Clinical trial results:
A Randomized, Double-blind, Placebo Controlled, Multicenter Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide and Radiotherapy Followed by Placebo and Temozolomide in Patients With Newly Diagnosed Glioblastoma

Summary

EudraCT number	2008-006146-26
Trial protocol	FR PT DE GB BE ES HU NL SE DK IT GR
Global end of trial date	08 September 2015

Results information

Result version number	v3 (current)
This version publication date	10 September 2017
First version publication date	15 March 2015
Version creation reason	
Summary attachment (see zip file)	BO21990 CTg receipt (BO21990 Receipt.pdf)

Trial information

Trial identification

Sponsor protocol code	BO21990

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00943826
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, 41 61 6878333, global.trial_information@roche.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	08 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To demonstrate the superiority in overall survival (OS) when bevacizumab is added to temozolomide with radiotherapy followed by temozolomide for the treatment of subjects with newly diagnosed glioblastoma • To demonstrate the superiority in progression-free survival (PFS) (using adapted MacDonald criteria) when bevacizumab is added to temozolomide with radiotherapy followed by temozolomide for the treatment of subjects with newly diagnosed glioblastoma

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP), or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the subject. The protocol and its amendments were approved by Independent Ethics Committees/Institutional review boards and written informed consent was obtained from each subject participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	31 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 61
Country: Number of subjects enrolled	Canada: 95
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	New Zealand: 30
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 29
Country: Number of subjects enrolled	Romania: 66
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 30

Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	France: 145
Country: Number of subjects enrolled	Germany: 56
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Italy: 53
Worldwide total number of subjects	921
EEA total number of subjects	575

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)	721
From 65 to 84 years	200
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1087 subjects were screened, out of which 921 subjects were randomized to the study treatment.

Period 1

Period 1 title	Concurrent Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received radiotherapy (RT) in daily fractions of 2 Gray (Gy) given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 milligrams per square meter (mg/m^2) daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 milligrams per kilogram (mg/kg) intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects received bevacizumab IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received bevacizumab every 3 weeks until disease progression/unacceptable toxicity.

Arm title	Placebo + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Number of subjects in period 1	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide
Started	458	463
Treated	452	459
Completed	397	421
Not completed	61	42
Consent withdrawn by subject	3	7
Administrative reasons	2	1
Refused treatment/Did not cooperate	5	7
Protocol Violation	1	-
Adverse Events	50	27

Period 2

Period 2 title	Maintenance Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects received bevacizumab IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received bevacizumab every 3 weeks until disease progression/unacceptable toxicity.

Arm title	Placebo + RT+Temozolomide

Arm description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Number of subjects in period 2[1]	Bevacizumab + RT + Temozolomide	Placebo + RT+Temozolomide
Started	396	370
Completed	353	331
Not completed	43	39
Consent withdrawn by subject	2	4
Failure to return	-	1
Administrative reasons	4	1
Refused treatment/Did not cooperate	6	3
Adverse Events	31	30

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some who completed previous period had discontinued, progressed, or died prior to this period.

Period 3

Period 3 title	Monotherapy Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects received bevacizumab IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received bevacizumab every 3 weeks until disease progression/unacceptable toxicity.

Arm title	Placebo + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Number of subjects in period 3[2]	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide
Started	269	159
Completed	204	143
Not completed	65	16
Consent withdrawn by subject	2	3
Failure to return	2	1
Administrative reasons	11	5

Refused treatment/Did not cooperate	8	2
Adverse Events	42	5

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some who completed previous period had discontinued, progressed, or died prior to this period.

Period 4

Period 4 title	After Primary Overall Survival Analysis
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + RT + Temozolomide

Arm description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects received bevacizumab IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received bevacizumab every 3 weeks until disease progression/unacceptable toxicity.

Arm title	Placebo + RT+Temozolomide

Arm description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase subjects placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Number of subjects in period 4[3]	Bevacizumab + RT + Temozolomide	Placebo + RT+Temozolomide
Started	27	20
Completed	0	0
Not completed	27	20
Consent withdrawn by subject	4	-
Progression of Disease	2	4
Administrative reasons	10	16
Adverse Events	11	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some who completed previous period had discontinued, progressed, or died prior to this period.

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy (RT) in daily fractions of 2 Gray (Gy) given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 milligrams per square meter (mg/m^2) daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 milligrams per kilogram (mg/kg) intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Placebo + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide	Total
Number of subjects	458	463	921
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	55.9	55.9	
full range (min-max)	20 to 84	18 to 79	-
Gender categorical			
Units: Subjects			
Female	176	165	341
Male	282	298	580

End points reporting groups

Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy (RT) in daily fractions of 2 Gray (Gy) given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 milligrams per square meter (mg/m^2) daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 milligrams per kilogram (mg/kg) intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Placebo + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Placebo + RT+Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Placebo + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Placebo + RT+Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Subject analysis set title	Bevacizumab + RT + Temozolomide
Subject analysis set type	Safety analysis

Subject analysis set description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Subject analysis set title	Placebo + RT + Temozolomide
Subject analysis set type	Safety analysis

Subject analysis set description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Primary: Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator

End point title	Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator

End point description:

PFS is defined as time from randomization to disease progression (PD) or death. PD was assessed using adapted Macdonald response criteria (modified World Health Organization [WHO] criteria) based on 3 components:radiological tumor assessments using Magnetic Resonance Imaging [MRI] scans,neurological assessment and changes in corticosteroid use. PD is assessed as greater than or equal to (>=) 25% increase in sum of products of the longest diameters of all index lesions(enhancing,measurable) compared with the smallest recorded sum (nadir); or unequivocal PD of existing non-index lesions (non-enhancing and enhancing,non-measurable); or unequivocal appearance of new lesions); or neurological worsening (if corticosteroid dose is stable or increased) compared to neurological evaluation at previous disease assessment with no need for a confirmatory scan. Participants without a PFS event were censored at last disease assessment.

End point type	Primary

End point timeframe:

Randomization until PFS Event [Until data cutoff= 31 March 2012 (up to 31.4 months)

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Months				
median (confidence interval 95%)	10.6 (10 to 11.4)	6.2 (6 to 7.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + RT + Temozolomide v Placebo + RT + Temozolomide
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.74

Notes:

[1] - Stratified by Region and Recursive partitioning analysis (RPA) Class

Primary: Co-Primary: Overall Survival (OS)

End point title	Co-Primary: Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Intent to treat population.

End point type	Primary

End point timeframe:

Randomization until OS Event [Until data cutoff= 28 February 2013 (up to 42.2 months)]

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Months				
median (confidence interval 95%)	16.8 (15.5 to 18.5)	16.7 (15.4 to 18.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + RT + Temozolomide v Bevacizumab + RT + Temozolomide
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0987 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.02

Notes:

[2] - Stratified by Region and RPA Class

Secondary: PFS as Assessed by an Independent Review Facility

End point title	PFS as Assessed by an Independent Review Facility

End point description:

An Independent Review Facility reviewed the MRI scans used by investigator to evaluate radiological tumor response. PFS is defined as time from randomization to PD or death. PD was assessed using adapted Macdonald response (modified WHO) criteria based on 3 components: radiological tumor assessments using MRI scans, neurological assessment and changes in corticosteroid use. PD is assessed as >=25% increase in sum of products of the longest diameters of all index lesions (enhancing,measurable) compared with the smallest recorded sum (nadir); or unequivocal PD of existing non-index lesions (non-enhancing and enhancing, non-measurable); or unequivocal appearance of new lesions); or neurological worsening (if corticosteroid dose is stable or increased) compared to neurological evaluation at previous disease assessment with no need for a confirmatory scan. Participants without a PFS event were censored at last disease assessment.

End point type	Secondary

End point timeframe:

Randomization until PFS Event (Until data cutoff= 31 March 2012 [up to 29.5 months])

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Months				
median (confidence interval 95%)	8.4 (7.9 to 9.7)	4.3 (4.1 to 5.1)		

Statistical analyses

Statistical analysis title	PFS as Assessed by an Independent Review Facility
Comparison groups	Bevacizumab + RT + Temozolomide v Placebo + RT + Temozolomide
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.71

Notes:

[3] - Stratified by Region and RPA Class

Secondary: Kaplan-Meier (KM) Estimate of One Year Overall Survival

End point title	Kaplan-Meier (KM) Estimate of One Year Overall Survival

End point description:

KM estimate of one year overall survival (probability to survive for at least 1 year) was reported. Corresponding 95% confidence interval (CI) was calculated using Greenwood’s formula. Intent to treat (ITT) population.

End point type	Secondary

End point timeframe:

Randomization until Overall Survival Event (Until data cutoff= 28 February 2013 [up to 42.2 months])

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Probability of being alive				
number (confidence interval 95%)	0.72 (0.68 to 0.77)	0.66 (0.62 to 0.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier (KM) Estimate of Two Year Overall Survival

End point title	Kaplan-Meier (KM) Estimate of Two Year Overall Survival

End point description:

KM estimate of two year overall survival was reported (probability to survive for at least 2 years). Corresponding 95% CI was calculated using Greenwood's formula. Intent to treat population.

End point type	Secondary

End point timeframe:

Randomization until Overall Survival Event (Until data cutoff= 28 February 2013 [up to 42.2 months])

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Probability of being alive				
number (confidence interval 95%)	0.34 (0.29 to 0.38)	0.3 (0.26 to 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable/Improved Health Related Quality of Life (HRQoL) Using the European Organisation for Research and Treatment of Cancer Scales (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Supplemented by a Brain Cancer Module 20 (BN20)

End point title	Duration of Stable/Improved Health Related Quality of Life (HRQoL) Using the European Organisation for Research and Treatment of Cancer Scales (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Supplemented by a Brain Cancer Module 20 (BN20)

End point description:

EORTC QLQ-C30,BN20 questionnaires were used during PFS time.EORTC QLQ-C30:30-item questionnaire in 5 functional scales(physical,role,emotional,cognitive,social),3 symptoms scales,6 item measures and global health status/QoL scale.Items rated:1=not at all to 4=very much.Global health status/QoL items were rated:1=very poor to 7=excellent.The BN20:20 questions in 4 scales(future uncertainty,visual disorder,motor dysfunction,communication deficit)and 7 single-item measures rated as:1=not at all to 4=very much.All scores and single-items to a 0 to 100 scale were standardized.Stable HRQoL:Change from baseline within 10 points.Improved HRQoL:Increase of at least 10 points for functioning/global health status or decrease of at least 10 points for symptom.PFS:time from randomization to PD or death.PD:>=25% rise in SPD of longest diameters of all index lesions;or unequivocal progression of existing non-index lesions;or unequivocal 1 or more new lesions;or neurologically worsened.ITT population

End point type	Secondary

End point timeframe:

Randomization until PFS Event [Until data cutoff= 31 March 2012 (up to 31.4 months)

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	463		
Units: Months				
median (full range (min-max))				
Global health status	8 (0 to 26)	4 (1 to 29)		
Physical functioning	7 (0 to 27)	5 (1 to 29)		
Social functioning	8 (0 to 26)	4 (0 to 27)		
Motor dysfunction	7 (1 to 27)	4 (0 to 26)		
Communication deficit	8 (0 to 27)	4 (1 to 24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Non-Serious Adverse Events (non-SAEs), SAEs and Death

End point title	Number of Participants With Non-Serious Adverse Events (non-SAEs), SAEs and Death

End point description:

An AE was any unfavorable and unintended sign,symptom,or disease associated with the use of the study drug,whether or not considered related to the study drug.Preexisting conditions that worsened during the study were reported as AEs.SAE is any experience that suggests a significant hazard,contraindication,side effect or precaution that:results in death,is life-threatening,required in-patient hospitalization or prolongation of existing hospitalization,results in persistent or significant disability/incapacity,is a congenital anomaly/birth defect or is medically significant.Non-SAE included all AEs except SAE(non-SAE =all AE-SAEs).Safety Population:all randomized participants who received study treatment(10 participants did not receive at least 1 dose of study treatment and were excluded,4 in Placebo & 6 in Bevacizumab.9 participants randomized to the Placebo+RT+Temozolomide arm incorrectly received at least 1 dose of bevacizumab and were added to the Bevacizumab+RT+Temozolomide arm.

End point type	Secondary

End point timeframe:

Randomization until Overall Survival Event (Until data cutoff= 28 February 2013 [up to 44.4 months])

End point values	Bevacizumab + RT + Temozolomide	Placebo + RT + Temozolomide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	461	450		
Units: Subjects				
Non-SAEs	437	412		
SAEs	179	115		
Death	335	337		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization until Overall Survival Event (Until data cutoff= 28 February 2013 [up to 44.4 months])

Adverse event reporting additional description:

Safety Population. Ten participants did not receive at least one dose of study treatment and were therefore excluded, 4 in Placebo and 6 in Bevacizumab. Nine participants randomized to the Placebo+RT+Temozolomide arm incorrectly received at least 1 dose of bevacizumab and were added to the Bevacizumab+RT+Temozolomide arm for Safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Placebo + RT+Temozolomide

Reporting group description:

In the Concurrent Phase subjects received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6.1 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Reporting group title	Bevacizumab + RT + Temozolomide

Reporting group description:

In the Concurrent Phase subjects received RT in daily fractions of 2 Gy given 5 days per weeks for 6.1 weeks (for a total of 60 Gy) and temozolomide 75 mg/m^2 daily from the first day to the last day of radiotherapy (for a maximum of 49 days in case of delay to the end of radiation therapy) and bevacizumab (Avastin) 10 mg/kg IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Subjects then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The subjects then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.

Serious adverse events	Placebo + RT+Temozolomide	Bevacizumab + RT + Temozolomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	115 / 450 (25.56%)	179 / 461 (38.83%)	
number of deaths (all causes)	337	336	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 450 (0.22%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Basal cell carcinoma			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	6 / 450 (1.33%)	11 / 461 (2.39%)	
occurrences causally related to treatment / all	4 / 6	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 450 (0.22%)	4 / 461 (0.87%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 450 (0.67%)	8 / 461 (1.74%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	2 / 450 (0.44%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Fatigue			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Impaired Healing			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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			
Scrotal cyst			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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			
Pulmonary embolism			
subjects affected / exposed	12 / 450 (2.67%)	13 / 461 (2.82%)	
occurrences causally related to treatment / all	10 / 12	13 / 13	
deaths causally related to treatment / all	0 / 1	2 / 2	
Lung disorder			
subjects affected / exposed	1 / 450 (0.22%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

Acute respiratory distress syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin increased			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	2 / 450 (0.44%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haemorrhage			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			

subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (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	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (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			
convulsion			
subjects affected / exposed	6 / 450 (1.33%)	5 / 461 (1.08%)	
occurrences causally related to treatment / all	4 / 6	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 450 (0.44%)	8 / 461 (1.74%)	
occurrences causally related to treatment / all	2 / 2	9 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Brain oedema			
subjects affected / exposed	4 / 450 (0.89%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 450 (0.44%)	4 / 461 (0.87%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 450 (0.44%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 450 (0.44%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 450 (0.22%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia stroke			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			

subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (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	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 450 (1.78%)	17 / 461 (3.69%)	
occurrences causally related to treatment / all	8 / 8	18 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 450 (0.44%)	4 / 461 (0.87%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 450 (0.22%)	5 / 461 (1.08%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	5 / 450 (1.11%)	5 / 461 (1.08%)	
occurrences causally related to treatment / all	5 / 6	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 450 (0.00%)	4 / 461 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 450 (0.22%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Anal prolapse			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
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	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatic function abnormal			

subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prurigo			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
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	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 450 (1.11%)	10 / 461 (2.17%)	
occurrences causally related to treatment / all	2 / 5	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sepsis			
subjects affected / exposed	1 / 450 (0.22%)	6 / 461 (1.30%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	2 / 3	
Brain abscess			
subjects affected / exposed	3 / 450 (0.67%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	3 / 450 (0.67%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 450 (0.67%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 450 (0.44%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 450 (0.44%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 450 (0.22%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection			
subjects affected / exposed	0 / 450 (0.00%)	3 / 461 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infection			
subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			

subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	2 / 450 (0.44%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 450 (0.22%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumonia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis herpes			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (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	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			

subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Tonsilitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (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			
Hyperglycaemia			
subjects affected / exposed	5 / 450 (1.11%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 450 (0.67%)	2 / 461 (0.43%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	3 / 450 (0.67%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 450 (0.00%)	1 / 461 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			

subjects affected / exposed	1 / 450 (0.22%)	0 / 461 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + RT+Temozolomide	Bevacizumab + RT + Temozolomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	412 / 450 (91.56%)	437 / 461 (94.79%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	51 / 450 (11.33%)	175 / 461 (37.96%)	
occurrences (all)	62	270	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	178 / 450 (39.56%)	191 / 461 (41.43%)	
occurrences (all)	220	277	
Asthenia			
subjects affected / exposed	63 / 450 (14.00%)	86 / 461 (18.66%)	
occurrences (all)	76	107	
Oedema peripheral			
subjects affected / exposed	34 / 450 (7.56%)	36 / 461 (7.81%)	
occurrences (all)	42	43	
Pyrexia			
subjects affected / exposed	26 / 450 (5.78%)	39 / 461 (8.46%)	
occurrences (all)	28	50	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	22 / 450 (4.89%)	98 / 461 (21.26%)	
occurrences (all)	23	140	
Cough			
subjects affected / exposed	46 / 450 (10.22%)	55 / 461 (11.93%)	
occurrences (all)	54	67	
Dyspnoea			

subjects affected / exposed	18 / 450 (4.00%)	26 / 461 (5.64%)	
occurrences (all)	19	30	
Oropharyngeal pain			
subjects affected / exposed	12 / 450 (2.67%)	29 / 461 (6.29%)	
occurrences (all)	14	32	
Dysphonia			
subjects affected / exposed	7 / 450 (1.56%)	42 / 461 (9.11%)	
occurrences (all)	8	46	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	42 / 450 (9.33%)	53 / 461 (11.50%)	
occurrences (all)	46	59	
Depression			
subjects affected / exposed	30 / 450 (6.67%)	43 / 461 (9.33%)	
occurrences (all)	30	44	
Anxiety			
subjects affected / exposed	25 / 450 (5.56%)	29 / 461 (6.29%)	
occurrences (all)	26	32	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 450 (4.00%)	36 / 461 (7.81%)	
occurrences (all)	19	36	
Alanine aminotransferase increased			
subjects affected / exposed	25 / 450 (5.56%)	22 / 461 (4.77%)	
occurrences (all)	29	25	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	42 / 450 (9.33%)	38 / 461 (8.24%)	
occurrences (all)	43	38	
Nervous system disorders			
Headache			
subjects affected / exposed	130 / 450 (28.89%)	172 / 461 (37.31%)	
occurrences (all)	183	265	
Dizziness			
subjects affected / exposed	53 / 450 (11.78%)	46 / 461 (9.98%)	
occurrences (all)	57	61	

Dysgeusia			
subjects affected / exposed	33 / 450 (7.33%)	39 / 461 (8.46%)	
occurrences (all)	36	43	
Convulsion			
subjects affected / exposed	39 / 450 (8.67%)	36 / 461 (7.81%)	
occurrences (all)	64	60	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	120 / 450 (26.67%)	148 / 461 (32.10%)	
occurrences (all)	205	297	
Neutropenia			
subjects affected / exposed	53 / 450 (11.78%)	66 / 461 (14.32%)	
occurrences (all)	82	121	
Leukopenia			
subjects affected / exposed	40 / 450 (8.89%)	56 / 461 (12.15%)	
occurrences (all)	84	124	
Lymphopenia			
subjects affected / exposed	39 / 450 (8.67%)	34 / 461 (7.38%)	
occurrences (all)	53	46	
Anaemia			
subjects affected / exposed	34 / 450 (7.56%)	27 / 461 (5.86%)	
occurrences (all)	48	40	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	191 / 450 (42.44%)	223 / 461 (48.37%)	
occurrences (all)	278	367	
Constipation			
subjects affected / exposed	137 / 450 (30.44%)	178 / 461 (38.61%)	
occurrences (all)	178	247	
Vomiting			
subjects affected / exposed	100 / 450 (22.22%)	145 / 461 (31.45%)	
occurrences (all)	149	224	
Diarrhoea			
subjects affected / exposed	69 / 450 (15.33%)	95 / 461 (20.61%)	
occurrences (all)	90	149	
Abdominal pain			

subjects affected / exposed	17 / 450 (3.78%)	33 / 461 (7.16%)	
occurrences (all)	20	39	
Dyspepsia			
subjects affected / exposed	16 / 450 (3.56%)	31 / 461 (6.72%)	
occurrences (all)	18	37	
Abdominal pain upper			
subjects affected / exposed	12 / 450 (2.67%)	35 / 461 (7.59%)	
occurrences (all)	12	39	
Gingival bleeding			
subjects affected / exposed	6 / 450 (1.33%)	36 / 461 (7.81%)	
occurrences (all)	8	46	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	162 / 450 (36.00%)	180 / 461 (39.05%)	
occurrences (all)	165	186	
Rash			
subjects affected / exposed	60 / 450 (13.33%)	76 / 461 (16.49%)	
occurrences (all)	81	95	
Pruritus			
subjects affected / exposed	37 / 450 (8.22%)	54 / 461 (11.71%)	
occurrences (all)	44	68	
Dry skin			
subjects affected / exposed	24 / 450 (5.33%)	34 / 461 (7.38%)	
occurrences (all)	25	38	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	19 / 450 (4.22%)	72 / 461 (15.62%)	
occurrences (all)	21	122	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 450 (6.67%)	71 / 461 (15.40%)	
occurrences (all)	32	86	
Pain in extremity			
subjects affected / exposed	22 / 450 (4.89%)	48 / 461 (10.41%)	
occurrences (all)	28	54	
Back pain			

subjects affected / exposed	29 / 450 (6.44%)	37 / 461 (8.03%)	
occurrences (all)	32	40	
Muscular weakness			
subjects affected / exposed	33 / 450 (7.33%)	29 / 461 (6.29%)	
occurrences (all)	36	32	
Musculoskeletal pain			
subjects affected / exposed	12 / 450 (2.67%)	39 / 461 (8.46%)	
occurrences (all)	12	44	
Myalgia			
subjects affected / exposed	12 / 450 (2.67%)	28 / 461 (6.07%)	
occurrences (all)	13	30	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 450 (5.78%)	63 / 461 (13.67%)	
occurrences (all)	50	90	
Urinary tract infection			
subjects affected / exposed	27 / 450 (6.00%)	49 / 461 (10.63%)	
occurrences (all)	31	70	
Upper respiratory tract infection			
subjects affected / exposed	13 / 450 (2.89%)	31 / 461 (6.72%)	
occurrences (all)	16	40	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	74 / 450 (16.44%)	116 / 461 (25.16%)	
occurrences (all)	89	157	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2010	An additional interim analysis was introduced to be triggered when approximately 50% of the deaths required for the final OS analysis had occurred. In the statistical plan, the difference between the arms for the 1-year and 2-year OS rates was tested using a z test rather than a Cochran Mantel Haenzel test.
28 August 2012	The amendment ensured continuity of Bevacizumab treatment for those subjects still on active treatment at the time of final unblinding at the sites (after the final OS analysis). Data collection was restricted to the reporting of related SAEs and adverse events of special interest (AESIs) via the SAE forms only. At the time of the treatment allocation unblinding, all subjects receiving placebo were discontinued from study treatment. Safety data was to be collected for 90 days (AEs), 183 days (AESI), or indefinitely (relates SAEs) following the last administration of study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported