundary for statistical significance required the p-value to be less than 0.0148 at the interim analyses.

Secondary: Investigator-assessed Objective Response Rate (ORR)

End point title	Investigator-assessed Objective Response Rate (ORR)

End point description:

ORR is defined as Percentage of participants with a best response of complete response (CR) or partial response (PR) divided by number of randomized participants. CR=Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.; PR=At least a 30% decrease in the sum of diameters of target lesions, the baseline sum diameters used as reference. Tumor assessments began at 8 weeks following randomization and continued every 8 weeks for the first year, then every 12 weeks thereafter until disease progression or death. CIs used Clopper and Pearson.

End point type	Secondary

End point timeframe:

from randomization up to disease progression or death (approximately up to 105 Months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: percentage of participants				
number (confidence interval 95%)	25.9 (21.7 to 30.4)	6.1 (4.0 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-assessed Duration of Objective Response

End point title	Investigator-assessed Duration of Objective Response

End point description:

Duration of objective response is defined as the time from study start date to response, CR or partial response, PR) to the date of the first documented tumor progression as determined by the investigator

(per RECIST 1.1 criteria or clinical) or death due to any cause, whichever occurred first. For participants who neither progress nor die, the duration of objective response were censored at the same time they were censored for the primary definition. CR=Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.; PR=At least a 30% decrease in the sum of diameters of target lesions, the baseline sum diameters used as reference. Based on Kaplan-Meier Estimates.

End point type	Secondary

End point timeframe:

From randomization to date of disease progression or death or censoring if no progression or death occurred (approximately 105 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	25		
Units: months				
median (confidence interval 95%)	13.11 (9.26 to 19.75)	10.18 (5.39 to 18.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-assessed Time to Objective Response

End point title	Investigator-assessed Time to Objective Response

End point description:

Time to objective response is defined as the time from randomization to first response (complete response, CR or partial response, PR). CR=Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.; PR=At least a 30% decrease in the sum of diameters of target lesions, the baseline sum diameters used as reference.

End point type	Secondary

End point timeframe:

Randomization to date of first response (approximately 105 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	25		
Units: months				
median (full range (min-max))	3.55 (1.4 to 24.8)	3.71 (1.5 to 68.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-assessed Time of Progression-free Survival (PFS)

End point title	Investigator-assessed Time of Progression-free Survival (PFS)

End point description:

PFS=time from randomization to date of first documented tumor progression as determined by investigator (per RECIST 1.1 criteria or clinical) or death due to any cause, whichever occurred first. Participants who die without a reported prior progression and without subsequent anti-cancer therapy 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 date they were randomized. Participants who received any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumor assessment prior to or on initiation date of the subsequent anti-cancer therapy. Progressive disease: >=20% increase in sum of target lesion diameters and sum must show absolute increase of >=5mm; smallest sum on study as reference. Based on Kaplan-Meier Estimates.

End point type	Secondary

End point timeframe:

from randomization up to disease progression or death (approximately up to 105 Months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: months				
median (confidence interval 95%)	4.21 (3.68 to 5.36)	4.50 (3.71 to 5.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Nivolumab v Everolimus
Number of subjects included in analysis	821
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.034
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.99

Secondary: Overall survival (OS) by Programmed Death-Ligand 1 (PD-L1) Expression Level

End point title	Overall survival (OS) by Programmed Death-Ligand 1 (PD-L1) Expression Level

End point description:

Quantifiable PD-L1 expression=percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per Dako PD-L1 IHC assay. If the PD-L1 staining could not be quantified it was classified as: indeterminate=tumor cell membrane staining hampered for reasons attributed to biology of tumor biopsy specimen and not due to improper sample preparation or handling; not evaluable=tumor biopsy specimen was not optimally collected or prepared. Not evaluable determined from H&E process before the tumor biopsy specimen was sent for evaluation or from H&E process during PD-L1 evaluation; baseline PD-L1 expression=if more than one tumor biopsy specimen was available, the most recently collected specimen with a quantifiable result. If all specimens for a given participant are either indeterminate or not evaluable, then the PD-L1 expression was considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression was considered not evaluable.

End point type	Secondary

End point timeframe:

Randomization to date of death or date of last contact for patients without documentation of death, up to May 2015 (approximately 30 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370	386		
Units: months				
median (confidence interval 95%)				
Participant PD-L1 expression >=1%	5.36 (2.04 to 7.46)	4.17 (3.09 to 5.52)		
Participant PD-L1 expression <1%	3.94 (3.68 to 5.36)	4.67 (3.71 to 5.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Serious Adverse Events, Death, Discontinuation Due to Adverse Events

End point title	Number of Participants With Serious Adverse Events, Death, Discontinuation Due to Adverse Events

End point description:

Adverse event (AE) defined: any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. Serious adverse event (SAE) defined: a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization.

End point type	Secondary

End point timeframe:

Day of first dose to 30 days post study completion (approximately 106 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	397		
Units: participants				
Deaths	324	342		
SAEs	211	177		
Drug related SAEs	51	55		
Drug related AEs	327	353		
Discontinued due to Drug-related AEs	40	51		
Discontinued due to AEs	85	82		
Adverse Events	398	387		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Disease-related Symptom Progression (DRSP)

End point title	Percentage of Participants with Disease-related Symptom Progression (DRSP)

End point description:

Disease-related symptom progression rate (DRSPR)=a decrease of two points in the Functional Assessment of Cancer Therapy-Kidney Symptom Index - Disease Related Symptoms (FKSI-DRS) questionnaire relative to the participant's baseline FKSI-DRS score with no later increase above this threshold observed during the course of the study. The 9 items of the FKSI-DRS were summarized into a symptom scale ranging in score from 0 to 36, with 0 being the worst possible score and 36 being the best possible score. A single measure reporting a decrease of at least 2 units was considered disease-related symptom progression only if it was the last one available for the participant. In order to consider a questionnaire received as valid, over 50% of the items were to be completed. Calculated by the Clopper-Pearson method for each treatment group.

End point type	Secondary

End point timeframe:

from randomization up to disease progression or death (approximately up to 105 Months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: percentage of participants				
number (confidence interval 95%)				
Disease-related Symptom Progression Rate (DRSPR)	44.6 (39.0 to 50.3)	54.6 (49.2 to 60.0)		
DRSPR Including Death and Investigator Progression	95.5 (92.6 to 97.5)	99.4 (97.9 to 99.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Meeting Marked Laboratory Abnormality Criteria in Specific Liver and Thyroid Tests

End point title	Number of Participants Meeting Marked Laboratory Abnormality Criteria in Specific Liver and Thyroid Tests

End point description:

Aspartate aminotransferase, AST. Alanine aminotransaminase, ALT. Total bilirubin, tBIL. Thyroid stimulating hormone, TSH. Upper limit of normal (ULN). Units per Liter (U/L). Results reported in International System of Units (SI).

End point type	Secondary

End point timeframe:

Day 1 to 30 days post study completion (approximately 106 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	397		
Units: participants				
ALT or AST > 3.0*ULN	32	15		
ALT or AST > 5.0*ULN	20	7		
ALT or AST > 10.0*ULN	9	1		
ALT or AST > 20.0*ULN	2	0		
Total Bilirubin > 2.0*ULN	6	2		
ALT or AST>3.0*ULN, tBIL>2.0 ULN, 1day	3	0		
ALT or AST>3.0*ULN, tBIL>2.0 ULN,30day	4	1		
TSH > ULN	159	78		
TSH < LLN	60	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Hematology and Serum Chemistry Laboratory Parameters by Worse CTC Grade - SI Units

End point title	Number of Participants with Abnormal Hematology and Serum Chemistry Laboratory Parameters by Worse CTC Grade - SI Units

End point description:

Common Terminology Criteria (CTC) version 4.0 in International System of Units (SI); Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling. Hematology parameters=Hemoglobin (Gr 3: < 8.0 g/dL), Platelet Count (Gr 3: 25.0 -< 50.0*10^9 c/L; Gr 4: < 25.0*10^9 c/L), Leukocyte Count (Gr 3: 1.0 -< 2.0*10^3 c/µL; Gr4: < 1.0*10^3 c/µL), Absolute Lymphocyte Count (Gr 3: 0.2 -< 0.5*10^3 c/µL; Gr 4: < 0.2*10^3 c/µL), Absolute Neutrophil Count (Gr 3: 0.5 - < 1.0*10^3 c/µL; Gr 4: < 0.5*10^3 c/µL). Liver Function parameters=Alkaline Phosphatase (Gr 3: > 5.0 - 20.0 U/L * ULN; Gr 4: > 20.0 U/L * ULN), AST (Gr 3: > 5.0 - 20.0 U/L * ULN; Gr 4: > 20.0 U/L * ULN), ALT (Gr 3: > 5.0 - 20.0 U/L * ULN; Gr 4: > 20.0 U/L * ULN), tBIL (Gr 3: > 3.0 - 10.0 mg/dL * ULN; Gr 4: > 10.0 mg/dL * ULN). Renal parameter=Creatinine (Grade: Gr3: > 3.0 - 6.0 mg/dL *ULN; Gr4: > 6.0 mg/dL *ULN). Cells per microliter (c/µL). Cells per Liter (c/L). Grams per deciliter (g/dL). Milligrams per deciliter (mg/dL).

End point type	Secondary

End point timeframe:

Day 1 to 30 days post study completion (approximately 106 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	397		
Units: participants				
Hemoglobin, Grade 3	33	61		
Platelet Count, Grade 3	1	6		
Platelet Count, Grade 4	0	1		
Leukocytes, Grade 3	0	1		
Leukocytes, Grade 4	1	0		
Lymphocytes (absolute), Grade 3	28	43		
Lymphocytes (absolute), Grade 4	3	6		
Absolute Neutrophil Count, Grade 3	0	2		
Absolute Neutrophil Count, Grade 4	0	1		
Alkaline Phosphatase, Grade 3	11	3		
Aspartate Aminotransferase, Grade 3	9	6		
Aspartate Aminotransferase, Grade 4	2	0		
Alanine Aminotransferase, Grade 3	12	3		
Alanine Aminotransferase, Grade 4	1	0		
Bilirubin Total, Grade 3	3	2		
Creatinine, Grade 3	5	5		
Creatinine, Grade 4	3	1		
Hypercalcemia, Grade 3	7	1		
Hypercalcemia, Grade 4	4	1		
Hypocalcemia, Grade 3	2	4		
Hypocalcemia, Grade 4	1	0		
Hyperkalemia, Grade 3	11	7		
Hyperkalemia, Grade 4	3	0		
Hypokalemia, Grade 3	5	3		
Hypermagnesmia, Grade 3	3	0		
Hypomagnesmia, Grade 3	1	0		
Hyponatremia, Grade 3	26	22		
Hyponatremia, Grade 4	1	1		

Statistical analyses

No statistical analyses for this end point

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

End point title	Extended Collection to Post Hoc Overall Survival (OS)

End point description:

Overall Survival (OS) was defined as the time from randomization to the date of death. Participants that had not died were censored at last known date alive. Median OS time was calculated using Kaplan-Meier Estimates. Interim analysis for the Primary Endpoint occurred after 398 deaths (70% of the total OS

events needed for final analysis). At that time the data monitoring committee noted that the pre-specified boundary for OS (nominal significance level p < 0.0148) was crossed while no new safety signals that would affect continuation of the study were found. The study was stopped early by the Sponsor, Bristol-Myers Squibb (BMS) and the interim analysis became the final analysis. As a result, participants in the everolimus groups could be assessed for a crossover to nivolumab treatment if they met all inclusion criteria.
This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date.

End point type	Post-hoc

End point timeframe:

from randomization up to disease progression or death (approximately up to 105 months)

End point values	Nivolumab	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	411		
Units: Months				
median (confidence interval 95%)	25.82 (22.21 to 29.77)	19.55 (17.64 to 21.88)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Post Hoc OS
Comparison groups	Nivolumab v Everolimus
Number of subjects included in analysis	821
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.0001
Method	Logrank
Parameter estimate	Stratified Cox Proportional hazard Model
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.86

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from first dose to study completion (up to 105 months).
SAEs and Other AEs were assessed from first dose to 100 days following last dose (approximately up to 107 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	MedDRA24.0

Reporting groups

Reporting group title	EVEROLIMUS

Reporting group description:

Everolimus provided in 10 mg tablets by mouth daily until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Reporting group title	NIVOLUMAB

Reporting group description:

Nivolumab at 3 mg/kg solution provided intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.

Serious adverse events	EVEROLIMUS	NIVOLUMAB	
Total subjects affected by serious adverse events			
subjects affected / exposed	243 / 397 (61.21%)	248 / 406 (61.08%)	
number of deaths (all causes)	342	324	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			
subjects affected / exposed	1 / 397 (0.25%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 397 (0.25%)	7 / 406 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to pancreas			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	2 / 397 (0.50%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	0 / 397 (0.00%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal neoplasm			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	85 / 397 (21.41%)	64 / 406 (15.76%)	
occurrences causally related to treatment / all	0 / 87	0 / 66	
deaths causally related to treatment / all	0 / 80	0 / 48	
Metastatic neoplasm			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 397 (0.50%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	3 / 397 (0.76%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acoustic neuroma			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to abdominal cavity			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to thyroid			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma recurrent			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer metastatic			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Performance status decreased			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 397 (0.76%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	5 / 397 (1.26%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pain			
subjects affected / exposed	3 / 397 (0.76%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	6 / 397 (1.51%)	7 / 406 (1.72%)	
occurrences causally related to treatment / all	4 / 10	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 397 (0.50%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 397 (0.50%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia pain			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inadequate analgesia			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Peripheral swelling			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 397 (2.02%)	9 / 406 (2.22%)	
occurrences causally related to treatment / all	1 / 9	1 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
subjects affected / exposed	4 / 397 (1.01%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 6	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 397 (0.50%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease			
subjects affected / exposed	3 / 397 (0.76%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
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	8 / 397 (2.02%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	13 / 397 (3.27%)	10 / 406 (2.46%)	
occurrences causally related to treatment / all	14 / 14	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			

subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	19 / 397 (4.79%)	16 / 406 (3.94%)	
occurrences causally related to treatment / all	1 / 22	1 / 20	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	3 / 397 (0.76%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Confusional state			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood culture positive			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	3 / 397 (0.76%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral test positive			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
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 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site impaired healing			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural swelling			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration error			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pancreas divisum			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 397 (0.76%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure chronic			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 397 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 397 (0.25%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	3 / 397 (0.76%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 397 (0.50%)	7 / 406 (1.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pericardial effusion			

subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nerve compression			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Spinal cord compression			
subjects affected / exposed	1 / 397 (0.25%)	9 / 406 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thalamus haemorrhage			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	6 / 397 (1.51%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Dural arteriovenous fistula			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial spasm			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemic encephalopathy			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated encephalitis			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 397 (3.78%)	9 / 406 (2.22%)	
occurrences causally related to treatment / all	14 / 24	3 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Methaemoglobinaemia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal disorder			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	3 / 397 (0.76%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal ischaemia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	6 / 397 (1.51%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 397 (0.50%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 397 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 397 (0.50%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 397 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 397 (1.01%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 397 (0.76%)	8 / 406 (1.97%)	
occurrences causally related to treatment / all	1 / 3	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal failure			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			

subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal tubular necrosis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	6 / 397 (1.51%)	12 / 406 (2.96%)	
occurrences causally related to treatment / all	2 / 6	3 / 12	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal colic			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal mass			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 397 (0.76%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	6 / 397 (1.51%)	7 / 406 (1.72%)	
occurrences causally related to treatment / all	2 / 6	1 / 8	
deaths causally related to treatment / all	0 / 2	0 / 2	
Nephrolithiasis			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	2 / 397 (0.50%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 397 (0.25%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone disorder			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 397 (0.76%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	4 / 397 (1.01%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Back pain			
subjects affected / exposed	7 / 397 (1.76%)	9 / 406 (2.22%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteonecrosis of jaw			

subjects affected / exposed	0 / 397 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back disorder			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal pain			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 397 (1.26%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	25 / 397 (6.30%)	19 / 406 (4.68%)	
occurrences causally related to treatment / all	6 / 25	1 / 22	
deaths causally related to treatment / all	1 / 2	0 / 2	
Sepsis			
subjects affected / exposed	3 / 397 (0.76%)	9 / 406 (2.22%)	
occurrences causally related to treatment / all	1 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
Bronchiolitis			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 397 (0.00%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 397 (0.50%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infection			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 397 (0.00%)	4 / 406 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain abscess			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			

subjects affected / exposed	2 / 397 (0.50%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 397 (0.25%)	2 / 406 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection fungal			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psoas abscess			
subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
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	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 397 (0.00%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	5 / 397 (1.26%)	10 / 406 (2.46%)	
occurrences causally related to treatment / all	0 / 7	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 397 (0.50%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 397 (1.26%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 397 (0.25%)	1 / 406 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	0 / 397 (0.00%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	5 / 397 (1.26%)	5 / 406 (1.23%)	
occurrences causally related to treatment / all	2 / 5	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 397 (1.01%)	3 / 406 (0.74%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 397 (0.25%)	0 / 406 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EVEROLIMUS	NIVOLUMAB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	379 / 397 (95.47%)	392 / 406 (96.55%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	47 / 397 (11.84%)	49 / 406 (12.07%)	
occurrences (all)	58	60	
Hypotension			

subjects affected / exposed	11 / 397 (2.77%)	24 / 406 (5.91%)	
occurrences (all)	11	25	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	196 / 397 (49.37%)	215 / 406 (52.96%)	
occurrences (all)	289	306	
Pyrexia			
subjects affected / exposed	84 / 397 (21.16%)	81 / 406 (19.95%)	
occurrences (all)	131	118	
Asthenia			
subjects affected / exposed	71 / 397 (17.88%)	44 / 406 (10.84%)	
occurrences (all)	91	64	
Mucosal inflammation			
subjects affected / exposed	89 / 397 (22.42%)	21 / 406 (5.17%)	
occurrences (all)	121	25	
Oedema peripheral			
subjects affected / exposed	110 / 397 (27.71%)	73 / 406 (17.98%)	
occurrences (all)	157	81	
Chills			
subjects affected / exposed	30 / 397 (7.56%)	32 / 406 (7.88%)	
occurrences (all)	33	41	
Malaise			
subjects affected / exposed	14 / 397 (3.53%)	22 / 406 (5.42%)	
occurrences (all)	15	26	
Pain			
subjects affected / exposed	26 / 397 (6.55%)	21 / 406 (5.17%)	
occurrences (all)	28	21	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	114 / 397 (28.72%)	101 / 406 (24.88%)	
occurrences (all)	157	121	
Epistaxis			
subjects affected / exposed	66 / 397 (16.62%)	19 / 406 (4.68%)	
occurrences (all)	75	20	
Nasal congestion			

subjects affected / exposed	15 / 397 (3.78%)	24 / 406 (5.91%)	
occurrences (all)	16	28	
Haemoptysis			
subjects affected / exposed	17 / 397 (4.28%)	22 / 406 (5.42%)	
occurrences (all)	19	28	
Oropharyngeal pain			
subjects affected / exposed	27 / 397 (6.80%)	21 / 406 (5.17%)	
occurrences (all)	34	23	
Dyspnoea exertional			
subjects affected / exposed	28 / 397 (7.05%)	26 / 406 (6.40%)	
occurrences (all)	31	28	
Pneumonitis			
subjects affected / exposed	56 / 397 (14.11%)	24 / 406 (5.91%)	
occurrences (all)	66	27	
Cough			
subjects affected / exposed	152 / 397 (38.29%)	146 / 406 (35.96%)	
occurrences (all)	224	201	
Dysphonia			
subjects affected / exposed	32 / 397 (8.06%)	36 / 406 (8.87%)	
occurrences (all)	37	38	
Productive cough			
subjects affected / exposed	25 / 397 (6.30%)	23 / 406 (5.67%)	
occurrences (all)	26	28	
Pleural effusion			
subjects affected / exposed	22 / 397 (5.54%)	13 / 406 (3.20%)	
occurrences (all)	24	13	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	25 / 397 (6.30%)	33 / 406 (8.13%)	
occurrences (all)	27	35	
Insomnia			
subjects affected / exposed	38 / 397 (9.57%)	40 / 406 (9.85%)	
occurrences (all)	45	45	
Depression			
subjects affected / exposed	14 / 397 (3.53%)	25 / 406 (6.16%)	
occurrences (all)	14	26	

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	18 / 397 (4.53%)	29 / 406 (7.14%)	
occurrences (all)	30	41	
Blood cholesterol increased			
subjects affected / exposed	31 / 397 (7.81%)	8 / 406 (1.97%)	
occurrences (all)	34	11	
Weight decreased			
subjects affected / exposed	67 / 397 (16.88%)	58 / 406 (14.29%)	
occurrences (all)	68	62	
Blood creatinine increased			
subjects affected / exposed	61 / 397 (15.37%)	62 / 406 (15.27%)	
occurrences (all)	77	94	
Alanine aminotransferase increased			
subjects affected / exposed	30 / 397 (7.56%)	29 / 406 (7.14%)	
occurrences (all)	33	36	
Aspartate aminotransferase increased			
subjects affected / exposed	33 / 397 (8.31%)	34 / 406 (8.37%)	
occurrences (all)	42	46	
Platelet count decreased			
subjects affected / exposed	21 / 397 (5.29%)	11 / 406 (2.71%)	
occurrences (all)	32	15	
Nervous system disorders			
Dizziness			
subjects affected / exposed	37 / 397 (9.32%)	40 / 406 (9.85%)	
occurrences (all)	54	50	
Headache			
subjects affected / exposed	66 / 397 (16.62%)	65 / 406 (16.01%)	
occurrences (all)	96	97	
Dysgeusia			
subjects affected / exposed	40 / 397 (10.08%)	9 / 406 (2.22%)	
occurrences (all)	43	9	
Taste disorder			
subjects affected / exposed	21 / 397 (5.29%)	9 / 406 (2.22%)	
occurrences (all)	22	9	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	149 / 397 (37.53%)	93 / 406 (22.91%)	
occurrences (all)	192	115	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	25 / 397 (6.30%)	30 / 406 (7.39%)	
occurrences (all)	27	38	
Stomatitis			
subjects affected / exposed	125 / 397 (31.49%)	29 / 406 (7.14%)	
occurrences (all)	218	32	
Abdominal pain upper			
subjects affected / exposed	22 / 397 (5.54%)	27 / 406 (6.65%)	
occurrences (all)	22	32	
Constipation			
subjects affected / exposed	93 / 397 (23.43%)	110 / 406 (27.09%)	
occurrences (all)	134	157	
Nausea			
subjects affected / exposed	139 / 397 (35.01%)	135 / 406 (33.25%)	
occurrences (all)	192	214	
Abdominal pain			
subjects affected / exposed	44 / 397 (11.08%)	46 / 406 (11.33%)	
occurrences (all)	52	58	
Vomiting			
subjects affected / exposed	80 / 397 (20.15%)	77 / 406 (18.97%)	
occurrences (all)	125	119	
Diarrhoea			
subjects affected / exposed	141 / 397 (35.52%)	122 / 406 (30.05%)	
occurrences (all)	247	207	
Dyspepsia			
subjects affected / exposed	20 / 397 (5.04%)	15 / 406 (3.69%)	
occurrences (all)	25	26	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	64 / 397 (16.12%)	92 / 406 (22.66%)	
occurrences (all)	79	118	
Rash			

subjects affected / exposed	101 / 397 (25.44%)	86 / 406 (21.18%)	
occurrences (all)	140	124	
Rash maculo-papular			
subjects affected / exposed	24 / 397 (6.05%)	21 / 406 (5.17%)	
occurrences (all)	31	25	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	38 / 397 (9.57%)	22 / 406 (5.42%)	
occurrences (all)	46	22	
Dry skin			
subjects affected / exposed	50 / 397 (12.59%)	50 / 406 (12.32%)	
occurrences (all)	56	55	
Dermatitis acneiform			
subjects affected / exposed	24 / 397 (6.05%)	14 / 406 (3.45%)	
occurrences (all)	27	17	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	15 / 397 (3.78%)	21 / 406 (5.17%)	
occurrences (all)	16	23	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	15 / 397 (3.78%)	39 / 406 (9.61%)	
occurrences (all)	16	40	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	79 / 397 (19.90%)	120 / 406 (29.56%)	
occurrences (all)	105	164	
Pain in extremity			
subjects affected / exposed	45 / 397 (11.34%)	60 / 406 (14.78%)	
occurrences (all)	59	72	
Back pain			
subjects affected / exposed	77 / 397 (19.40%)	99 / 406 (24.38%)	
occurrences (all)	89	121	
Flank pain			
subjects affected / exposed	18 / 397 (4.53%)	22 / 406 (5.42%)	
occurrences (all)	18	25	
Musculoskeletal chest pain			

subjects affected / exposed	22 / 397 (5.54%)	32 / 406 (7.88%)	
occurrences (all)	22	36	
Myalgia			
subjects affected / exposed	24 / 397 (6.05%)	40 / 406 (9.85%)	
occurrences (all)	28	47	
Muscle spasms			
subjects affected / exposed	18 / 397 (4.53%)	23 / 406 (5.67%)	
occurrences (all)	21	25	
Bone pain			
subjects affected / exposed	22 / 397 (5.54%)	19 / 406 (4.68%)	
occurrences (all)	23	19	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	25 / 397 (6.30%)	24 / 406 (5.91%)	
occurrences (all)	29	34	
Nasopharyngitis			
subjects affected / exposed	25 / 397 (6.30%)	43 / 406 (10.59%)	
occurrences (all)	38	78	
Upper respiratory tract infection			
subjects affected / exposed	26 / 397 (6.55%)	34 / 406 (8.37%)	
occurrences (all)	36	44	
Pneumonia			
subjects affected / exposed	29 / 397 (7.30%)	11 / 406 (2.71%)	
occurrences (all)	31	12	
Sinusitis			
subjects affected / exposed	22 / 397 (5.54%)	10 / 406 (2.46%)	
occurrences (all)	28	11	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	17 / 397 (4.28%)	27 / 406 (6.65%)	
occurrences (all)	21	31	
Hypercholesterolaemia			
subjects affected / exposed	38 / 397 (9.57%)	3 / 406 (0.74%)	
occurrences (all)	38	3	
Hypertriglyceridaemia			

subjects affected / exposed	77 / 397 (19.40%)	24 / 406 (5.91%)	
occurrences (all)	87	38	
Hyperkalaemia			
subjects affected / exposed	20 / 397 (5.04%)	27 / 406 (6.65%)	
occurrences (all)	26	37	
Decreased appetite			
subjects affected / exposed	145 / 397 (36.52%)	109 / 406 (26.85%)	
occurrences (all)	169	140	
Hyperglycaemia			
subjects affected / exposed	66 / 397 (16.62%)	38 / 406 (9.36%)	
occurrences (all)	93	58	
Hyponatraemia			
subjects affected / exposed	24 / 397 (6.05%)	27 / 406 (6.65%)	
occurrences (all)	30	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2013	Update to the Summary of Safety section to include new preliminary reproductive toxicology data that was distributed as a Non-clinical Expedited Safety Report and to include changes to the guidance on contraception. Tables were renumbered per new model template Section 3.3.1 Inclusion criteria 3a and 3d were updated to add clarifying language for length of time of contraceptive use. Update Appendix 3 - Guide on Contraception
11 June 2013	CA209025 protocol is additionally identified as "CheckMate 025, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation" Approved generic name "nivolumab" for BMS-936558 has been added throughout the document. Clarification of 4th secondary objective added Information on Opportunistic Infections added to Summary of Safety Clarifications added to Inclusion criteria 2e and 2h and Exclusion criteria 2h and 2k Section 3.4.1 added clarification regarding palliative radiation and added information regarding palliative surgical resection. Added clarifying information on subject follow-up in section 3.6 Updated product information in Table 4.1-1 Added clarifying information on weight used for nivolumab dose in section 4.3 Added Nephrotoxicity to list of management guidelines available in IB Added clarification and guidance to Tables in section 5.1, removed HCO3, added albumin, allow for serum urea or BUN, HCV Ab or HCV RNA and added additional sample collections to Table 5.1-6 Clarifying information added to section 5.3 Safety Assessments Added Section 5.3.1 - Follow-up and Survival Procedures; including addition of EQ5D collection during the survival follow-up period. Section 5.4 added clarification regarding bone scans. Section 5.6 added clarifications throughout and information on PBMC and Peripheral Blood RNA Clarification/update to section 8.2 (Population for Analysis), 8.3(Endpoints), 8.4.2.2 (Methods for Secondary Endpoints), 8.45 (Biomarker Analyses) Section 9.3 updated to reflect criteria for Signatory Investigator Reference 50 & 51 added Additional minor clarifications and grammatical corrections made throughout document
27 August 2014	Changed the order of secondary objectives throughout document to indicate that ORR will be first and PFS secondDefinition of PFS updated to include investigator assessed RECIST 1.1 or clinical progression Updated nivolumab preparation information in Section 4.1.3 regarding filter size, acceptable diluents and IV components and minimal drug concentration
24 December 2014	Updated Section 4.1.3 to refer to the current Investigator Brochure for nivolumab preparation information. Clarification added to Section 6.1 and 6.4 indicating SAE and pregnancy forms are to be submitted within 24 hours of awareness of the event. Clarification indicating SAEs for subjects who were randomized but never received study treatment need to be reported for a period of 30 days from date of randomization.
02 April 2015	Updated Section 5.3.1 to include language that allows the potential for the collection of additional survival data.

12 August 2015	Protocol amendment is being implemented to provide modifications to the protocol based on recommendations of the study's independent Data Monitoring Committee (DMC). The DMC for the CA209025 study convened on 17-Jul-2015 to evaluate data from a planned, formal Interim Analysis of overall survival (OS). The DMC declared superiority for OS in subjects receiving nivolumab as compared to everolimus. As a result of the DMC assessment, this protocol amendment is being implemented to provide a mechanism for eligible subjects randomized to the everolimus treatment Arm B to receive subsequent nivolumab therapy as part of a nivolumab extension phase. Protocol amendment also indicates that the interim analysis results should now be considered the final primary analysis results of the protocol. Protocol amendment also indicates the assignment of Helene Hardy and Elmer Berghorn as the BMS Study Directors.
23 November 2016	The main purpose of this amendment is to include the option for patients receiving nivolumab at the dose of 3mg/ kg every 2 weeks to switch to a flat dose of nivolumab at 480mg every 4 weeks. This amendment will also allow nivolumab infusions to be administered over 30 minutes. This amendment also includes updates based on the most recent nivolumab Investigator Brochure, updated contraception requirements, and scan frequency for responders (CR, PR or SD) on study beyond 2 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported