Clinical trial results:
A Randomized Phase 3 Single Blind Study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in Newly Diagnosed Adult Subjects with MGMT-Methylated (tumor O6-methylguanine DNA methyltransferase) Glioblastoma

Summary

EudraCT number	2015-004722-34
Trial protocol	DE AT BE ES GB SE NL PL FR DK IT
Global end of trial date	09 April 2024

Results information

Result version number	v1 (current)
This version publication date	24 April 2025
First version publication date	24 April 2025

Trial information

Trial identification

Sponsor protocol code	CA209-548

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	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, mg-gsm-ct@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	09 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The two primary objective of the trial will be OS in the randomized population with no corticosteroids at baseline as well as in the overall randomized population, and PFS determined by BICR, based on RANO criteria

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 May 2016
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	Australia: 26
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 87
Country: Number of subjects enrolled	Germany: 71
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 64
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 23
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 228

Worldwide total number of subjects	716
EEA total number of subjects	321

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)	482
From 65 to 84 years	234
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

716 participants were randomized into the study, 709 participants received study treatment

Period 1

Period 1 title	Pre-Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Radiotherapy, Temozolomide plus Nivolumab

Arm description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

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

Dosage and administration details:

100mg

Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg

Arm title	Radiotherapy, Temozolomide plus Placebo

Arm description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Arm type	Experimental

Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Single blind refers to site blinding, which includes subjects and investigators

Number of subjects in period 1	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo
Started	358	358
Completed	354	355
Not completed	4	3
Participant withdrew consent	-	1
Not reported	1	-
Participant no longer meets study criteria	2	2
Adverse event unrelated to study drug	1	-

Period 2

Period 2 title	End of Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Radiotherapy, Temozolomide plus Nivolumab

Arm description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg

Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

100mg

Arm title	Radiotherapy, Temozolomide plus Placebo

Arm description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Arm type	Experimental
Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Single blind refers to site blinding, which includes subjects and investigators

Number of subjects in period 2	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo
Started	355	354
Completed	0	0
Not completed	355	354
Adverse event, serious fatal	2	1
Participant withdrew consent	5	6
other reasonse	21	10
poor or non compliant	-	1
Participant no longer meets study criteria	1	1
administrative reason by sponsor	1	29
maximum clinical benefit	4	4
Adverse event unrelated to study drug	19	20
Study Drug Toxicity	75	19
participant request to discontinue treatment	33	35
Lost to follow-up	1	2
Disease Progression	193	226

Baseline characteristics

Reporting groups	
Reporting group title	Radiotherapy, Temozolomide plus Nivolumab
Reporting group description:	
Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.	
Reporting group title	Radiotherapy, Temozolomide plus Placebo
Reporting group description:	
Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.	

Reporting group values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo	Total
Number of subjects	358	358	716
Age categorical Units: Subjects			
Adults (18-64 years)	237	245	482
From 65-84 years	121	113	234
Age Continuous Units: Years			
arithmetic mean	57.9	58.7	
standard deviation	± 12.2	± 11.4	-
Sex: Female, Male Units: Participants			
Female	153	161	314
Male	205	197	402
Race/Ethnicity, Customized Units: Subjects			
White	301	318	619
Black or African American	4	4	8
Asian	35	33	68
Other	17	3	20
Not Reported	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	11	18
Not Hispanic or Latino	171	178	349
Unknown or Not Reported	180	169	349

End points

End points reporting groups

Reporting group title	Radiotherapy, Temozolomide plus Nivolumab

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Reporting group title	Radiotherapy, Temozolomide plus Placebo

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Reporting group title	Radiotherapy, Temozolomide plus Nivolumab

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Reporting group title	Radiotherapy, Temozolomide plus Placebo

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Primary: Progression-free survival (PFS) determined by BICR

End point title	Progression-free survival (PFS) determined by BICR

End point description:

The time from randomization to the date of the first documented tumor progression or death by any cause. PFS will be determined by a Blinded Independent Central Review (BICR) assessed based on Radiologic Assessment in Neuro-Oncology (RANO) criteria. Specifically, RANO response criteria indicates that within the first 12 weeks of completion of radiotherapy, progression can only be assessed if the majority of the new enhancement is outside of the radiation field or if there is pathologic confirmation of progressive disease.

End point type	Primary

End point timeframe:

From randomization to the date of the first documented tumor progression or death by any cause. (up to approximately 4.5 years)

End point values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	358		
Units: Months				
median (confidence interval 95%)	9.89 (8.31 to 11.60)	10.25 (9.46 to 12.09)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Radiotherapy, Temozolomide plus Nivolumab v Radiotherapy, Temozolomide plus Placebo
Number of subjects included in analysis	716
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.4

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The time from the date of randomization to the date of death. who have not died by the end of the study will be censored to last known date alive.

End point type	Primary

End point timeframe:

From randomization to date of death (up to approximately 4.5 years)

End point values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	358		
Units: Months				
median (confidence interval 95%)				
Overall Survival	28.94 (24.57 to 31.64)	31.84 (28.94 to 33.77)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
Statistical analysis description:	
All Randomized No Baseline Corticosteroids Participants	
Comparison groups	Radiotherapy, Temozolomide plus Nivolumab v Radiotherapy, Temozolomide plus Placebo
Number of subjects included in analysis	716
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.26

Secondary: Overall Survival (OS) rates at 12 Months

End point title	Overall Survival (OS) rates at 12 Months
End point description:	
Overall Survival (OS) rate is defined as the percentage of participants surviving at 12 months	
End point type	Secondary
End point timeframe:	
From randomization to 12 months after first dose	

End point values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	358		
Units: percentage of participants				
number (confidence interval 95%)	43.2 (37.6 to 48.7)	45.7 (40.2 to 51.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) rates at 24 months

End point title	Overall Survival (OS) rates at 24 months
End point description:	
Overall Survival (OS) rate is defined as the percentage of participants surviving at 24 months	
End point type	Secondary

End point timeframe:

From randomization to 24 months after first dose

End point values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	358		
Units: percentage of participants				
number (confidence interval 95%)	17.3 (13.2 to 21.8)	17.3 (13.3 to 21.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) based on investigator assessment

End point title	Progression free survival (PFS) based on investigator assessment

End point description:

The time from randomization to the date of the first documented tumor progression or death by any cause. PFS will be determined by investigator assessment based Radiologic Assessment in Neuro-Oncology (RANO) criteria. Specifically, RANO response criteria indicates that within the first 12 weeks of completion of radiotherapy, progression can only be assessed if the majority of the new enhancement is outside of the radiation field or if there is pathologic confirmation of progressive disease.

End point type	Secondary

End point timeframe:

From randomization to the date of the first documented tumor progression or death by any cause. (up to approximately 4.5 years)

End point values	Radiotherapy, Temozolomide plus Nivolumab	Radiotherapy, Temozolomide plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	358		
Units: Months				
median (confidence interval 95%)	14.09 (12.62 to 16.56)	15.18 (13.11 to 17.12)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: (From first dose to last dose + 100 days): Approximately 48 Months

All-Cause mortality (From randomization to end of study): Approximately up to 52 months

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Radiotherapy, Temozolomide plus Placebo

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions).

Placebo: administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by a 30 minute infusion every 4 weeks beginning after 8 doses

Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Reporting group title	Radiotherapy, Temozolomide plus Nivolumab

Reporting group description:

Radiotherapy: A total dose of 60 Gy [Gray (radiotherapy dose)], in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions).

Nivolumab: 240 mg administered intravenously (IV) as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses

Temozolomide: 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in Cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

Serious adverse events	Radiotherapy, Temozolomide plus Placebo	Radiotherapy, Temozolomide plus Nivolumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	217 / 354 (61.30%)	259 / 355 (72.96%)	
number of deaths (all causes)	255	262	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			

subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic leukaemia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	12 / 354 (3.39%)	7 / 355 (1.97%)	
occurrences causally related to treatment / all	0 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	73 / 354 (20.62%)	75 / 355 (21.13%)	
occurrences causally related to treatment / all	0 / 75	0 / 82	
deaths causally related to treatment / all	0 / 19	0 / 26	
Metastases to meninges			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			

subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	11 / 354 (3.11%)	6 / 355 (1.69%)	
occurrences causally related to treatment / all	0 / 12	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm recurrence			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritumoural oedema			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	7 / 354 (1.98%)	10 / 355 (2.82%)	
occurrences causally related to treatment / all	8 / 9	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pseudoprogression			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent cancer			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	5 / 354 (1.41%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 354 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystectomy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Assisted suicide			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 354 (0.85%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 354 (0.85%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 4	
Drowning			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait inability			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 354 (1.13%)	16 / 355 (4.51%)	
occurrences causally related to treatment / all	2 / 6	9 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	3 / 354 (0.85%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 354 (1.13%)	8 / 355 (2.25%)	
occurrences causally related to treatment / all	1 / 4	3 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 354 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunodeficiency			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			

subjects affected / exposed	1 / 354 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 354 (0.85%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	13 / 354 (3.67%)	9 / 355 (2.54%)	
occurrences causally related to treatment / all	0 / 13	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary oedema			

subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 354 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 354 (0.00%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 354 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic hepatic cyst			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 354 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 354 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 354 (0.85%)	6 / 355 (1.69%)	
occurrences causally related to treatment / all	3 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 354 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			

subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 354 (0.56%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site swelling			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 354 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	2 / 354 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 354 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Branchial cyst			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	6 / 354 (1.69%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute disseminated encephalomyelitis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	5 / 354 (1.41%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	7 / 354 (1.98%)	8 / 355 (2.25%)	
occurrences causally related to treatment / all	0 / 7	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system necrosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			

subjects affected / exposed	3 / 354 (0.85%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	3 / 354 (0.85%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 354 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 354 (0.56%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Change in seizure presentation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drooling			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	12 / 354 (3.39%)	15 / 355 (4.23%)	
occurrences causally related to treatment / all	0 / 12	1 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 354 (0.56%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	6 / 354 (1.69%)	8 / 355 (2.25%)	
occurrences causally related to treatment / all	1 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	9 / 354 (2.54%)	7 / 355 (1.97%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 354 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	9 / 354 (2.54%)	10 / 355 (2.82%)	
occurrences causally related to treatment / all	1 / 10	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	3 / 354 (0.85%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle contractions involuntary			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	4 / 354 (1.13%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	5 / 354 (1.41%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurological symptom			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor skills impaired			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	40 / 354 (11.30%)	48 / 355 (13.52%)	
occurrences causally related to treatment / all	1 / 53	5 / 65	
deaths causally related to treatment / all	0 / 2	0 / 1	
Simple partial seizures			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasogenic cerebral oedema			
subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 354 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 354 (0.28%)	6 / 355 (1.69%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 354 (0.56%)	8 / 355 (2.25%)	
occurrences causally related to treatment / all	2 / 2	8 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	7 / 354 (1.98%)	7 / 355 (1.97%)	
occurrences causally related to treatment / all	6 / 7	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 354 (0.56%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye swelling			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iridocyclitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 354 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 354 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 354 (0.85%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 354 (0.00%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 354 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	2 / 354 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar pain			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephropathy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 354 (0.56%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder stenosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 354 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes insipidus			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 354 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myositis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic fasciitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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 / 354 (0.85%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis aseptic			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			

subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	2 / 354 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 354 (0.28%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 354 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	5 / 354 (1.41%)	14 / 355 (3.94%)	
occurrences causally related to treatment / all	0 / 5	3 / 17	
deaths causally related to treatment / all	0 / 1	0 / 4	
Pneumonia aspiration			
subjects affected / exposed	1 / 354 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 1	1 / 2	
Pneumonia viral			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 354 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyometra			

subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 354 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 354 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
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 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 354 (1.13%)	7 / 355 (1.97%)	
occurrences causally related to treatment / all	0 / 4	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adult failure to thrive			
subjects affected / exposed	1 / 354 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 354 (1.13%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 354 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	1 / 354 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Radiotherapy, Temozolomide plus Placebo	Radiotherapy, Temozolomide plus Nivolumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	343 / 354 (96.89%)	351 / 355 (98.87%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	32 / 354 (9.04%)	29 / 355 (8.17%)	
occurrences (all)	47	36	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	176 / 354 (49.72%)	186 / 355 (52.39%)	
occurrences (all)	223	250	
Asthenia			
subjects affected / exposed	40 / 354 (11.30%)	42 / 355 (11.83%)	
occurrences (all)	52	50	
Chills			
subjects affected / exposed	13 / 354 (3.67%)	25 / 355 (7.04%)	
occurrences (all)	15	32	
Gait disturbance			
subjects affected / exposed	34 / 354 (9.60%)	29 / 355 (8.17%)	
occurrences (all)	38	29	
Malaise			
subjects affected / exposed	18 / 354 (5.08%)	17 / 355 (4.79%)	
occurrences (all)	21	19	
Oedema peripheral			

subjects affected / exposed	28 / 354 (7.91%)	30 / 355 (8.45%)	
occurrences (all)	34	36	
Pain			
subjects affected / exposed	9 / 354 (2.54%)	18 / 355 (5.07%)	
occurrences (all)	9	19	
Pyrexia			
subjects affected / exposed	31 / 354 (8.76%)	70 / 355 (19.72%)	
occurrences (all)	37	114	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	51 / 354 (14.41%)	59 / 355 (16.62%)	
occurrences (all)	63	70	
Dyspnoea			
subjects affected / exposed	20 / 354 (5.65%)	27 / 355 (7.61%)	
occurrences (all)	21	29	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	34 / 354 (9.60%)	32 / 355 (9.01%)	
occurrences (all)	36	32	
Confusional state			
subjects affected / exposed	21 / 354 (5.93%)	20 / 355 (5.63%)	
occurrences (all)	21	24	
Depression			
subjects affected / exposed	34 / 354 (9.60%)	30 / 355 (8.45%)	
occurrences (all)	35	32	
Insomnia			
subjects affected / exposed	47 / 354 (13.28%)	54 / 355 (15.21%)	
occurrences (all)	52	63	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	39 / 354 (11.02%)	63 / 355 (17.75%)	
occurrences (all)	52	81	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 354 (4.52%)	46 / 355 (12.96%)	
occurrences (all)	22	57	
Blood creatinine increased			

subjects affected / exposed	14 / 354 (3.95%)	23 / 355 (6.48%)	
occurrences (all)	20	30	
Lymphocyte count decreased			
subjects affected / exposed	62 / 354 (17.51%)	67 / 355 (18.87%)	
occurrences (all)	129	170	
Neutrophil count decreased			
subjects affected / exposed	40 / 354 (11.30%)	34 / 355 (9.58%)	
occurrences (all)	74	79	
Platelet count decreased			
subjects affected / exposed	75 / 354 (21.19%)	75 / 355 (21.13%)	
occurrences (all)	131	127	
Weight decreased			
subjects affected / exposed	33 / 354 (9.32%)	50 / 355 (14.08%)	
occurrences (all)	36	57	
Weight increased			
subjects affected / exposed	21 / 354 (5.93%)	13 / 355 (3.66%)	
occurrences (all)	24	15	
White blood cell count decreased			
subjects affected / exposed	44 / 354 (12.43%)	40 / 355 (11.27%)	
occurrences (all)	78	105	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	46 / 354 (12.99%)	37 / 355 (10.42%)	
occurrences (all)	64	51	
Radiation skin injury			
subjects affected / exposed	38 / 354 (10.73%)	35 / 355 (9.86%)	
occurrences (all)	39	36	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	19 / 354 (5.37%)	19 / 355 (5.35%)	
occurrences (all)	19	20	
Dizziness			
subjects affected / exposed	53 / 354 (14.97%)	47 / 355 (13.24%)	
occurrences (all)	61	50	
Dysgeusia			

subjects affected / exposed	27 / 354 (7.63%)	36 / 355 (10.14%)	
occurrences (all)	28	39	
Headache			
subjects affected / exposed	135 / 354 (38.14%)	142 / 355 (40.00%)	
occurrences (all)	192	220	
Hemiparesis			
subjects affected / exposed	25 / 354 (7.06%)	23 / 355 (6.48%)	
occurrences (all)	27	24	
Memory impairment			
subjects affected / exposed	36 / 354 (10.17%)	26 / 355 (7.32%)	
occurrences (all)	37	28	
Paraesthesia			
subjects affected / exposed	23 / 354 (6.50%)	26 / 355 (7.32%)	
occurrences (all)	28	30	
Seizure			
subjects affected / exposed	76 / 354 (21.47%)	63 / 355 (17.75%)	
occurrences (all)	112	82	
Tremor			
subjects affected / exposed	26 / 354 (7.34%)	22 / 355 (6.20%)	
occurrences (all)	30	26	
Aphasia			
subjects affected / exposed	32 / 354 (9.04%)	30 / 355 (8.45%)	
occurrences (all)	39	31	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 354 (7.34%)	42 / 355 (11.83%)	
occurrences (all)	32	64	
Lymphopenia			
subjects affected / exposed	39 / 354 (11.02%)	43 / 355 (12.11%)	
occurrences (all)	56	63	
Neutropenia			
subjects affected / exposed	32 / 354 (9.04%)	33 / 355 (9.30%)	
occurrences (all)	60	51	
Thrombocytopenia			
subjects affected / exposed	67 / 354 (18.93%)	69 / 355 (19.44%)	
occurrences (all)	89	110	

Leukopenia			
subjects affected / exposed	30 / 354 (8.47%)	20 / 355 (5.63%)	
occurrences (all)	36	29	
Eye disorders			
Dry eye			
subjects affected / exposed	15 / 354 (4.24%)	18 / 355 (5.07%)	
occurrences (all)	15	18	
Vision blurred			
subjects affected / exposed	23 / 354 (6.50%)	30 / 355 (8.45%)	
occurrences (all)	23	31	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 354 (7.63%)	32 / 355 (9.01%)	
occurrences (all)	33	36	
Constipation			
subjects affected / exposed	145 / 354 (40.96%)	163 / 355 (45.92%)	
occurrences (all)	215	221	
Diarrhoea			
subjects affected / exposed	72 / 354 (20.34%)	77 / 355 (21.69%)	
occurrences (all)	98	108	
Nausea			
subjects affected / exposed	159 / 354 (44.92%)	187 / 355 (52.68%)	
occurrences (all)	247	265	
Stomatitis			
subjects affected / exposed	9 / 354 (2.54%)	25 / 355 (7.04%)	
occurrences (all)	9	30	
Vomiting			
subjects affected / exposed	75 / 354 (21.19%)	90 / 355 (25.35%)	
occurrences (all)	99	135	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	109 / 354 (30.79%)	115 / 355 (32.39%)	
occurrences (all)	111	119	
Dry skin			
subjects affected / exposed	27 / 354 (7.63%)	24 / 355 (6.76%)	
occurrences (all)	31	25	
Erythema			

subjects affected / exposed	22 / 354 (6.21%)	29 / 355 (8.17%)	
occurrences (all)	25	30	
Pruritus			
subjects affected / exposed	77 / 354 (21.75%)	86 / 355 (24.23%)	
occurrences (all)	92	113	
Rash			
subjects affected / exposed	58 / 354 (16.38%)	85 / 355 (23.94%)	
occurrences (all)	70	105	
Rash maculo-papular			
subjects affected / exposed	13 / 354 (3.67%)	32 / 355 (9.01%)	
occurrences (all)	18	45	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	13 / 354 (3.67%)	18 / 355 (5.07%)	
occurrences (all)	13	19	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	9 / 354 (2.54%)	28 / 355 (7.89%)	
occurrences (all)	9	30	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	53 / 354 (14.97%)	61 / 355 (17.18%)	
occurrences (all)	72	71	
Back pain			
subjects affected / exposed	34 / 354 (9.60%)	41 / 355 (11.55%)	
occurrences (all)	42	47	
Muscular weakness			
subjects affected / exposed	28 / 354 (7.91%)	35 / 355 (9.86%)	
occurrences (all)	29	37	
Myalgia			
subjects affected / exposed	15 / 354 (4.24%)	30 / 355 (8.45%)	
occurrences (all)	18	37	
Pain in extremity			
subjects affected / exposed	16 / 354 (4.52%)	28 / 355 (7.89%)	
occurrences (all)	20	34	
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	12 / 354 (3.39%)	20 / 355 (5.63%)	
occurrences (all)	12	22	
Nasopharyngitis			
subjects affected / exposed	31 / 354 (8.76%)	37 / 355 (10.42%)	
occurrences (all)	45	51	
Oral candidiasis			
subjects affected / exposed	12 / 354 (3.39%)	20 / 355 (5.63%)	
occurrences (all)	13	24	
Upper respiratory tract infection			
subjects affected / exposed	19 / 354 (5.37%)	21 / 355 (5.92%)	
occurrences (all)	25	26	
Urinary tract infection			
subjects affected / exposed	34 / 354 (9.60%)	45 / 355 (12.68%)	
occurrences (all)	38	59	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	87 / 354 (24.58%)	97 / 355 (27.32%)	
occurrences (all)	104	115	
Hyperglycaemia			
subjects affected / exposed	34 / 354 (9.60%)	25 / 355 (7.04%)	
occurrences (all)	54	34	
Hypokalaemia			
subjects affected / exposed	15 / 354 (4.24%)	34 / 355 (9.58%)	
occurrences (all)	20	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2016	The main purpose of the first global amendment is to provide additional clarification on several items in response to questions arising from investigators and IRB/IEC/HAs:
26 October 2016	This amendment updates the nivolumab clinical information in GBM and safety management algorithms as a result of most recent version of the Investigator Brochure (version 15). The amendment also clarifies several items as well as corrects minor errors. Safety data from protocol CA209-143 added to the nivolumab clinical information in GBM. Renal, Pulmonary, Hepatic, and Skin safety management algorithms revised based on IBv.15 Time windows and technical descriptions around assessments and administration schedule have been added or expanded to allow for flexibility at the site level while not affecting the conduct or the analysis of the data.
03 June 2017	Changed to a Phase 3 trial with Primary Objective of OS
17 June 2017	Corrects an error in the Dose Delay Criteria and aligns the Dose Delay Criteria and Dose Discontinuation Criteria with the nivolumab program standards.
08 November 2018	Major Changes Progression Free Survival is now a primary objective of the study, changed from secondary. Overall survival (OS) rate at 12 and 24 months and PFS based on investigator assessment by RANO criteria are added as secondary objectives. The evaluation of tumor mutational burden (TMB) with efficacy endpoints is now an exploratory objective, changed from secondary. Blinded Independent Central Review (BICR) of study images has been added to the study. The statistical section has been revised to support changes in the study objectives. The study will now include 1 formal interim analysis for PFS and 1 formal interim analysis for OS for superiority.
26 February 2021	The Data Monitoring Committee (DMC) determined that there was no possibility for the study to have a positive overall survival (OS) result, and recommended to unblind the sites and subjects, which was approved by BMS. The study was officially unblinded on 22-Dec-2020. As a consequence, the timing of the primary OS analysis, originally planned for when 337 and 494 events were to be reached respectively for the population without corticosteroids at baseline and the overall population, has been updated. To prevent any bias due to unblinding of subjects, the primary OS analysis will be conducted using the unblinding date of 22-Dec-2020. Study procedures for subjects remaining on treatment and in safety follow-up have been simplified, and OS follow-up after unblinding has been removed. Protocol language per BMS standards for nivolumab studies and for COVID-19 has been incorporated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported