



Clinical trial results:

A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination With Radiation Therapy in Newly Diagnosed Adult Subjects With Unmethylated MGMT (Tumor O-6-methylguanine DNA Methyltransferase) Glioblastoma (CheckMate 498: CHECKpoint Pathway and Nivolumab Clinical Trial Evaluation 498)

Summary

EudraCT number	2015-003739-37
Trial protocol	NL AT BE DE SE ES PL DK GB IT
Global end of trial date	04 March 2022

Results information

Result version number	v1 (current)
This version publication date	19 March 2023
First version publication date	19 March 2023

Trial information

Trial identification

Sponsor protocol code	CA209-498
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02617589
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 April 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety and long-term efficacy of nivolumab plus radiation therapy vs temozolomide plus radiation therapy in participants with newly diagnosed, unmethylated enzyme O-6-methylguanine DNA methyltransferase (MGMT) glioblastoma (GBM) after surgical resection.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 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: 20
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	United States: 127
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 86
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Netherlands: 28
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Switzerland: 11

Worldwide total number of subjects	560
EEA total number of subjects	310

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)	397
From 65 to 84 years	163
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

560 participants were randomized and 553 treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Radiation Therapy

Arm description:

Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously

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

Dosage and administration details:

Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously

Arm title	Temozolomide + Radiation Therapy
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Arm description:

Temozolomide 75 mg/m² daily during radiation therapy, then 150 mg/m² Days 1-5 for Cycle 1, then increased to 200 mg/m² Days 1-5 for Cycles 2-6 administered orally

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:

Temozolomide 75 mg/m² daily during radiation therapy, then 150 mg/m² Days 1-5 for Cycle 1, then increased to 200 mg/m² Days 1-5 for Cycles 2-6 administered orally

Number of subjects in period 1	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy
Started	280	280
Completed	278	275
Not completed	2	5
Request to discontinue study treatment	1	3

Participant Withdrew Consent	1	2
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Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab + Radiation Therapy

Arm description:

Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously

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

Dosage and administration details:

Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously

Arm title	Temozolomide + Radiation Therapy
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Arm description:

Temozolomide 75 mg/m² daily during radiation therapy, then 150 mg/m² Days 1-5 for Cycle 1, then increased to 200 mg/m² Days 1-5 for Cycles 2-6 administered orally

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:

Temozolomide 75 mg/m² daily during radiation therapy, then 150 mg/m² Days 1-5 for Cycle 1, then increased to 200 mg/m² Days 1-5 for Cycles 2-6 administered orally

Number of subjects in period 2	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy
Started	278	275
Completed	0	76
Not completed	278	199
Adverse event, serious fatal	1	1
Poor/Non compliance	1	1
Other Reasons	3	3
Participant Request to discontinue	12	21
Maximum Clinical Benefit	-	2
Adverse event unrelated to study drug	16	9
Study Drug Toxicity	27	20
Participant Withdrew Consent	2	6
Disease Progression	216	136

Baseline characteristics

Reporting groups

Reporting group title	Nivolumab + Radiation Therapy
Reporting group description:	
Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously	
Reporting group title	Temozolomide + Radiation Therapy
Reporting group description:	
Temozolomide 75 mg/m ² daily during radiation therapy, then 150 mg/m ² Days 1-5 for Cycle 1, then increased to 200 mg/m ² Days 1-5 for Cycles 2-6 administered orally	

Reporting group values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy	Total
Number of subjects	280	280	560
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	190	207	397
From 65-84 years	90	73	163
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	58.8	56.5	
standard deviation	± 10.8	± 11.3	-
Sex: Female, Male			
Units: Participants			
Female	90	105	195
Male	190	175	365
Race/Ethnicity, Customized			
Units: Subjects			
White	231	240	471
Black or African American	4	3	7
Asian	33	28	61
Other	12	9	21
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	112	95	207
Unknown or Not Reported	165	183	348

End points

End points reporting groups

Reporting group title	Nivolumab + Radiation Therapy
Reporting group description: Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously	
Reporting group title	Temozolomide + Radiation Therapy
Reporting group description: Temozolomide 75 mg/m ² daily during radiation therapy, then 150 mg/m ² Days 1-5 for Cycle 1, then increased to 200 mg/m ² Days 1-5 for Cycles 2-6 administered orally	
Reporting group title	Nivolumab + Radiation Therapy
Reporting group description: Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously	
Reporting group title	Temozolomide + Radiation Therapy
Reporting group description: Temozolomide 75 mg/m ² daily during radiation therapy, then 150 mg/m ² Days 1-5 for Cycle 1, then increased to 200 mg/m ² Days 1-5 for Cycles 2-6 administered orally	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS is defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died will be censored at the last known alive date.	
End point type	Primary
End point timeframe: up to 3 years	

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	280		
Units: Months				
median (confidence interval 95%)	13.40 (12.62 to 14.29)	14.88 (13.27 to 16.13)		

Statistical analyses

Statistical analysis title	Nivolumab over Temozolomide
Comparison groups	Temozolomide + Radiation Therapy v Nivolumab + Radiation Therapy

Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0037
Method	Log-rank test stratified
Parameter estimate	Stratified Cox proportional hazard model
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.58

Secondary: Kaplan-Meier Plot of Progression Free Survival

End point title	Kaplan-Meier Plot of Progression Free Survival
End point description:	<p>PFS was defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Participants who did not have disease progression or who did not die were censored at the date of last tumor assessment. Participants who did not have any on study tumor assessment and did not have tumor progression or die were censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Participants who had surgical resection post start of study treatment were censored at the last tumor assessment date prior to initiation of surgical resection. PFS was determined by investigator reported response based on the Radiologic Assessment in Neuro-Oncology criteria.</p>
End point type	Secondary
End point timeframe:	<p>From randomization to the date of the first documented tumor progression or death due to any cause (up to approximately 6 years)</p>

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	280		
Units: Months				
median (confidence interval 95%)	6.01 (5.65 to 6.21)	6.21 (5.98 to 6.90)		

Statistical analyses

Statistical analysis title	Nivolumab over Temozolomide
Comparison groups	Nivolumab + Radiation Therapy v Temozolomide + Radiation Therapy

Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	
Method	Log-rank test stratified
Parameter estimate	Stratified Cox proportional hazard model
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.71

Secondary: Overall Survival Rate at 24 Months

End point title	Overall Survival Rate at 24 Months
End point description: The overall survival (OS) rate of (nivolumab + radiation therapy) and (temozolomide + radiation therapy) estimated as Kaplan-Meier probability of survival at 24 months. OS was defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died was censored at the last known alive date.	
End point type	Secondary
End point timeframe: At 24 Months	

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	280		
Units: Percentage of participants				
number (confidence interval 95%)	10.6 (7.3 to 14.6)	21.2 (16.5 to 26.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival in Tumor Mutational Burden (TMB) High Population

End point title	Overall Survival in Tumor Mutational Burden (TMB) High Population
End point description: OS in all randomized participants that are tumor mutational burden high. OS was defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died was censored at the last known alive date.	
End point type	Secondary
End point timeframe: From randomization to the date of death due to any cause (up to approximately 6 years)	

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - Data was not and will never be collected

[2] - Data was not and will never be collected

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival in Tumor Mutational Burden (TMB) High Population

End point title	Progression Free Survival in Tumor Mutational Burden (TMB) High Population
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End point description:

PFS in all randomized participants that are tumor mutational burden high. PFS was defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Participants who did not have disease progression or who did not die were censored at the date of last tumor assessment. Participants who did not have any on study tumor assessment and did not have tumor progression or die were censored at the randomization date. Participants who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy. Participants who had surgical resection post start of study treatment were censored at the last tumor assessment date prior to initiation of surgical resection. PFS was determined by investigator reported response based on the Radiologic Assessment in Neuro-Oncology criteria.

End point type	Secondary
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End point timeframe:

From randomization to the date of the first documented tumor progression or death due to any cause (up to approximately 6 years)

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - Data was not and will never be collected

[4] - Data was not and will never be collected

Statistical analyses

No statistical analyses for this end point

Post-hoc: Kaplan-Meier Plot of Overall Survival (OS) - Extended Collection

End point title	Kaplan-Meier Plot of Overall Survival (OS) - Extended Collection
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End point description:

OS was defined as the time between the date of randomization and the date of death due to any cause. A participant who has not died was censored at the last known alive date. Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date (assessments were made until March 4, 2022).

End point type	Post-hoc
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End point timeframe:

From randomization to the date of death due to any cause (up to approximately 6 years)

End point values	Nivolumab + Radiation Therapy	Temozolomide + Radiation Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	280		
Units: Months				
median (confidence interval 95%)	13.34 (12.55 to 14.16)	14.92 (13.27 to 16.10)		

Statistical analyses

Statistical analysis title	Nivolumab over Temozolomide
Comparison groups	Nivolumab + Radiation Therapy v Temozolomide + Radiation Therapy
Number of subjects included in analysis	560
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.0024
Method	Log-rank test stratified
Parameter estimate	Stratified Cox proportional hazard model
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.55

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs assessed from first dose to 100 days after last dose (up to 67 months).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Temozolomide + Radiation Therapy
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Reporting group description:

Temozolomide 75 mg/m² daily during radiation therapy, then 150 mg/m² Days 1-5 for Cycle 1, then increased to 200 mg/m² Days 1-5 for Cycles 2-6 administered orally

Reporting group title	Nivolumab + Radiation Therapy
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Reporting group description:

Nivolumab 240 mg every 2 weeks for 8 doses, then 480 mg every 4 weeks administered intravenously

Serious adverse events	Temozolomide + Radiation Therapy	Nivolumab + Radiation Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	141 / 275 (51.27%)	206 / 278 (74.10%)	
number of deaths (all causes)	253	269	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 275 (0.00%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Glioblastoma multiforme			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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	57 / 275 (20.73%)	89 / 278 (32.01%)	
occurrences causally related to treatment / all	0 / 59	1 / 93	
deaths causally related to treatment / all	0 / 36	0 / 41	
Metastases to meninges			

subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Recurrent cancer			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	3 / 275 (1.09%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	0 / 275 (0.00%)	15 / 278 (5.40%)	
occurrences causally related to treatment / all	0 / 0	16 / 18	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pseudoprogression			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 275 (1.82%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Embolism			

subjects affected / exposed	2 / 275 (0.73%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 275 (0.73%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse event			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 275 (1.09%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	

Gait disturbance			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Impaired healing			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 275 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Polyserositis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pyrexia			
subjects affected / exposed	2 / 275 (0.73%)	7 / 278 (2.52%)	
occurrences causally related to treatment / all	0 / 2	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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			
Testicular disorder			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (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	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 275 (3.64%)	7 / 278 (2.52%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anxiety			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apathy			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	4 / 275 (1.45%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Drug dependence			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 275 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	4 / 275 (1.45%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transaminases increased			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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			
Compression fracture			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 275 (0.36%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal compression fracture			

subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomeningocele			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			

subjects affected / exposed	2 / 275 (0.73%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	8 / 275 (2.91%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ataxia			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aphasia			
subjects affected / exposed	3 / 275 (1.09%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebellar stroke			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 275 (0.36%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	11 / 275 (4.00%)	9 / 278 (3.24%)	
occurrences causally related to treatment / all	0 / 15	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	5 / 275 (1.82%)	11 / 278 (3.96%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 275 (0.73%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianopia			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	6 / 275 (2.18%)	9 / 278 (3.24%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve disorder			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	3 / 275 (1.09%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorder			
subjects affected / exposed	2 / 275 (0.73%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 275 (0.36%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	30 / 275 (10.91%)	37 / 278 (13.31%)	
occurrences causally related to treatment / all	0 / 38	3 / 42	
deaths causally related to treatment / all	0 / 1	0 / 3	
Subdural hygroma			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (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 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 275 (0.73%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			

subjects affected / exposed	8 / 275 (2.91%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	8 / 8	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 275 (0.73%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 275 (0.36%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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 / 275 (0.36%)	0 / 278 (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	4 / 275 (1.45%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 275 (0.73%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 275 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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			
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 275 (0.36%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			

subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	2 / 275 (0.73%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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			
Fistula			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	4 / 275 (1.45%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	1 / 275 (0.36%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
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	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 275 (0.73%)	6 / 278 (2.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 275 (0.73%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 275 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 275 (0.36%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 275 (0.00%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 275 (0.73%)	5 / 278 (1.80%)	
occurrences causally related to treatment / all	0 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 275 (0.36%)	4 / 278 (1.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Steroid diabetes			

subjects affected / exposed	1 / 275 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 275 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Temozolomide + Radiation Therapy	Nivolumab + Radiation Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	259 / 275 (94.18%)	262 / 278 (94.24%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 275 (4.36%)	16 / 278 (5.76%)	
occurrences (all)	13	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 275 (9.82%)	25 / 278 (8.99%)	
occurrences (all)	33	30	
Gait disturbance			
subjects affected / exposed	7 / 275 (2.55%)	24 / 278 (8.63%)	
occurrences (all)	7	27	
Fatigue			
subjects affected / exposed	128 / 275 (46.55%)	123 / 278 (44.24%)	
occurrences (all)	155	137	
Pyrexia			
subjects affected / exposed	16 / 275 (5.82%)	30 / 278 (10.79%)	
occurrences (all)	18	39	
Malaise			
subjects affected / exposed	13 / 275 (4.73%)	14 / 278 (5.04%)	
occurrences (all)	13	15	
Oedema peripheral			

subjects affected / exposed occurrences (all)	15 / 275 (5.45%) 15	17 / 278 (6.12%) 17	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 275 (4.00%) 11	21 / 278 (7.55%) 21	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all)	9 / 275 (3.27%) 9 18 / 275 (6.55%) 20 12 / 275 (4.36%) 12 14 / 275 (5.09%) 14	18 / 278 (6.47%) 19 29 / 278 (10.43%) 30 22 / 278 (7.91%) 23 23 / 278 (8.27%) 23	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) White blood cell count decreased	20 / 275 (7.27%) 20 32 / 275 (11.64%) 43 18 / 275 (6.55%) 30 41 / 275 (14.91%) 58 20 / 275 (7.27%) 20 White blood cell count decreased	23 / 278 (8.27%) 26 15 / 278 (5.40%) 24 3 / 278 (1.08%) 6 8 / 278 (2.88%) 11 20 / 278 (7.19%) 21	

subjects affected / exposed occurrences (all)	15 / 275 (5.45%) 22	6 / 278 (2.16%) 9	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 275 (4.73%)	14 / 278 (5.04%)	
occurrences (all)	19	14	
Radiation skin injury			
subjects affected / exposed	23 / 275 (8.36%)	30 / 278 (10.79%)	
occurrences (all)	23	31	
Nervous system disorders			
Headache			
subjects affected / exposed	96 / 275 (34.91%)	115 / 278 (41.37%)	
occurrences (all)	121	157	
Cognitive disorder			
subjects affected / exposed	12 / 275 (4.36%)	14 / 278 (5.04%)	
occurrences (all)	13	14	
Aphasia			
subjects affected / exposed	20 / 275 (7.27%)	30 / 278 (10.79%)	
occurrences (all)	23	35	
Dizziness			
subjects affected / exposed	19 / 275 (6.91%)	41 / 278 (14.75%)	
occurrences (all)	19	49	
Dysgeusia			
subjects affected / exposed	16 / 275 (5.82%)	14 / 278 (5.04%)	
occurrences (all)	16	14	
Somnolence			
subjects affected / exposed	8 / 275 (2.91%)	19 / 278 (6.83%)	
occurrences (all)	9	19	
Hemiparesis			
subjects affected / exposed	12 / 275 (4.36%)	24 / 278 (8.63%)	
occurrences (all)	15	24	
Memory impairment			
subjects affected / exposed	14 / 275 (5.09%)	19 / 278 (6.83%)	
occurrences (all)	14	19	
Seizure			

subjects affected / exposed occurrences (all)	36 / 275 (13.09%) 43	35 / 278 (12.59%) 48	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 275 (4.00%)	16 / 278 (5.76%)	
occurrences (all)	13	18	
Thrombocytopenia			
subjects affected / exposed	26 / 275 (9.45%)	4 / 278 (1.44%)	
occurrences (all)	41	4	
Lymphopenia			
subjects affected / exposed	24 / 275 (8.73%)	7 / 278 (2.52%)	
occurrences (all)	30	10	
Neutropenia			
subjects affected / exposed	16 / 275 (5.82%)	1 / 278 (0.36%)	
occurrences (all)	22	1	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 275 (1.09%)	14 / 278 (5.04%)	
occurrences (all)	3	14	
Vision blurred			
subjects affected / exposed	4 / 275 (1.45%)	16 / 278 (5.76%)	
occurrences (all)	4	17	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	80 / 275 (29.09%)	54 / 278 (19.42%)	
occurrences (all)	90	61	
Abdominal pain			
subjects affected / exposed	7 / 275 (2.55%)	16 / 278 (5.76%)	
occurrences (all)	7	16	
Nausea			
subjects affected / exposed	105 / 275 (38.18%)	66 / 278 (23.74%)	
occurrences (all)	142	85	
Diarrhoea			
subjects affected / exposed	23 / 275 (8.36%)	44 / 278 (15.83%)	
occurrences (all)	32	71	
Vomiting			

subjects affected / exposed occurrences (all)	63 / 275 (22.91%) 74	35 / 278 (12.59%) 44	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	88 / 275 (32.00%)	73 / 278 (26.26%)	
occurrences (all)	89	73	
Pruritus			
subjects affected / exposed	22 / 275 (8.00%)	31 / 278 (11.15%)	
occurrences (all)	23	36	
Rash			
subjects affected / exposed	18 / 275 (6.55%)	40 / 278 (14.39%)	
occurrences (all)	20	43	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 275 (0.73%)	18 / 278 (6.47%)	
occurrences (all)	2	19	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	12 / 275 (4.36%)	15 / 278 (5.40%)	
occurrences (all)	12	16	
Back pain			
subjects affected / exposed	17 / 275 (6.18%)	17 / 278 (6.12%)	
occurrences (all)	18	18	
Arthralgia			
subjects affected / exposed	13 / 275 (4.73%)	25 / 278 (8.99%)	
occurrences (all)	14	29	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 275 (4.73%)	21 / 278 (7.55%)	
occurrences (all)	15	23	
Urinary tract infection			
subjects affected / exposed	14 / 275 (5.09%)	23 / 278 (8.27%)	
occurrences (all)	14	25	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	50 / 275 (18.18%)	33 / 278 (11.87%)	
occurrences (all)	60	36	
Hyperglycaemia			
subjects affected / exposed	9 / 275 (3.27%)	15 / 278 (5.40%)	
occurrences (all)	13	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2016	Added exclusion for subjects with prior hypersensitivity to dacarbazine (DTIC); Added definition of Suspected, Unexpected Serious Adverse Event Reaction (SUSAR) and statement of SUSAR reporting responsibilities.
24 February 2016	Corrected the temozolomide dose modification guidance during maintenance temozolomide dosing; modified nivolumab dose delay and discontinuation criteria.
04 May 2016	Modify cutoff values used to define complete vs partial resection for purposes of randomization. Remove the requirement to perform NANO evaluation prior to discussing MRI results. Replace RANO table for evaluation of response with table for evaluation of progression, applicable to the secondary endpoint of PFS.
15 November 2017	Removal of the interim analysis for superiority of the primary endpoint of OS. Addition of a secondary endpoint that evaluates, in newly diagnosed, unmethylated O-6-methylguanine DNA methyltransferase glioblastoma, any relationship between OS or PFS and tumor mutational burden in the radiation therapy (RT) + nivolumab arm compared to the RT + TMZ control arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported