

**Clinical trial results:
Randomized Non Comparative Phase II Trial With Bevacizumab and
Fotemustine in the Treatment of Recurrent Glioblastoma
Summary**

EudraCT number	2011-001363-46
Trial protocol	IT
Global end of trial date	12 December 2013

Results information

Result version number	v3 (current)
This version publication date	19 June 2016
First version publication date	07 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set We have identified data errors in the EudraCT record of ML25739 whilst undergoing QC due to system bug.

Trial information**Trial identification**

Sponsor protocol code	ML25739
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01474239
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 68783333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 68783333, 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	12 December 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of bevacizumab in terms of the 6-month overall survival rate (OS-6), measured from the beginning of study drug administration to the death of the participant from any cause.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) and investigators were trained according to applicable Sponsor standard operating procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	71
From 65 to 84 years	20

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study included 28-day screening period. Participants were randomized according to a 2:1 ratio to one of the 2 treatment groups. A total of 99 participants were screened, of which 91 were randomized.

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

Arm description:

Participants received bevacizumab 10 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 14 days until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

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:

Bevacizumab was supplied in 4 milliliter (mL) ampoules of injectable 25 milligram per milliliter (mg/mL) solution to be given by infusion. The bevacizumab solution was not to be mixed with glucose solutions or any other products except saline solution (0.9 percent [%]). The final concentration had to be maintained within 1.4-16.5 mg/mL.

Arm title	Fotemustine
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Arm description:

Participants received fotemustine 75 milligrams per square meter (mg/m²) via IV infusion on Days 1, 8, and 15 (induction phase), followed by a 35-day drug-free interval, and then fotemustine 100 mg/m² every 21 days (maintenance phase) until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

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

Dosage and administration details:

Fotemustine was supplied in 4 mL ampoules containing 200 mg in a sterile alcohol solution. Fotemustine solution was diluted in 250-400 mL 5% glucose solution and administered by infusion.

Number of subjects in period 1	Bevacizumab	Fotemustine
Started	59	32
Completed	0	0
Not completed	59	32
Adverse Event	12	3
Death	1	1
Withdrawal for Economic Reason	1	-
Clinical Disease Progression	7	1
Consent Withdrawn by Subject	1	2
Disease Progression	37	25

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

Participants received bevacizumab 10 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 14 days until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Reporting group title	Fotemustine
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Reporting group description:

Participants received fotemustine 75 milligrams per square meter (mg/m²) via IV infusion on Days 1, 8, and 15 (induction phase), followed by a 35-day drug-free interval, and then fotemustine 100 mg/m² every 21 days (maintenance phase) until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Reporting group values	Bevacizumab	Fotemustine	Total
Number of subjects	59	32	91
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	56.86 ± 9.4	55.63 ± 10.64	-
Gender categorical Units: Subjects			
Female	20	9	29
Male	39	23	62

End points

End points reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

Participants received bevacizumab 10 milligrams per kilogram (mg/kg) via intravenous (IV) infusion every 14 days until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Reporting group title	Fotemustine
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Reporting group description:

Participants received fotemustine 75 milligrams per square meter (mg/m²) via IV infusion on Days 1, 8, and 15 (induction phase), followed by a 35-day drug-free interval, and then fotemustine 100 mg/m² every 21 days (maintenance phase) until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Primary: Percentage of Participants Alive 6 Months After Start of Treatment

End point title	Percentage of Participants Alive 6 Months After Start of Treatment ^[1]
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End point description:

Overall survival (OS) was defined as the time in months from the start of treatment to death due to any cause. If a participant was not known to have died, time was censored at the last date the participant was known to be alive, which was defined as the latest among date of last visit, date of last sample collected for laboratory exam, date of magnetic resonance imaging (MRI) assessment, date of last treatment, date of discontinuation, and date of last available follow-up visit. Participants with no information after baseline were censored at Day 1. OS was estimated by the Kaplan-Meier method. Analysis was performed on intent-to-treat (ITT) population defined as all randomized participants with at least one administration of the study drug.

End point type	Primary
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End point timeframe:

6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The performed statistical analysis was single arm analysis and in EudraCT it is not possible to report single arm statistical analysis.

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: percentage of participants				
number (confidence interval 95%)	62.07 (48.37 to 74.49)	73.33 (54.11 to 87.72)		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[2]
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End point description:

OS was defined as the time in months from the start of treatment to death due to any cause. If a participant was not known to have died, time was censored at the last date the participant was known to be alive, which was defined as the latest among date of last visit, date of last sample collected for laboratory exam, date of MRI assessment, date of last treatment, date of discontinuation, and date of last available follow-up visit. Participants with no information after baseline were censored at Day 1. OS was estimated by the Kaplan-Meier method. Analysis was performed on ITT population.

End point type | Primary

End point timeframe:

Baseline until death (up to 691 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The performed statistical analysis was single arm analysis and in EudraCT it is not possible to report single arm statistical analysis.

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: months				
median (confidence interval 95%)	7.26 (5.82 to 9.2)	8.66 (6.34 to 15.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Alive and Progression Free 6 Months After Start of Treatment

End point title | Percentage of Participants Who Were Alive and Progression Free 6 Months After Start of Treatment

End point description:

Progression-free survival (PFS) was defined as the time in months from the start of treatment to the date of the first occurrence of disease progression or death from any cause, whichever occurred first. PFS was estimated by the Kaplan-Meier method. Progression was assessed using Response Assessment in Neuro-Oncology (RANO) or the Macdonald Response Criteria, whichever occurred first. As per the RANO criteria, progression was defined as 25 percent (%) or more increase in enhancing lesions despite stable or increasing steroid dose; increase (significant) in non-enhancing T2/FLAIR lesions, not attributable to other non-tumor causes; any new lesions; and clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease). As per the Macdonald criteria, progression was defined as 25% or more increase in enhancing lesions; any new lesions; and clinical deterioration. Analysis was performed on ITT population.

End point type | Secondary

End point timeframe:

6 months

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: percentage of participants				
number (confidence interval 95%)	26.32 (15.54 to 39.66)	10.71 (2.27 to 28.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
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End point description:

PFS was defined as the time in months from the start of treatment to the date of the first occurrence of disease progression or death from any cause, whichever occurred first. PFS was estimated by Kaplan-Meier method. Progression was assessed using the RANO or the Macdonald Response Criteria, whichever occurred first. As per the RANO criteria, progression was defined as 25% or more increase in enhancing lesions despite stable or increasing steroid dose; increase (significant) in non-enhancing T2/FLAIR lesions, not attributable to other non-tumor causes; any new lesions; and clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease). As per the Macdonald criteria, progression was defined as 25% or more increase in enhancing lesions; any new lesions; and clinical deterioration. Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death (baseline, 46 days after first administration of study drug, and thereafter every 56 days up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: months				
median (confidence interval 95%)	3.38 (3.15 to 4.37)	3.45 (1.87 to 3.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive 9 Months After Start of Treatment

End point title	Percentage of Participants Alive 9 Months After Start of Treatment
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End point description:

OS was defined as the time in months from the start of treatment to death due to any cause. If a participant was not known to have died, time was censored at the last date the participant was known to be alive, which was defined as the latest among date of last visit, date of last sample collected for laboratory exam, date of MRI assessment, date of last treatment, date of discontinuation and date of last available follow-up visit. Participants with no information after baseline were censored at Day 1. OS

was estimated by the Kaplan-Meier method. Analysis was performed on ITT population.

End point type	Secondary
End point timeframe:	
9 months	

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: percentage of participants				
number (confidence interval 95%)	37.93 (25.51 to 51.63)	46.67 (28.34 to 65.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive 12 Months After Start of Treatment

End point title	Percentage of Participants Alive 12 Months After Start of Treatment
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End point description:

OS was defined as the time in months from the start of treatment to death due to any cause. If a participant was not known to have died, time was censored at the last date the participant was known to be alive, which was defined as the latest among date of last visit, date of last sample collected for laboratory exam, date of MRI assessment, date of last treatment, date of discontinuation and date of last available follow-up visit. Participants with no information after baseline were censored at Day 1. OS was estimated by the Kaplan-Meier method. Analysis was performed on ITT population and included only participants with evaluable data.

End point type	Secondary
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End point timeframe:

12 months

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: percentage of participants				
number (confidence interval 95%)	25.86 (15.26 to 39.04)	40 (22.66 to 59.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive 30 Days After Last Dose of Study Drug

End point title	Percentage of Participants Alive 30 Days After Last Dose of Study Drug
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End point description:

OS was defined as the time in months from the start of treatment to death due to any cause. If a participant was not known to have died, time was censored at the last date the participant was known to be alive, which was defined as the latest among date of last visit, date of last sample collected for laboratory exam, date of MRI assessment, date of last treatment, date of discontinuation and date of last available follow-up visit. Participants with no information after baseline were censored at Day 1. OS was estimated by the Kaplan-Meier method. Analysis was performed on ITT population and included only participants with evaluable data.

End point type	Secondary
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End point timeframe:

30 days after last dose of study drug (up to Day 600)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	30		
Units: percentage of participants				
number (confidence interval 95%)	93.1 (83.27 to 98.09)	90 (73.47 to 97.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR)

End point title	Percentage of Participants With a Best Overall Response of Complete Response (CR) or Partial Response (PR)
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End point description:

Percentage of participants achieving CR or PR as overall response between first drug administration and documented disease progression were calculated. Tumor response was evaluated according to both, the RANO and the Macdonald response criteria. As per Macdonald criteria, CR was defined as the disappearance of all enhancing disease, sustained for at least 4 weeks, and no new lesions along with clinical features of clinically stable or improved, with no corticosteroid; PR was defined as a 50% or more decrease of all measurable enhancing lesions, sustained for at least 4 weeks, and no new lesion along with clinical features of clinically stable or improved, with stable or reduced corticosteroids. RANO criteria defined CR and PR the same as Macdonald criteria with the following additions: CR - improved non enhancing T2/FLAIR lesions; PR - no progression of non-measurable disease, stable or improved non enhancing FLAIR/T2 lesions. Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline until disease progression or death (baseline, 46 days after first administration of study drug, and thereafter every 56 days up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: percentage of participants				
number (not applicable)				
RANO Evaluation	28.81	9.38		
MacDonald Evaluation	28.81	6.25		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Screening in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Scores at Weeks 8, 16, 24, 32, 40, 48, 56, 64, and 72

End point title	Change From Screening in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Scores at Weeks 8, 16, 24, 32, 40, 48, 56, 64, and 72
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End point description:

EORTC QLQ-C30: included global health status/quality of life (QOL), functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). Most questions used a 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores were averaged and transformed to a 0-100 scale; a higher score for Global QoL/functional scales indicates better level of QoL/functioning, or a higher score for symptom scale indicates greater degree of symptoms. Analysis was performed on ITT population and included only participants with evaluable data. The number 99999 signifies data not available either because no participant was evaluable (when 99999 is reported for both mean and standard deviation) or only one participant was evaluable (when 99999 is reported only for standard deviation).

End point type	Secondary
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End point timeframe:

Screening, Weeks 8, 16, 24, 32, 40, 48, 56, 64, and 72

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58 ^[3]	31 ^[4]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Functioning (Fn): Screening (n=58,31)	71.95 (± 25.65)	78.92 (± 25.07)		
Physical Fn: Change at Week 8 (n=27,16)	10.37 (± 19.07)	7.08 (± 12.76)		
Physical Fn: Change at Week 16 (n=15,7)	7.56 (± 19.17)	8.57 (± 13.72)		
Physical Fn: Change at Week 24 (n=14,1)	13.81 (± 24.17)	0 (± 99999)		
Physical Fn: Change at Week 32 (n=7,2)	18.1 (± 28.21)	13.33 (± 9.43)		
Physical Fn: Change at Week 40 (n=9,1)	4.44 (± 19.72)	6.67 (± 99999)		

Physical Fn: Change at Week 48 (n=4,1)	3.33 (± 16.78)	6.67 (± 99999)		
Physical Fn: Change at Week 56 (n=4,0)	6.67 (± 9.43)	99999 (± 99999)		
Physical Fn: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Physical Fn: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Role Fn: Screening (n=58,31)	67.82 (± 31.04)	73.66 (± 32.14)		
Role Fn: Change at Week 8 (n=27,16)	6.17 (± 34.01)	4.17 (± 21.52)		
Role Fn: Change at Week 16 (n=15,7)	2.22 (± 25.87)	2.38 (± 26.23)		
Role Fn: Change at Week 24 (n=14,1)	14.29 (± 33.88)	0 (± 99999)		
Role Fn: Change at Week 32 (n=7,2)	16.67 (± 28.87)	0 (± 0)		
Role Fn: Change at Week 40 (n=9,1)	0 (± 22.05)	0 (± 99999)		
Role Fn: Change at Week 48 (n=4,1)	0 (± 36)	0 (± 99999)		
Role Fn: Change at Week 56 (n=4,0)	-12.5 (± 36.96)	99999 (± 99999)		
Role Fn: Change at Week 64 (n=1,0)	-50 (± 99999)	99999 (± 99999)		
Role Fn: Change at Week 72 (n=1,0)	-50 (± 99999)	99999 (± 99999)		
Emotional Fn: Screening (n=58,31)	73.56 (± 23.47)	74.19 (± 23.41)		
Emotional Fn: Change at Week 8 (n=27,16)	-8.02 (± 23.62)	8.33 (± 24.91)		
Emotional Fn: Change at Week 16 (n=15,7)	-0.56 (± 14.25)	-2.38 (± 27.52)		
Emotional Fn: Change at Week 24 (n=14,1)	10.12 (± 29.63)	-33.33 (± 99999)		
Emotional Fn: Change at Week 32 (n=7,2)	-2.38 (± 15)	16.67 (± 0)		
Emotional Fn: Change at Week 40 (n=9,1)	-5.56 (± 24.65)	8.33 (± 99999)		
Emotional Fn: Change at Week 48 (n=4,1)	14.58 (± 27.53)	8.33 (± 99999)		
Emotional Fn: Change at Week 56 (n=4,0)	-4.17 (± 27.64)	99999 (± 99999)		
Emotional Fn: Change at Week 64 (n=1,0)	8.33 (± 99999)	99999 (± 99999)		
Emotional Fn: Change at Week 72 (n=1,0)	8.33 (± 99999)	99999 (± 99999)		
Cognitive Fn: Screening (n=58,31)	70.4 (± 25.18)	79.03 (± 24.33)		
Cognitive Fn: Change at Week 8 (n=27,16)	4.94 (± 23.49)	7.29 (± 23.55)		
Cognitive Fn: Change at Week 16 (n=15,7)	2.22 (± 17.67)	-4.76 (± 34.31)		
Cognitive Fn: Change at Week 24 (n=14,1)	10.71 (± 24.11)	0 (± 99999)		
Cognitive Fn: Change at Week 32 (n=7,2)	0 (± 16.67)	8.33 (± 11.79)		
Cognitive Fn: Change at Week 40 (n=9,1)	-1.85 (± 19.44)	0 (± 99999)		
Cognitive Fn: Change at Week 48 (n=4,1)	0 (± 0)	0 (± 99999)		
Cognitive Fn: Change at Week 56 (n=4,0)	-4.17 (± 20.97)	99999 (± 99999)		

Cognitive Fn: Change at Week 64 (n=1,0)	16.67 (± 99999)	99999 (± 99999)		
Cognitive Fn: Change at Week 72 (n=1,0)	16.67 (± 99999)	99999 (± 99999)		
Social Fn: Screening (n=58,31)	72.99 (± 28.07)	81.18 (± 24.24)		
Social Fn: Change at Week 8 (n=27,16)	1.85 (± 31.12)	4.17 (± 23.96)		
Social Fn: Change at Week 16 (n=15,7)	1.11 (± 27.07)	-2.38 (± 26.23)		
Social Fn: Change at Week 24 (n=14,1)	13.1 (± 39.32)	0 (± 99999)		
Social Fn: Change at Week 32 (n=7,2)	-7.14 (± 38.32)	8.33 (± 11.79)		
Social Fn: Change at Week 40 (n=9,1)	-5.56 (± 22.05)	16.67 (± 99999)		
Social Fn: Change at Week 48 (n=4,1)	-4.17 (± 36.96)	16.67 (± 99999)		
Social Fn: Change at Week 56 (n=4,0)	-12.5 (± 28.46)	99999 (± 99999)		
Social Fn: Change at Week 64 (n=1,0)	-66.67 (± 99999)	99999 (± 99999)		
Social Fn: Change at Week 72 (n=1,0)	-66.67 (± 99999)	99999 (± 99999)		
QOL: Screening (n=58,31)	58.05 (± 26.4)	66.13 (± 24.9)		
QOL: Change at Week 8 (n=27,16)	-3.09 (± 20.17)	6.25 (± 22.87)		
QOL: Change at Week 16 (n=15,7)	-4.44 (± 14.39)	7.14 (± 23.78)		
QOL: Change at Week 24 (n=14,1)	4.76 (± 21.11)	0 (± 99999)		
QOL: Change at Week 32 (n=7,2)	3.57 (± 17.91)	-12.5 (± 17.68)		
QOL: Change at Week 40 (n=9,1)	-2.78 (± 25.34)	0 (± 99999)		
QOL: Change at Week 48 (n=4,1)	10.42 (± 14.23)	0 (± 99999)		
QOL: Change at Week 56 (n=4,0)	2.08 (± 34.94)	99999 (± 99999)		
QOL: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
QOL: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Fatigue: Screening (n=58,31)	31.99 (± 25.5)	24.01 (± 22.05)		
Fatigue: Change at Week 8 (n=27,16)	-3.29 (± 32.59)	-13.19 (± 25.73)		
Fatigue: Change at Week 16 (n=15,7)	2.22 (± 21.5)	-9.52 (± 17.48)		
Fatigue: Change at Week 24 (n=14,1)	-6.35 (± 29.79)	-11.11 (± 99999)		
Fatigue: Change at Week 32 (n=7,2)	3.17 (± 17.82)	-5.56 (± 7.86)		
Fatigue: Change at Week 40 (n=9,1)	9.88 (± 23.2)	-11.11 (± 99999)		
Fatigue: Change at Week 48 (n=4,1)	-8.33 (± 18.98)	-11.11 (± 99999)		
Fatigue: Change at Week 56 (n=4,0)	2.78 (± 30.6)	99999 (± 99999)		
Fatigue: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Fatigue: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Nausea: Screening (n=58,31)	2.01 (± 7.7)	1.08 (± 4.16)		

Nausea: Change at Week 8 (n=27,16)	1.85 (± 10.68)	-8.33 (± 14.91)		
Nausea: Change at Week 16 (n=15,7)	0 (± 6.3)	-14.29 (± 20.25)		
Nausea: Change at Week 24 (n=14,1)	-5.95 (± 10.56)	0 (± 99999)		
Nausea: Change at Week 32 (n=7,2)	-2.38 (± 6.3)	0 (± 0)		
Nausea: Change at Week 40 (n=9,1)	-9.26 (± 8.78)	0 (± 99999)		
Nausea: Change at Week 48 (n=4,1)	0 (± 0)	-16.67 (± 99999)		
Nausea: Change at Week 56 (n=4,0)	-4.17 (± 8.33)	99999 (± 99999)		
Nausea: Change at Week 64 (n=1,0)	-16.67 (± 99999)	99999 (± 99999)		
Nausea: Change at Week 72 (n=1,0)	-16.67 (± 99999)	99999 (± 99999)		
Pain: Screening (n=58,31)	6.9 (± 16.82)	14.52 (± 23.47)		
Pain: Change at Week 8 (n=27,16)	-1.85 (± 24.61)	-6.25 (± 26.44)		
Pain: Change at Week 16 (n=15,7)	-10 (± 19.72)	-2.38 (± 20.25)		
Pain: Change at Week 24 (n=14,1)	-8.33 (± 28.31)	0 (± 99999)		
Pain: Change at Week 32 (n=7,2)	0 (± 16.67)	-8.33 (± 11.79)		
Pain: Change at Week 40 (n=9,1)	-7.41 (± 18.84)	0 (± 99999)		
Pain: Change at Week 48 (n=4,1)	-29.17 (± 28.46)	0 (± 99999)		
Pain: Change at Week 56 (n=4,0)	0 (± 19.25)	99999 (± 99999)		
Pain: Change at Week 64 (n=1,0)	-16.67 (± 99999)	99999 (± 99999)		
Pain: Change at Week 72 (n=1,0)	-16.67 (± 99999)	99999 (± 99999)		
Dyspnea: Screening (n=58,31)	11.49 (± 22.12)	3.23 (± 10.02)		
Dyspnea: Change at Week 8 (n=27,16)	4.94 (± 28.8)	-6.25 (± 21.84)		
Dyspnea: Change at Week 16 (n=15,7)	0 (± 25.2)	4.76 (± 12.6)		
Dyspnea: Change at Week 24 (n=14,1)	-9.52 (± 27.51)	0 (± 99999)		
Dyspnea: Change at Week 32 (n=7,2)	0 (± 27.22)	0 (± 0)		
Dyspnea: Change at Week 40 (n=9,1)	3.7 (± 20.03)	0 (± 99999)		
Dyspnea: Change at Week 48 (n=4,1)	-8.33 (± 16.67)	0 (± 99999)		
Dyspnea: Change at Week 56 (n=4,0)	0 (± 27.22)	99999 (± 99999)		
Dyspnea: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Dyspnea: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Insomnia: Screening (n=58,31)	18.39 (± 28.73)	18.28 (± 22.51)		
Insomnia: Change at Week 8 (n=27,16)	1.23 (± 25.29)	-8.33 (± 33.33)		
Insomnia: Change at Week 16 (n=15,7)	2.22 (± 32.04)	-4.76 (± 29.99)		
Insomnia: Change at Week 24 (n=14,1)	-9.52 (± 46.09)	-33.33 (± 99999)		

Insomnia: Change at Week 32 (n=7,2)	28.57 (± 23)	16.67 (± 23.57)		
Insomnia: Change at Week 40 (n=9,1)	14.81 (± 24.22)	33.33 (± 99999)		
Insomnia: Change at Week 48 (n=4,1)	25 (± 31.91)	33.33 (± 99999)		
Insomnia: Change at Week 56 (n=4,0)	33.33 (± 27.22)	99999 (± 99999)		
Insomnia: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Insomnia: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Appetite loss: Screening (n=58,31)	7.47 (± 19.79)	5.38 (± 12.46)		
Appetite loss: Change at Week 8 (n=27,16)	0 (± 22.65)	-10.42 (± 23.47)		
Appetite loss: Change at Week 16 (n=15,7)	-2.22 (± 8.61)	-14.29 (± 26.23)		
Appetite loss: Change at Week 24 (n=14,1)	-7.14 (± 19.3)	0 (± 99999)		
Appetite loss: Change at Week 32 (n=7,2)	-4.76 (± 12.6)	0 (± 0)		
Appetite loss: Change at Week 40 (n=9,1)	-7.41 (± 14.7)	0 (± 99999)		
Appetite loss: Change at Week 48 (n=4,1)	-16.67 (± 19.25)	0 (± 99999)		
Appetite loss: Change at Week 56 (n=4,0)	-16.67 (± 19.25)	99999 (± 99999)		
Appetite loss: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Appetite loss: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Constipation: Screening (n=58,31)	17.82 (± 24.36)	17.2 (± 25.63)		
Constipation: Change at Week 8 (n=26,16)	3.85 (± 25.52)	-4.17 (± 26.87)		
Constipation: Change at Week 16 (n=15,7)	4.44 (± 17.21)	-9.52 (± 25.2)		
Constipation: Change at Week 24 (n=14,1)	2.38 (± 20.52)	0 (± 99999)		
Constipation: Change at Week 32 (n=7,2)	0 (± 38.49)	16.67 (± 23.57)		
Constipation: Change at Week 40 (n=9,1)	3.7 (± 26.06)	0 (± 99999)		
Constipation: Change at Week 48 (n=4,1)	-16.67 (± 19.25)	0 (± 99999)		
Constipation: Change at Week 56 (n=4,0)	0 (± 27.22)	99999 (± 99999)		
Constipation: Change at Week 64 (n=1,0)	-33.33 (± 99999)	99999 (± 99999)		
Constipation: Change at Week 72 (n=1,0)	-33.33 (± 99999)	99999 (± 99999)		
Diarrhea: Screening (n=58,31)	1.15 (± 6.14)	2.15 (± 8.32)		
Diarrhea: Change at Week 8 (n=27,16)	0 (± 9.25)	0 (± 0)		
Diarrhea: Change at Week 16 (n=15,7)	-6.67 (± 18.69)	0 (± 0)		
Diarrhea: Change at Week 24 (n=14,1)	-7.14 (± 19.3)	0 (± 99999)		
Diarrhea: Change at Week 32 (n=7,2)	-4.76 (± 12.6)	0 (± 0)		
Diarrhea: Change at Week 40 (n=9,1)	0 (± 0)	0 (± 99999)		
Diarrhea: Change at Week 48 (n=4,1)	0 (± 0)	0 (± 99999)		
Diarrhea: Change at Week 56 (n=4,0)	0 (± 0)	99999 (± 99999)		

Diarrhea: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Diarrhea: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Financial Fn: Screening (n=58,31)	17.82 (± 25.91)	25.81 (± 34.11)		
Financial Fn: Change at Week 8 (n=27,16)	6.17 (± 26.21)	-4.17 (± 11.39)		
Financial Fn: Change at Week 16 (n=15,7)	2.22 (± 15.26)	9.52 (± 46)		
Financial Fn: Change at Week 24 (n=14,1)	-4.76 (± 22.1)	0 (± 99999)		
Financial Fn: Change at Week 32 (n=7,2)	0 (± 19.25)	-16.67 (± 23.57)		
Financial Fn: Change at Week 40 (n=9,1)	-3.7 (± 26.06)	0 (± 99999)		
Financial Fn: Change at Week 48 (n=4,1)	-16.67 (± 19.25)	0 (± 99999)		
Financial Fn: Change at Week 56 (n=4,0)	-8.33 (± 31.91)	99999 (± 99999)		
Financial Fn: Change at Week 64 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Financial Fn: Change at Week 72 (n=1,0)	0 (± 99999)	99999 (± 99999)		

Notes:

[3] - n (number of participants) = participants with evaluable data for specified category.

[4] - n (number of participants) = participants with evaluable data for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Corticosteroid Initiation During the Study Period

End point title	Percentage of Participants With Corticosteroid Initiation During the Study Period
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End point description:

Corticosteroid initiation was assessed in participants not receiving corticosteroids at screening. The participant had the event if he/she started on corticosteroids with a dosage greater than equal to (>/=) 2 mg dexamethasone equivalent. Analysis was performed on ITT population and included only participants who were not receiving corticosteroids at screening.

End point type	Secondary
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End point timeframe:

Baseline until recurrence (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	12		
Units: percentage of participants				
number (not applicable)	58.82	41.67		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Corticosteroid Initiation

End point title | Time to Corticosteroid Initiation

End point description:

Time to corticosteroid initiation was defined as the time from screening to the start date of the first corticosteroid administration in participants not receiving corticosteroids at screening. The participant had the event if he/she started on corticosteroids with a dosage ≥ 2 mg dexamethasone equivalent. Instead, if the participant was not known to have the event, time was censored at the last available visit date. Time to corticosteroid initiation was estimated using the Kaplan Meier method. Analysis was performed on ITT population and included only participants who were not receiving corticosteroids at screening. The number 99999 signifies data not available due to higher number (>40%) of censored participants.

End point type | Secondary

End point timeframe:

Baseline until recurrence (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	12		
Units: months				
median (confidence interval 95%)	4.49 (1.87 to 99999)	5.93 (0.3 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Class of Corticosteroid Use

End point title | Percentage of Participants in Each Class of Corticosteroid Use

End point description:

Corticosteroid use was classified as: 1. No Change (if corticosteroid dose at each assessment was equal to baseline); 2. Decreased (if corticosteroid dose at each assessment was lower than baseline); 3. Increased (corticosteroid dose at each assessment was greater than baseline). Analysis was performed on ITT population and included only participants with evaluable data.

End point type | Secondary

End point timeframe:

Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, post-treatment follow-up (up to Day 691)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 ^[5]	28 ^[6]		
Units: percentage of participants				
number (not applicable)				
Week 8: Increased (n=52,28)	17.31	17.86		
Week 8: Decreased (n=52,28)	23.08	21.43		
Week 8: No Change (n=52,28)	59.62	60.71		
Week 16: Increased (n=33,18)	21.21	22.22		
Week 16: Decreased (n=33,18)	36.36	27.78		
Week 16: No Change (n=33,18)	42.42	50		
Week 24: Increased (n=21,5)	28.57	20		
Week 24: Decreased (n=21,5)	33.33	40		
Week 24: No Change (n=21,5)	38.1	40		
Week 32: Increased (n=14,3)	14.29	33.33		
Week 32: Decreased (n=14,3)	42.86	0		
Week 32: No Change (n=14,3)	42.86	66.67		
Week 40: Increased (n=10,2)	0	50		
Week 40: Decreased (n=10,2)	60	0		
Week 40: No Change (n=10,2)	40	50		
Week 48: Increased (n=8,1)	0	0		
Week 48: Decreased (n=8,1)	50	0		
Week 48: No Change (n=8,1)	50	100		
Week 56: Increased (n=6,1)	0	0		
Week 56: Decreased (n=6,1)	33.33	0		
Week 56: No Change (n=6,1)	66.67	100		
Week 64: Increased (n=3,1)	0	0		
Week 64: Decreased (n=3,1)	0	0		
Week 64: No Change (n=3,1)	100	100		
Week 72: Increased (n=3,0)	0	99999		
Week 72: Decreased (n=3,0)	0	99999		
Week 72: No Change (n=3,0)	100	99999		
Week 80: Increased (n=1,0)	0	99999		
Week 80: Decreased (n=1,0)	0	99999		
Week 80: No Change (n=1,0)	100	99999		
Week 88: Increased (n=1,0)	100	99999		
Week 88: Decreased (n=1,0)	0	99999		
Week 88: No Change (n=1,0)	0	99999		
Follow-up: Increased (n=9,3)	33.33	0		
Follow-up: Decreased (n=9,3)	0	33.33		
Follow-up: No Change (n=9,3)	66.67	66.67		

Notes:

[5] - n (number of participants) = participants with evaluable data for specified category.

[6] - n (number of participants) = participants with evaluable data for specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Karnofsky Performance Status (KPS) Deterioration

End point title	Percentage of Participants With Karnofsky Performance Status
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End point description:

Deterioration of KPS was defined as a decrease of at least 20 percentage points with respect to the screening. KPS is an 11-level score which ranges between 0 (death) to 100 (complete healthy status); a higher score represents a higher ability to perform daily tasks. Analysis was performed on ITT population and included only participants with evaluable data.

End point type	Secondary
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End point timeframe:

Baseline until KPS deterioration (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	14		
Units: percentage of participants				
number (not applicable)	18.92	14.29		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Karnofsky Performance Status (KPS) Deterioration

End point title	Time to Karnofsky Performance Status (KPS) Deterioration
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End point description:

Time to KPS deterioration was defined as the time from screening to the first date of deterioration of the KPS score. Deterioration of KPS was defined as a decrease of at least 20 percentage points with respect to the screening. KPS is an 11-level score which ranges between 0 (death) to 100 (complete healthy status); a higher score represents a higher ability to perform daily tasks. Time to KPS deterioration was estimated using Kaplan Meier method. If the participant was not known to have the event, time was censored at the last available visit date. Analysis was performed on ITT population and included only participants with evaluable data. The number 99999 signify data not available as <50% of participants had an event of interest.

End point type	Secondary
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End point timeframe:

Baseline until KPS deterioration (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	14		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With World Health Organization (WHO) Performance Status (PS) Deterioration

End point title	Percentage of Participants With World Health Organization (WHO) Performance Status (PS) Deterioration
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End point description:

WHO PS deterioration was defined as a decrease of at least 1 point with respect to the screening value. WHO PS is a 6-level score which ranges between 0 (fully active) to 5 (death); a lower score represents a higher ability to perform daily tasks. Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline until WHO PS deterioration (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: percentage of participants				
number (not applicable)	47.46	37.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to WHO PS Deterioration

End point title	Time to WHO PS Deterioration
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End point description:

Time to WHO PS deterioration was defined as the time from randomization to the first date of deterioration of the WHO performance status score. WHO PS score was defined as a decrease of at least 1 point with respect to the screening. WHO PS is a 6-level score which ranges between 0 (fully active) to 5 (death); a lower score represents a higher ability to perform daily tasks. Analysis was performed on ITT population. The number 99999 signify data not available as <50% of participants had an event of interest.

End point type	Secondary
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End point timeframe:

Baseline until WHO PS deterioration (up to 691 days)

End point values	Bevacizumab	Fotemustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	32		
Units: months				
median (confidence interval 95%)	8.87 (4.17 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:

Up to 691 days

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Fotemustine
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Reporting group description:

Fotemustine 75 mg/m² IV infusion on Days 1, 8, and 15 (induction phase), followed by 35-day treatment free interval, and then fotemustine 100 mg/m² every 21 days (maintenance phase) until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Reporting group title	Bevacizumab
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Reporting group description:

Bevacizumab 10 mg/kg IV infusion every 14 days until disease progression was radiographically documented or the onset of toxicity prevented treatment continuation.

Serious adverse events	Fotemustine	Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	17 / 59 (28.81%)	
number of deaths (all causes)	23	50	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
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			
Road traffic accident			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Thrombophlebitis			

subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
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 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (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			
Condition aggravated			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 32 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 32 (3.13%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Fotemustine	Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 32 (78.13%)	35 / 59 (59.32%)	
Investigations			
Weight increased			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	4 / 59 (6.78%) 4	
Transaminases increased subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 6	3 / 59 (5.08%) 3	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	13 / 59 (22.03%) 29	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	5 / 59 (8.47%) 6	
Epilepsy subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	2 / 59 (3.39%) 2	
Convulsion subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	4 / 59 (6.78%) 7	
Partial seizures with secondary generalisation subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	3 / 59 (5.08%) 7	
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 59 (1.69%) 1	
Anaemia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	1 / 59 (1.69%) 1	
Neutropenia subjects affected / exposed occurrences (all)	8 / 32 (25.00%) 13	2 / 59 (3.39%) 2	
Thrombocytopenia subjects affected / exposed occurrences (all)	14 / 32 (43.75%) 19	2 / 59 (3.39%) 2	
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	1 / 59 (1.69%) 1	
Asthenia subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 5	13 / 59 (22.03%) 13	
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 59 (1.69%) 1	
Pyrexia subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	5 / 59 (8.47%) 6	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	3 / 59 (5.08%) 3	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	3 / 59 (5.08%) 4	
Nausea subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	2 / 59 (3.39%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	3 / 59 (5.08%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	1 / 59 (1.69%) 1	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	3 / 59 (5.08%) 7	
Fungal infection			

subjects affected / exposed	3 / 32 (9.38%)	1 / 59 (1.69%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2013	Clarified the exclusion criteria; "previous treatment with bevacizumab or other anti-angiogenic drugs" was modified into "no prior treatment with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor signaling inhibitors here. Provided more time to perform magnetic resonance imaging (MRI) at baseline prior to randomization. Provided clear instructions about the determination of proteinuria by dipstick; this exam was required only for the participants treated with bevacizumab and not for those treated with fotemustine. Added an acronym to the study.
01 September 2013	Clarified the definition of database (DB) lock and end of study; the previous definition was modified into "follow up for survival will continue until 14 months after the randomization of the last participant or all participants have died whichever occurs first". Amended the inclusion criteria; "Histologically confirmed recurrent glioblastoma multiforme (Grade IV)" was amended into "Histologically confirmed glioblastoma multiforme (Grade IV)". The definition of follow-up period was changed to 14-months following randomization to provide additional information about the safety of Avastin not available at the time of first submission and first amendment. Adapted the time of serious adverse event (SAE) reporting in accordance with the latest safety directives.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported