



Clinical trial results:

A randomized, open-label, multi-center Phase II trial of bevacizumab and radiotherapy fol-lowed by bevacizumab and irinotecan vs. temozolomide and radiotherapy followed by temo-zolomide monotherapy in patients with newly diagnosed glioblastoma and a non-methylated MGMT-promoter (GLARIUS)

Summary

EudraCT number	2009-010390-21
Trial protocol	DE
Global end of trial date	24 November 2014

Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	25 February 2016

Trial information

Trial identification

Sponsor protocol code	ML21965
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00967330
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +49 41616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +49 41616878333, 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	24 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, open-label, multi-center Phase II trial was intended to investigate the efficacy and safety of bevacizumab and radiotherapy followed by bevacizumab and irinotecan (BEV/IRI) as compared with temozolomide (TMZ) and radiotherapy followed by 6 courses of maintenance with TMZ.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) standards and according to the all local laws and regulations concerning clinical study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 182
Worldwide total number of subjects	182
EEA total number of subjects	182

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)	144
From 65 to 84 years	38

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was done from Day 1-28 after resection.

Period 1

Period 1 title	Overall Study(overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + Irinotecan

Arm description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gray (Gy) given 5 fractions per week for 6 to 7 weeks and intravenous infusion (IV) of bevacizumab (BEV) 10 milligrams per kilogram (mg/kg) body weight every 14 ± 2 days starting during the first week to the last week of radiotherapy. Participants then entered the Maintenance Phase where they received BEV 10 mg/kg body weight and IV irinotecan (IRI) 125 milligrams per square meter (mg/m^2) body surface area (BSA) or $340 \text{ mg}/\text{m}^2$ BSA in participants not receiving enzyme-inducing antiepileptic drugs (EIAEDs) or receiving EIAEDs, respectively for every 14 ± 2 days until progressive disease (PD) or for a maximum treatment period of 2 years after inclusion of the last participant.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 weeks and IV infusion of BEV 10 mg/kg body weight every 14 ± 2 days starting during the first week to the last week of radiotherapy.

Arm title	Temozolomide
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Arm description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 week and temozolomide (TMZ) capsule $75 \text{ mg}/\text{m}^2$ BSA daily from the first day to the last day of radiotherapy . There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of TMZ 150 to $200 \text{ mg}/\text{m}^2$ BSA daily in the first 5 days of each cycle until PD or for a maximum treatment period of 2 years after inclusion of the last participant. Only participants with progressive disease during or after TMZ therapy could receive bevacizumab (BEV)/irinotecan (IRI) or BEV monotherapy as optional second-line study therapy at the discretion of the investigator, if eligible.

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 week and TMZ capsule $75 \text{ mg}/\text{m}^2$ BSA daily from the first day to the last

day of radiotherapy . There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of TMZ 150 to 200 mg/m² BSA daily in the first 5 days of each cycle until PD or for a maximum treatment period of 2 years after inclusion of the last participant.

Number of subjects in period 1	Bevacizumab + Irinotecan	Temozolomide
Started	122	60
Completed	0	0
Not completed	122	60
Adverse event, serious fatal	102	51
Consent withdrawn by subject	6	-
Regular	10	3
Does not meet Inclusion-Exclusion criteria	3	4
Lost to follow-up	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab + Irinotecan
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gray (Gy) given 5 fractions per week for 6 to 7 weeks and intravenous infusion (IV) of bevacizumab (BEV) 10 milligrams per kilogram (mg/kg) body weight every 14 ± 2 days starting during the first week to the last week of radiotherapy. Participants then entered the Maintenance Phase where they received BEV 10 mg/kg body weight and IV irinotecan (IRI) 125 milligrams per square meter (mg/m^2) body surface area (BSA) or 340 mg/m^2 BSA in participants not receiving enzyme-inducing antiepileptic drugs (EIAEDs) or receiving EIAEDs, respectively for every 14 ± 2 days until progressive disease (PD) or for a maximum treatment period of 2 years after inclusion of the last participant.

Reporting group title	Temozolomide
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 week and temozolomide (TMZ) capsule 75 mg/m^2 BSA daily from the first day to the last day of radiotherapy . There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of TMZ 150 to 200 mg/m^2 BSA daily in the first 5 days of each cycle until PD or for a maximum treatment period of 2 years after inclusion of the last participant. Only participants with progressive disease during or after TMZ therapy could receive bevacizumab (BEV)/irinotecan (IRI) or BEV monotherapy as optional second-line study therapy at the discretion of the investigator, if eligible.

Reporting group values	Bevacizumab + Irinotecan	Temozolomide	Total
Number of subjects	122	60	182
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	55.4 ± 10.17	56.4 ± 10.84	-
Gender categorical Units: Subjects			
Female	39	21	60
Male	83	39	122

End points

End points reporting groups

Reporting group title	Bevacizumab + Irinotecan
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gray (Gy) given 5 fractions per week for 6 to 7 weeks and intravenous infusion (IV) of bevacizumab (BEV) 10 milligrams per kilogram (mg/kg) body weight every 14 ± 2 days starting during the first week to the last week of radiotherapy. Participants then entered the Maintenance Phase where they received BEV 10 mg/kg body weight and IV irinotecan (IRI) 125 milligrams per square meter (mg/m^2) body surface area (BSA) or $340 \text{ mg}/\text{m}^2$ BSA in participants not receiving enzyme-inducing antiepileptic drugs (EIAEDs) or receiving EIAEDs, respectively for every 14 ± 2 days until progressive disease (PD) or for a maximum treatment period of 2 years after inclusion of the last participant.

Reporting group title	Temozolomide
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 week and temozolomide (TMZ) capsule $75 \text{ mg}/\text{m}^2$ BSA daily from the first day to the last day of radiotherapy. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of TMZ 150 to $200 \text{ mg}/\text{m}^2$ BSA daily in the first 5 days of each cycle until PD or for a maximum treatment period of 2 years after inclusion of the last participant. Only participants with progressive disease during or after TMZ therapy could receive bevacizumab (BEV)/irinotecan (IRI) or BEV monotherapy as optional second-line study therapy at the discretion of the investigator, if eligible.

Primary: Percentage of Participants Achieving Progression-Free Survival (PFS) Without Disease Progression or Death at 6 Months

End point title	Percentage of Participants Achieving Progression-Free Survival (PFS) Without Disease Progression or Death at 6 Months
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End point description:

Progression-free survival was defined as the time from randomization to objective tumor progression or death from any cause, whichever came first. Progression was defined as 25 percent (%) increase in size of enhancing tumor or any new tumor on gadolinium contrast agent magnetic resonance imaging (Gd-MRI) scans, or neurologically worse, and steroids stable or increased. Percentage of participants with achieving PFS without disease progression or death was reported. Intent-to-treat (ITT) population included participants randomized for whom it cannot be ruled out, that they took study medication at least once and where primary variable was measured at least once under study medication. Data were analyzed according to the treatment randomized (as randomized).

End point type	Primary
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End point timeframe:

6 months

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: Percentage of Participants				
number (confidence interval 95%)	79.31 (68.859 to 84.617)	42.59 (26.68 to 53.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Chi-squared

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description: Progression-free survival was defined as the time from randomization to objective tumor progression or death from any cause, whichever came first. Progression was defined as 25% increase in size of enhancing tumor or any new tumor on Gd-MRI scans, or neurologically worse, and steroids stable or increased. PFS was estimated using Kaplan-Meier method. ITT population. Data were analyzed according to the treatment randomized (as randomized).	
End point type	Secondary
End point timeframe: From baseline to the end of the study (up to 4.5 years)	

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: Months				
median (full range (min-max))	9.74 (8.72 to 10.76)	5.99 (2.73 to 6.15)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0012
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.588
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.423
upper limit	0.817

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival was defined as the time from randomization to death from any cause. OS was estimated using Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

From baseline until death (up to 4.5 years)

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: Months				
median (full range (min-max))	16.64 (15.43 to 18.36)	17.3 (14.77 to 20.36)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8283
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	0.963
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.354

Secondary: Percentage of Participants Who Discontinued

End point title	Percentage of Participants Who Discontinued
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End point description:

Discontinuation was defined as the percentage of participants who permanently discontinued treatment in either treatment arm. Percentage of participant with individual discontinuation reason are reported. CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events . Other reason refers to any other reason than the specified ones. ITT population.

End point type	Secondary
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End point timeframe:

From baseline until end of study (up to 4.5 years)

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: Percentage of participants				
number (not applicable)				
Persisting non-hematological toxicity CTCAE Grade3	0	1.9		
CNS hemorrhagic event (CTCAE Grade >1)	0.9	0		
Gastro-intestinal perforation (CTCAE Grade 1-4)	0.9	0		
Other	9.5	5.6		
Participant's wish	6	5.6		
Progressive disease	74.1	57.4		
Proteinuria (nephrotic syndrome) (CTCAE Grade 4)	0.9	0		
Regular	1.7	27.8		
Repeated CTCAE Grade 4 hematological toxicity	0	0.9		
Venous thrombosis/embolism	0.9	0		
Wound dehiscence requiring medical intervention	0.9	0		
Wound dehiscence requiring surgical intervention	4.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With A Best Overall Response (BOR) of Complete Response (CR) and With A BOR of CR or Partial Response (PR)

End point title	Number of Participants With A Best Overall Response (BOR) of Complete Response (CR) and With A BOR of CR or Partial Response (PR)
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End point description:

BOR was defined as the best response observed for a participant during assessment. Number of participants who had BOR as CR and number of participants who had BOR as CR or PR were reported. Complete response was defined as disappearance of all enhancing tumor on consecutive Gd-MRI scans at least 1 month apart, off steroids, and neurologically stable or improved. Partial response was defined as 50% reduction in size of enhancing tumor on consecutive Gd-MRI scans at least 1 month apart, steroids stable or reduced, and neurologically stable or improved. ITT population. Data were analyzed according to the treatment randomized (as randomized). Here, number of participants analyzed = participants who were evaluable for this outcome and n = participants who were evaluable of specified time-point.

End point type	Secondary
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End point timeframe:

4 week after radiotherapy (RT) (up to Week 4), >4 Week after RT (up to Week 8) and Month 6.

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	46		
Units: Participants				
number (not applicable)				
CR at 4 weeks after RT (n=110,46)	11	2		
CR at >4 weeks after RT (n=95,35)	11	1		
CR at Month 6 (n=91,28)	3	1		
CR or PR at 4 Week after RT (n=110,46)	42	6		
CR or PR at >4 Week after RT (n=95,35)	18	3		
CR or PR at Month 6 (n=91,28)	5	3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.34745
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.14

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17923
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.17

Statistical analysis title	Statistical Analysis 3
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.08

Statistical analysis title	Statistical Analysis 4
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0021
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.38

Statistical analysis title	Statistical Analysis 5
Comparison groups	Bevacizumab + Irinotecan v Temozolomide

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.18761
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.23

Statistical analysis title	Statistical Analysis 6
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38974
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.07

Secondary: Percentage of Participants With Response on FLAIR Imaging

End point title	Percentage of Participants With Response on FLAIR Imaging
End point description:	
FLAIR lesions were determined as "initial", "stable", "progressive" or "decreased". FLAIR lesions was determined as "progressive" only if they were not be attributed to causes apart from tumor infiltration (sequelae of radiation therapy, demyelination, ischemia, infection, seizures, or other treatment effects). Percentage of participants are based on ITT population. Here, n = participants with at least 1 assessment during specified time-point. Dis.=Discontinuation.	
End point type	Secondary
End point timeframe:	
At screening, Baseline, Month 6 and Therapy Discontinuation (Up to 4.5 years)	

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: Percentage of participant				
number (not applicable)				
Screening: Initial Flair Lesion (n=116,54)	72.4	72.2		
Screening:Stable Flair Lesion (n=116,54)	17.2	16.7		
Baseline:Decreased FLAIR Lesions (n=105,46)	16.4	20.4		
Baseline:Initial FLAIR Lesions (n=105,46)	18.1	18.5		
Baseline:Progressive FLAIR Lesions (n=105,46)	14.7	11.1		
Baseline: Stable FLAIR Lesions (n=105,46)	41.4	35.2		
Month 6:Progressive FLAIR Lesions (n=91,28)	16.4	22.2		
Month 6: Stable FLAIR Lesions (n=91,28)	62.1	29.6		
Therapy Dis.:Decreased FLAIR Lesions (n=55,31)	0.9	0		
Therapy Dis.:Progressiv FLAIR Lesions (n=55,31) 29	29.3	27.8		
Therapy Dis.:Stable FLAIR Lesions (n=55,31)	17.2	29.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ - C30) at Baseline, Post-Baseline (up to Month 30)

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ - C30) at Baseline, Post-Baseline (up to Month 30)
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End point description:

The EORTC QLQ-C30 incorporates: 5 functional scales (physical, role, cognitive, emotional, and social); 9 symptom scales (fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties); and a global health and quality-of-life scale. Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores were averaged and transformed to 0-100 scale; higher score for Global QoL/functional scales=better level of functioning or a higher score for symptom scale=greater degree of symptoms. The change in global health status was determined to be the difference in values at baseline and each specific visit. The term "baseline" refers to the time of randomization to the maintenance phase. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Post-Baseline (up to Month 30).

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Physical Functioning	-8.3513 (-11.8714 to -4.8312)	-6.2511 (-11.213 to -1.2892)		
Role Functioning	-0.7635 (-6.1695 to 4.6425)	-2.2339 (-9.9836 to 5.5159)		
Emotional Functioning	2.2774 (-1.7409 to 6.2958)	2.2547 (-3.4834 to 7.9928)		
Cognitive Functioning	-2.0188 (-6.2256 to 2.188)	-3.8401 (-9.8118 to 2.1317)		
Social Functioning	-6.2324 (-11.348 to -1.1169)	-4.6198 (-11.9009 to 2.6613)		
Global health Status /QoL (qI)	-3.1134 (-6.5412 to 0.3145)	0.3855 (-4.422 to 5.193)		
Fatigue	5.5228 (1.6424 to 9.4031)	2.1779 (-3.322 to 7.6781)		
Nausea/Vomitting	8.9557 (6.5139 to 11.3974)	4.7597 (1.3958 to 8.1235)		
Pain	10.6876 (5.8004 to 15.5747)	1.5926 (-5.3301 to 8.5152)		
Dyspnoea	3.7134 (-0.3957 to 7.8226)	0.5046 (-5.2542 to 6.2635)		
Insomnia	-2.6266 (-7.8402 to 2.587)	-7.5026 (-14.8641 to -0.1411)		
Appetite loss	13.7423 (9.9118 to 17.5727)	10.9601 (5.6151 to 16.3051)		
Constipation	8.023 (3.9214 to 12.1246)	4.0855 (-1.6913 to 9.8624)		
Diarrhoea	6.023 (2.9313 to 9.1147)	-0.1455 (-4.3834 to 4.0925)		
Financial Problems	4.8435 (0.03603 to 9.651)	2.114 (-4.7005 to 8.9284)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4975
Method	ANOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	2.1002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9855
upper limit	8.186

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.76
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.4704
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9358
upper limit	7.9951

Statistical analysis title	Statistical Analysis 3
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9949
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.02278
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.035
upper limit	6.9895

Statistical analysis title	Statistical Analysis 4
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Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6253
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.8213
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.155
upper limit	5.5125

Statistical analysis title	Statistical Analysis 5
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7219
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	1.6126
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2953
upper limit	10.5205

Statistical analysis title	Statistical Analysis 6
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2443
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	3.4989
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4046
upper limit	9.4023

Statistical analysis title	Statistical Analysis 7
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3287
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.3449
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.0739
upper limit	3.3841

Statistical analysis title	Statistical Analysis 8
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0485
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3635
upper limit	-0.0285

Statistical analysis title	Statistical Analysis 9
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0354
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-9.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5629
upper limit	-0.6271

Statistical analysis title	Statistical Analysis 10
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3724
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.2088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2784
upper limit	3.8608

Statistical analysis title	Statistical Analysis 11
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2884
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.876
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9002
upper limit	4.1482

Statistical analysis title	Statistical Analysis 12
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4081
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.782

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3926
upper limit	3.8282

Statistical analysis title	Statistical Analysis 13
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.275
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.9375
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.0245
upper limit	3.1495

Statistical analysis title	Statistical Analysis 14
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0213
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-6.1685
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4129
upper limit	-0.9241

Statistical analysis title	Statistical Analysis 15
Comparison groups	Bevacizumab + Irinotecan v Temozolomide

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5201
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.7295
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.0727
upper limit	5.6137

Secondary: Change From Baseline for EORTC QLQ Brain Neoplasm 20 (BN20) at Baseline, Post-Baseline (up to Month 30)

End point title	Change From Baseline for EORTC QLQ Brain Neoplasm 20 (BN20) at Baseline, Post-Baseline (up to Month 30)
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End point description:

EORTC QLQ-BN20 consisted of 20 items assessing visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g. headaches and seizures), treatment toxicities (e.g. hair loss) and future uncertainty. All of the 20 items are rated on a 4 point Likert scale from 1=not at all, 2=a little, 3=quite a bit and 4=very much, and were linearly transformed to a 0-100 scale, with higher scores indicating more severe symptoms. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Post-Baseline (up to Month 30)

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Future uncertainty	-5.2779 (-9.2589 to -1.2968)	-8.5478 (-14.3337 to -2.7619)		
Visual disorder	-2.0869 (-4.5092 to 0.3354)	-3.202 (-6.7584 to 0.3528)		
Motor dysfunction	5.4416 (2.3943 to 8.4888)	6.5429 (2.1426 to 10.9433)		
Communication deficit	4.744 (1.6899 to 7.798)	4.6431 (0.2253 to 9.0609)		
Headaches	4.3905 (0.6465 to 8.1345)	-3.9389 (-9.2879 to 1.4101)		
Drowsines	11.7204 (7.6425 to 15.7983)	8.2805 (2.3973 to 14.1637)		

Hair loss	11.9235 (7.6344 to 16.2127)	7.3328 (1.0111 to 13.6545)		
Itchy skin	5.4882 (2.0875 to 8.889)	6.469 (1.5048 to 11.4331)		
Weakness of legs	8.9586 (4.9123 to 13.0048)	7.9245 (2.0687 to 13.7804)		
Bladder control	1.502 (-1.0917 to 4.0957)	1.971 (-1.8122 to 5.7543)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3613
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.2699
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2983
upper limit	3.7585

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6146
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.1159
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4654
upper limit	3.2336

Statistical analysis title	Statistical Analysis 3
Comparison groups	Bevacizumab + Irinotecan v Temozolomide

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.686
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	1.1014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2449
upper limit	6.4477

Statistical analysis title	Statistical Analysis 4
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9706
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.468
upper limit	5.2663

Statistical analysis title	Statistical Analysis 5
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0124
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-8.3294
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.855
upper limit	-1.8037

Statistical analysis title	Statistical Analysis 6
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Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5997
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.0054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7654
upper limit	2.7545

Statistical analysis title	Statistical Analysis 7
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3458
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.4399
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6002
upper limit	3.7204

Statistical analysis title	Statistical Analysis 8
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2383
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-4.5908
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2279
upper limit	3.0464

Statistical analysis title	Statistical Analysis 9
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7491
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.9807
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.0373
upper limit	6.9988

Statistical analysis title	Statistical Analysis 10
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7755
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.0341
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1508
upper limit	6.0827

Statistical analysis title	Statistical Analysis 11
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.841
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.469
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1211
upper limit	5.0591

Secondary: Change From Baseline for Mini-Mental Status Examination (MMSE) at Baseline, Post-Baseline (up to Month 30)

End point title	Change From Baseline for Mini-Mental Status Examination (MMSE) at Baseline, Post-Baseline (up to Month 30)
End point description: The MMSE briefly measures orientation to time and place, immediate recall, short-term verbal memory, calculation, language and construct ability. Each area tested had a designated point value, the total score can range from 0 to 30, with a higher score indicating better function.	
End point type	Secondary
End point timeframe: Baseline, Post-Baseline (up to Month 30)	

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Orientation to time and place	-0.01771 (-0.1406 to 0.1052)	-0.211 (-0.3907 to -0.03135)		
Immediate recall	-0.00264 (-0.02163 to 0.01635)	-0.03219 (-0.05888 to -0.00551)		
Repetitions required	-0.05763 (-0.1971 to 0.0818)	0.0853 (-0.1212 to 0.2918)		
Calculations	-0.2153 (-0.3911 to -0.03952)	-0.212 (-0.4706 to 0.04652)		
Short-term verbal memory	0.2012 (0.106 to 0.2964)	0.1634 (0.02332 to 0.3034)		
Language and construct ability	-0.1254 (-0.2416 to -0.00908)	-0.2057 (-0.3765 to -0.03499)		
Total Score	-0.2871 (-0.7647 to 0.1905)	-0.5999 (-1.3069 to 0.1071)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Bevacizumab + Irinotecan v Temozolomide

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0817
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1933
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.411
upper limit	0.02438

Statistical analysis title	Statistical Analysis 2
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0773
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.02955
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06234
upper limit	0.003241

Statistical analysis title	Statistical Analysis 3
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2608
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1429
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1065
upper limit	0.3924

Statistical analysis title	Statistical Analysis 4
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Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9836
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.003262
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3092
upper limit	0.3158

Statistical analysis title	Statistical Analysis 5
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.661
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.03782
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2071
upper limit	0.1315

Statistical analysis title	Statistical Analysis 6
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4464
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.08037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2875
upper limit	0.1268

Statistical analysis title	Statistical Analysis 7
Comparison groups	Bevacizumab + Irinotecan v Temozolomide
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4717
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1658
upper limit	0.5402

Secondary: Change From Baseline for Karnofsky Performance Status (KPS) Score at Baseline, Post-Baseline (up to Month 30)

End point title	Change From Baseline for Karnofsky Performance Status (KPS) Score at Baseline, Post-Baseline (up to Month 30)
End point description:	
KPS is an 11-level score (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100) which ranges between 0 (death) to 100 (complete healthy status); a higher score represents a higher ability to perform daily tasks. Deterioration in KPS was defined as decrease of 20 or more points in KPS score. ITT population.	
End point type	Secondary
End point timeframe:	
Baseline, Post-Baseline (up to Month 30)	

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	54		
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.3399 (-5.2132 to -1.4666)	-5.4909 (-8.2693 to -2.7126)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Temozolomide v Bevacizumab + Irinotecan

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2078
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4983
upper limit	1.1963

Secondary: Percentage of Participants Who Received Corticosteroid for Glioblastoma

End point title	Percentage of Participants Who Received Corticosteroid for Glioblastoma
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End point description:

Participants used corticosteroids for the glioblastoma condition. Corticosteroids included dexamethasone, methylprednisone, fortectortin, hydrocortisone, urbason, and prednisolone. Safety population was used for this analysis. The safety population (SAF) was defined to include all participants who received at least 1 dose of study medication. Data were analyzed according to the treatment actually received (as treated).

End point type	Secondary
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End point timeframe:

From baseline to Month 6

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	55		
Units: percentage of participants				
number (not applicable)	80	78.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure
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End point description:

The data "99999" signifies data not available as no data collected for the specified arm. Data for time to treatment failure were not collected as this outcome was removed as per changes in planned analysis.

End point type	Secondary
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End point timeframe:

From baseline until end of study (up to 4.5 years)

End point values	Bevacizumab + Irinotecan	Temozolomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	55		
Units: months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to the end of the study (up to 4.5 years)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Bevacizumab + Irinotecan
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gray (Gy) given 5 fractions per week for 6 to 7 weeks and intravenous infusion (IV) of bevacizumab (BEV) 10 milligrams per kilogram (mg/kg) body weight every 14 ± 2 days starting during the first week to the last week of radiotherapy. Participants then entered the Maintenance Phase where they received BEV 10 mg/kg body weight and IV irinotecan (IRI) 125 milligrams per square meter (mg/m^2) body surface area (BSA) or $340 \text{ mg}/\text{m}^2$ BSA in participants not receiving enzyme-inducing antiepileptic drugs (EIAEDs) or receiving EIAEDs, respectively for every 14 ± 2 days until progressive disease (PD) or for a maximum treatment period of 2 years after inclusion of the last participant.

Reporting group title	Temozolomide
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Reporting group description:

In the Concurrent Phase participants received radiotherapy in daily fractions of 1.8 to 2 Gy given 5 fractions per week for 6 to 7 week and temozolomide (TMZ) capsule $75 \text{ mg}/\text{m}^2$ BSA daily from the first day to the last day of radiotherapy. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of TMZ 150 to $200 \text{ mg}/\text{m}^2$ BSA daily in the first 5 days of each cycle until PD or for a maximum treatment period of 2 years after inclusion of the last participant. Only participants with progressive disease during or after TMZ therapy could receive bevacizumab (BEV)/irinotecan (IRI) or BEV monotherapy as optional second-line study therapy at the discretion of the investigator, if eligible.

Serious adverse events	Bevacizumab + Irinotecan	Temozolomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 119 (72.27%)	46 / 55 (83.64%)	
number of deaths (all causes)	102	51	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Therapeutic procedure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	41 / 119 (34.45%)	20 / 55 (36.36%)	
occurrences causally related to treatment / all	1 / 47	0 / 22	
deaths causally related to treatment / all	1 / 29	0 / 14	
Hernia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	2 / 119 (1.68%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 119 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Oedema			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
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			
Dyspnoea			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 119 (2.52%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fistula			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
General physical condition abnormal			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 119 (0.84%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound dehiscence			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular insufficiency			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 119 (0.00%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 119 (1.68%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebrovascular accident			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Complex partial seizures			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	17 / 119 (14.29%)	9 / 55 (16.36%)	
occurrences causally related to treatment / all	0 / 30	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	6 / 119 (5.04%)	6 / 55 (10.91%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	5 / 119 (4.20%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	2 / 119 (1.68%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 119 (0.84%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
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	2 / 119 (1.68%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal paralysis			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 119 (0.84%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 119 (3.36%)	5 / 55 (9.09%)	
occurrences causally related to treatment / all	1 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Otorrhoea			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Nausea			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis glandularis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
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			
Back pain			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bone abscess			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Brain abscess			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (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 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 119 (2.52%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 119 (2.52%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (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	0 / 119 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urosepsis			

subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection			
subjects affected / exposed	3 / 119 (2.52%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 119 (0.84%)	0 / 55 (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	2 / 119 (1.68%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 119 (0.84%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bevacizumab + Irinotecan	Temozolomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 119 (89.92%)	37 / 55 (67.27%)	
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 119 (50.42%)	22 / 55 (40.00%)	
occurrences (all)	128	51	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	54 / 119 (45.38%)	8 / 55 (14.55%)	
occurrences (all)	119	8	
Nausea			

subjects affected / exposed	88 / 119 (73.95%)	28 / 55 (50.91%)	
occurrences (all)	215	69	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2010	Amendment No.1, Protocol Version 2.0 (27 Oct 2010) was made in order to: Clarify the defined study procedures and time points; Revise the study flowchart; Ensure consistency between the study flow chart and the text describing the study visits; Ensure consistency between study protocol and other study documents, i.e., DSMB charter; Finally, minor typos or inconsistencies were corrected within this Amendment.
31 August 2011	Amendment No.2, Protocol Version 3.0 (31 Aug 2011) was made in order to: Document prolongation of recruitment phase; Allow for involvement of additional sites; Clarify study procedures; Update safety information according to new SmPCs.
18 April 2013	Amendment No.3, Protocol Version 4.0 (18 Apr 2013) was made in order to: Update responsible study personnel; Add evaluation in follow-up period; Revise the study flowchart; Clarify the defined study procedures.
14 October 2013	Amendment No.4, Protocol Version 5.0 (14 Oct 2013) was made in order to: Add biomarker analysis; Add evaluation in treatment period; Revise the study flowchart; Clarify the defined study procedures; Clarify statistical part of protocol.
27 August 2014	Amendment No.5, Protocol Version 6.0 (27 Aug 2014) was made in order to amend post-trial provision of care.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data for time to treatment failure were not collected as this outcome was removed as per changes in planned analysis.

Notes: