Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomised, Phase II Study Evaluating the Efficacy and Safety of Addition of Continuous Multiple Line Bevacizumab Treatment to Lomustine in Second (2nd)-Line Followed by Standard of Care (SOC) in Third (3rd)-Line and Beyond Compared to Addition of Placebo, Following First Progression of Disease (PD1) in Patients with Glioblastoma (GBM) After First (1st)-Line Treatment with Radiotherapy, Temozolomide and Bevacizumab

Summary

EudraCT number	2012-003138-17
Trial protocol	AT LT IT IE EE GB LV ES FI SE PT BG GR HR
Global end of trial date	05 May 2017

Results information

Result version number	v1 (current)
This version publication date	12 May 2018
First version publication date	12 May 2018

Trial information

Trial identification

Sponsor protocol code	MO28347

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01860638
WHO universal trial number (UTN)	-
Other trial identifiers	Study Acronym: TAMIGA

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 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of addition of continuous multiple line bevacizumab treatment to lomustine in 2nd-line followed by SOC in 3rd-line and beyond compared to addition of bevacizumab-placebo, as measured by overall survival (OS) from randomization at first-line disease progression (PD1).

Protection of trial subjects:

This study was conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). The study also complied with the European Union (EU) Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	United Kingdom: 22

Worldwide total number of subjects	296
EEA total number of subjects	286

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)	215
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 360 participants were screened, out of which, 296 participants were enrolled and treated at least once in this study.

Period 1

Period 1 title	1st-Line (1L) Treatment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	1L Bevacizumab

Arm description:

Participants received 1L treatment with radiotherapy, temozolomide, and bevacizumab. All 3 treatments were given concurrently for the first 6 weeks, followed by maintenance therapy consisting of 6 cycles (of 28 days each) of temozolomide plus bevacizumab, followed by bevacizumab monotherapy until PD1 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Bevacizumab was administered at a dose of 10 milligrams per kilogram (mg/kg) as intravenous (IV) infusion every 2 weeks (Q2W) for first 30 weeks, followed by bevacizumab at a dose of 15 mg/kg as IV infusion every 3 weeks (Q3W) as monotherapy until PD1 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 1	1L Bevacizumab
Started	296
Completed	123
Not completed	173
Adverse Event (AE)/Serious Adverse Event (SAE)	71
Participant Decision	12
Consent withdrawn by subject	15
Physician decision	24
Non-Compliance	9
Death	14
Administrative/Other	14
Protocol deviation	1

Treatment Ongoing at data cut-off date	13

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	2L: Placebo + Lomustine

Arm description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab-placebo plus lomustine until PD2 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Placebo matched to bevacizumab was administered as IV infusion Q2W until PD2 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Lomustine was administered at a dose of 90 milligrams per square meter (mg/m^2) orally (PO) every 6 weeks (Q6W), with a cap of 160 mg/m^2 per dose. In the absence of hematologic toxicity following the first dose, the second and subsequent doses could be increased up to 110 mg/m^2 PO Q6W, with a cap of 200 mg/m^2 per dose until PD2 or unacceptable toxicity/consent withdrawal.

Arm title	2L: Bevacizumab + Lomustine

Arm description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab plus lomustine until PD2 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Lomustine was administered at a dose of 90 mg/m^2 PO Q6W, with a cap of 160 mg/m^2 per dose. In the absence of hematologic toxicity following the first dose, the second and subsequent doses could be increased up to 110 mg/m^2 PO Q6W, with a cap of 200 mg/m^2 per dose until PD2 or unacceptable toxicity/consent withdrawal.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at a dose of 10 mg/kg as IV infusion Q2W until PD2 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 2	2L: Placebo + Lomustine	2L: Bevacizumab + Lomustine
Started	62	61
Completed	25	25
Not completed	37	36
Participant Decision	3	4
Consent withdrawn by subject	6	4
Physician decision	11	10
Non-Compliance	-	1
Death	3	5
Administrative/Other	5	4
AE/SAE	8	6
Treatment Ongoing at data cut-off date	1	2

Period 3

Period 3 title	3L Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	3L: Placebo + SOC

Arm description:

After PD2, participants continued 3L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD3 or unacceptable toxicity/consent withdrawal.

Arm type	Placebo

Investigational medicinal product name	Bevacizumab-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo matched to bevacizumab was administered as IV infusion Q2W until PD3 or unacceptable toxicity/consent withdrawal.

Arm title	3L: Bevacizumab + SOC

Arm description:

After PD2, participants continued 3L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD3 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Bevacizumab was administered at a dose of 10 mg/kg as IV infusion Q2W until PD3 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 3	3L: Placebo + SOC	3L: Bevacizumab + SOC
Started	25	25
Completed	9	9
Not completed	16	16
Participant Decision	2	3
Consent withdrawn by subject	1	-
Physician decision	5	7
Death	4	3
Administrative/Other	2	-
AE/SAE	-	2
Treatment Ongoing at data cut-off date	1	1
Protocol deviation	1	-

Period 4

Period 4 title	4L Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	4L: Placebo + SOC

Arm description:

After PD3, participants continued 4L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD4 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Placebo matched to bevacizumab was administered as IV infusion Q2W until PD4 or unacceptable toxicity/consent withdrawal.

Arm title	4L: Bevacizumab + SOC

Arm description:

After PD3, participants continued 4L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD4 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Bevacizumab was administered at a dose of 10 mg/kg as IV infusion Q2W until PD4 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 4	4L: Placebo + SOC	4L: Bevacizumab + SOC
Started	9	9
Completed	2	2
Not completed	7	7
Participant Decision	-	2
Physician decision	3	2
Death	-	1
Administrative/Other	2	1
AE/SAE	1	1
Treatment Ongoing at data cut-off date	1	-

Period 5

Period 5 title	5L Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	5L: Placebo + SOC

Arm description:

After PD4, participants continued 5L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD5 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Placebo matched to bevacizumab was administered as IV infusion Q2W until PD5 or unacceptable toxicity/consent withdrawal.

Arm title	5L: Bevacizumab + SOC

Arm description:

After PD4, participants continued 5L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD5 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Bevacizumab was administered at a dose of 10 mg/kg as IV infusion Q2W until PD5 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 5	5L: Placebo + SOC	5L: Bevacizumab + SOC
Started	2	2
Completed	0	1
Not completed	2	1
Physician decision	2	1

Period 6

Period 6 title	6L Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	6L: Bevacizumab + SOC

Arm description:

After PD5, participants continued 6L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD6 or unacceptable toxicity/consent withdrawal.

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

Dosage and administration details:

Bevacizumab was administered at a dose of 10 mg/kg as IV infusion Q2W until PD6 or unacceptable toxicity/consent withdrawal.

Number of subjects in period 6	6L: Bevacizumab + SOC
Started	1
Completed	0
Not completed	1
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	1L Bevacizumab

Reporting group description:

Participants received 1L treatment with radiotherapy, temozolomide, and bevacizumab. All 3 treatments were given concurrently for the first 6 weeks, followed by maintenance therapy consisting of 6 cycles (of 28 days each) of temozolomide plus bevacizumab, followed by bevacizumab monotherapy until PD1 or unacceptable toxicity/consent withdrawal.

Reporting group values	1L Bevacizumab	Total	
Number of subjects	296	296	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 55.9 ± 11.85	 -	
Gender Categorical Units: Subjects			
Female	104	104	
Male	192	192	

End points reporting groups

Reporting group title	1L Bevacizumab
Reporting group description:	
Participants received 1L treatment with radiotherapy, temozolomide, and bevacizumab. All 3 treatments were given concurrently for the first 6 weeks, followed by maintenance therapy consisting of 6 cycles (of 28 days each) of temozolomide plus bevacizumab, followed by bevacizumab monotherapy until PD1 or unacceptable toxicity/consent withdrawal.	
Reporting group title	2L: Placebo + Lomustine
Reporting group description:	
At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab-placebo plus lomustine until PD2 or unacceptable toxicity/consent withdrawal.	
Reporting group title	2L: Bevacizumab + Lomustine
Reporting group description:	
At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab plus lomustine until PD2 or unacceptable toxicity/consent withdrawal.	
Reporting group title	3L: Placebo + SOC
Reporting group description:	
After PD2, participants continued 3L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD3 or unacceptable toxicity/consent withdrawal.	
Reporting group title	3L: Bevacizumab + SOC
Reporting group description:	
After PD2, participants continued 3L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD3 or unacceptable toxicity/consent withdrawal.	
Reporting group title	4L: Placebo + SOC
Reporting group description:	
After PD3, participants continued 4L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD4 or unacceptable toxicity/consent withdrawal.	
Reporting group title	4L: Bevacizumab + SOC
Reporting group description:	
After PD3, participants continued 4L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD4 or unacceptable toxicity/consent withdrawal.	
Reporting group title	5L: Placebo + SOC
Reporting group description:	
After PD4, participants continued 5L treatment as per assigned arm and received bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD5 or unacceptable toxicity/consent withdrawal.	
Reporting group title	5L: Bevacizumab + SOC
Reporting group description:	
After PD4, participants continued 5L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD5 or unacceptable toxicity/consent withdrawal.	
Reporting group title	6L: Bevacizumab + SOC
Reporting group description:	
After PD5, participants continued 6L treatment as per assigned arm and received bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator until PD6 or unacceptable toxicity/consent withdrawal.	
Subject analysis set title	Placebo + Lomustine/SOC (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab-	

placebo plus lomustine until PD2. After PD2, participants continued 3L and subsequent lines of treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Participants were analyzed as randomized.

Subject analysis set title	Bevacizumab + Lomustine/SOC (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab plus lomustine until PD2. After PD2, participants continued 3L and subsequent lines of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Participants were analyzed as randomized.

Subject analysis set title	No 2L received (Safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who discontinued before randomization or who did not receive any study treatment after randomization were analyzed as 'No 2L received'.

Subject analysis set title	Placebo + Lomustine/SOC (Safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab-placebo plus lomustine until PD2. After PD2, participants continued 3L and subsequent lines of treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and. Participants were analyzed as treated.

Subject analysis set title	Bevacizumab + Lomustine/SOC (Safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab plus lomustine until PD2. After PD2, participants continued 3L and subsequent lines of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Participants were analyzed as treated.

Subject analysis set title	Placebo + Lomustine/SOC (Safety 2L+)
Subject analysis set type	Safety analysis

Subject analysis set description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab-placebo plus lomustine until PD2. After PD2, participants continued 3L treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Analysis set included all participants who received at least one dose of 2L study treatment. Participants were analyzed as treated during 2L and 3L.

Subject analysis set title	Bevacizumab + Lomustine/SOC (Safety 2L+)
Subject analysis set type	Safety analysis

Subject analysis set description:

At PD1, eligible participants for 2L therapy who were randomized to this group received bevacizumab plus lomustine until PD2. After PD2, participants continued 3L treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Analysis set included all participants who received at least one dose of 2L study treatment. Participants were analyzed as treated during 2L and 3L.

Subject analysis set title	Placebo + Lomustine/SOC (Safety 4L+)
Subject analysis set type	Safety analysis

Subject analysis set description:

After PD3, participants who chose to continue their assigned treatment received 4L and later lines of treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Subject analysis set title	Bevacizumab + Lomustine/SOC (Safety 4L+)
Subject analysis set type	Safety analysis

Subject analysis set description:

After PD3, participants who chose to continue their assigned treatment received 4L and later lines of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Subject analysis set title	Cross-over (Safety 4L+)
Subject analysis set type	Safety analysis

Subject analysis set description:

After PD3, participants who chose to cross-over their treatment from bevacizumab-placebo to bevacizumab received 4L and later lines of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Primary: Percentage of Participants Who Died of any Cause From Randomization until End of Study

End point title	Percentage of Participants Who Died of any Cause From Randomization until End of Study[1]

End point description:

Percentage of participants who died of any cause from randomization/PD1 until end of study was reported. Analysis was performed on Intent-to-treat (ITT) Population, which included all randomized participants. Participants were analyzed as randomized.

End point type	Primary

End point timeframe:

From randomization at PD1 until death from any cause or end of study (overall approximately 35 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: percentage of participants				
number (not applicable)	75.8	83.6		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from randomization until death from any cause. Participants who were alive at the time of analysis (clinical cut-off) and participants who were lost to follow-up were censored at their last clinical assessment date. Median OS time and 95 percent (%) confidence interval (CI) were estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

End point type	Primary

End point timeframe:

From randomization at PD1 until death from any cause or end of study (overall approximately 35 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: months				
median (confidence interval 95%)	5.5 (3.9 to 7.2)	6.4 (5.1 to 8.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at randomization (0 versus 1/2).	
Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.59

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.79
upper limit	1.37

Secondary: Percentage of Participants Alive at 6, 12, and 18 Months After Randomization

End point title	Percentage of Participants Alive at 6, 12, and 18 Months After Randomization

End point description:

Percentage of participants alive (event-free rate) and 95% CI were estimated using Kaplan-Meier method. Analysis was performed on ITT Population. Here, 'n' signifies number of participants remaining at risk at indicated time point for each arm, respectively.

End point type	Secondary

End point timeframe:

At 6, 12, and 18 months after randomization/PD1 (overall up to approximately 35 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: percentage of participants				
number (confidence interval 95%)				
6 months (n=24,30)	46.2 (32.8 to 58.5)	55.4 (41.4 to 67.3)		
12 months (n=7,5)	16.5 (7.5 to 28.5)	11.7 (4.6 to 22.5)		
18 months (n=4,2)	9.4 (3.1 to 20.1)	4.7 (0.9 to 13.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

6 Months: Two-sided log-rank test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS at randomization (0 versus 1/2). Correct number of subjects included in analysis=54.

Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Difference in OS Rate
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	27.7

Notes:

[2] - The 95% CI was calculated using Greenwood’s formula.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

18 Months: Two-sided log-rank test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS at randomization (0 versus 1/2). Correct number of subjects included in analysis=6.

Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab +

	Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Difference in OS Rate
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	5.9

Notes:

[3] - The 95% CI was calculated using Greenwood's formula.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

12 Months: Two-sided log-rank test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS at randomization (0 versus 1/2). Correct number of subjects included in analysis=12.

Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[4]
Parameter estimate	Difference in OS Rate
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	9.4

Notes:

[4] - The 95% CI was calculated using Greenwood's formula.

Secondary: Percentage of Participants with PD2 (Assessed According to Modified Response Assessment in Neuro-Oncology [RANO] Criteria) or Death From Any Cause

End point title	Percentage of Participants with PD2 (Assessed According to Modified Response Assessment in Neuro-Oncology [RANO] Criteria) or Death From Any Cause

End point description:

As per the modified RANO criteria, progression was defined as: greater than or equal to (>/=) 25% increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or at best response, on stable/increasing corticosteroids dose; significant increase in non-enhancing T2/fluid attenuated inversion recovery (FLAIR) lesions, not caused by comorbid events; any new lesions; clear clinical deterioration (not attributable to other non-tumor causes or decreases in corticosteroid dose); failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From first administration of randomized treatment until PD2 or death from any cause (overall approximately 18 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: percentage of participants				
number (not applicable)	95.2	95.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) on 2L Treatment Assessed According to Modified RANO Criteria

End point title	Progression-Free Survival (PFS) on 2L Treatment Assessed According to Modified RANO Criteria

End point description:

PFS on 2L treatment was defined as the time from randomization/PD1 until PD2 or death from any cause, whichever occurred first. As per the modified RANO criteria, progression was defined as: >/=25% increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained on study, on stable/increasing corticosteroid dose; significant increase in non-enhancing T2/FLAIR lesions, not caused by comorbid events; any new lesions; clear clinical deterioration (not attributable to other non-tumor causes or decreases in corticosteroid dose); failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Participants without an event were censored at the date of their last evaluable tumor assessment or, if this is not available, at date of randomization. Median PFS on 2L treatment and 95% CI were estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From first administration of randomized treatment until PD2 or death from any cause (overall approximately 18 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: months				
median (confidence interval 95%)	1.8 (1.4 to 2.1)	2.3 (1.9 to 2.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS

at randomization (0 versus 1/2).

Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.04

Secondary: Percentage of Participants with PD3 (Assessed According to Modified RANO Criteria) or Death from any Cause

End point title	Percentage of Participants with PD3 (Assessed According to Modified RANO Criteria) or Death from any Cause

End point description:

As per the modified RANO criteria, progression was defined as: >/=25% increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or at best response, on stable/increasing corticosteroid dose; significant increase in non-enhancing T2/FLAIR lesions, not caused by comorbid events; any new lesions; clear clinical deterioration (not attributable to other non-tumor causes or decreases in corticosteroid dose); failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From first administration of randomized treatment until PD3 or death from any cause (overall approximately 35 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: percentage of participants				
number (not applicable)	77.4	65.6		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS on 3L Treatment Assessed According to Modified RANO Criteria

End point title	PFS on 3L Treatment Assessed According to Modified RANO Criteria

End point description:

PFS on 3L treatment: the time from randomization/PD1 until PD3 or death from any cause, whichever occurred first. As per the modified RANO criteria, progression was defined as: >/=25% increase in sum of products of perpendicular diameters of enhancing lesions compared to smallest measurements on study, on stable/increasing corticosteroid dose; significant increase in non-enhancing T2/FLAIR lesions, not caused by comorbid events; any new lesions; clear clinical deterioration (not attributable to other non-tumor causes or decreases in corticosteroid dose); failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Participants who were alive and for whom PD3 was not observed were censored at the last time known to be alive. Participants who died (at PD2/before PD3) were censored at the date of death. Median PFS on 3L treatment and 95% CI were estimated using Kaplan-Meier method. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From first administration of randomized treatment until PD3 or death from any cause (overall approximately 35 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: months				
median (confidence interval 95%)	4.2 (3.9 to 4.9)	5.6 (3.9 to 6.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS at randomization (0 versus 1/2).

Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.28

Secondary: Percentage of Participants with PD3 after PD2 (Assessed According to Modified RANO Criteria) or Death from any Cause

End point title	Percentage of Participants with PD3 after PD2 (Assessed According to Modified RANO Criteria) or Death from any Cause

End point description:

As per the modified RANO criteria, progression was defined as: >/=25% increase in the sum of products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline or at best response, on stable/increasing corticosteroid dose; significant increase in non-enhancing T2/FLAIR lesions, not caused by comorbid events; any new lesions; clear clinical deterioration (not attributable to other non-tumor causes or decreases in corticosteroid dose); failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Analysis was performed on ITT Population. Participants without a PD2 and without the start of 3L treatment were excluded from this analysis.

End point type	Secondary

End point timeframe:

From first administration of treatment after PD2 until PD3 or death from any cause (overall approximately 26 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: percentage of participants				
number (not applicable)	96.0	96.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Restricted PFS on 3L Treatment (PFS3R) Assessed According to Modified RANO Criteria

End point title	Restricted PFS on 3L Treatment (PFS3R) Assessed According to Modified RANO Criteria

End point description:

PFS3R was defined as the time from first administration of randomized treatment after PD2 until PD3 or death from any cause, whichever occurred first. As per the modified RANO criteria, progression was defined as: >/=25% increase in the sum of products of perpendicular diameters of enhancing lesions, on stable/increasing corticosteroid dose; significant increase in non-enhancing T2/FLAIR lesions; any new lesions; clear clinical deterioration; failure to return for evaluation due to death or deteriorating condition; or clear progression of non-measurable disease. Participants without an event were censored at the date of their last evaluable tumor assessment or, if this was not available, at date of first administration of randomized treatment after PD2. Median PFS3R and 95% CI were estimated using Kaplan-Meier method. Analysis was performed on ITT Population. Participants without a PD2 and without the start of 3L treatment were excluded from this analysis.

End point type	Secondary

End point timeframe:

From first administration of treatment after PD2 until PD3 or death from any cause (overall approximately 26 months)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: months				
median (confidence interval 95%)	2.2 (1.3 to 2.7)	2.0 (1.8 to 2.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Test stratified by time to PD1 (before versus after completion of 1L maintenance therapy) and ECOG PS at randomization (0 versus 1/2).	
Comparison groups	Placebo + Lomustine/SOC (ITT) v Bevacizumab + Lomustine/SOC (ITT)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.33

Secondary: Percentage of Participants with 2L Objective Response of Complete Response (CR) or Partial Response (PR) Assessed According to Modified RANO Criteria

End point title	Percentage of Participants with 2L Objective Response of Complete Response (CR) or Partial Response (PR) Assessed According to Modified RANO Criteria
End point description:	
2L objective response was defined as the CR/PR recorded from the date of randomization/PD1 until PD2, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 2L-treatment, whichever occurred first. Modified RANO criteria: CR was defined as complete disappearance of all enhancing disease, sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; no corticosteroids; and clinical status of stable or improved. PR was defined as >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained for at least 4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions on the same or lower dose of corticosteroids compared to baseline; and clinical status of stable or improved. The 95% CI was computed using Clopper-Pearson approach. Analysis was performed on ITT Population.	
End point type	Secondary
End point timeframe:	
From randomization/PD1 until PD2, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 2L-treatment, whichever occurred first (approximately 18 months overall)	

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[5]	57[6]		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 6.5)	0.0 (0.0 to 6.3)		

Notes:

[5] - Participants with a valid response assessment

[6] - Participants with a valid response assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with 3L Objective Response of CR or PR Assessed According to Modified RANO Criteria

End point title	Percentage of Participants with 3L Objective Response of CR or PR Assessed According to Modified RANO Criteria

End point description:

3L objective response was defined as the CR/PR recorded from first administration of randomized treatment after PD2 until PD3, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 3L-treatment, whichever occurred first. Modified RANO criteria: CR was defined as complete disappearance of all enhancing disease, sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; no corticosteroids; and clinical status of stable or improved. PR was defined as >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained for at least 4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions on the same or lower dose of corticosteroids compared to baseline; and clinical status of stable or improved. The 95% CI was computed using Clopper-Pearson approach. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From PD2 until PD3, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of study treatment, whichever occurs first (approximately 26 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21[7]	21[8]		
Units: percentage of participants				
number (confidence interval 95%)	4.8 (0.1 to 23.8)	0.0 (0.0 to 16.1)		

Notes:

[7] - Participants with PD2, start of 3L treatment, and valid response assessment

[8] - Participants with PD2, start of 3L treatment, and valid response assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with 2L Disease Control as CR, PR, or Stable Disease (SD) Assessed According to Modified RANO Criteria

End point title	Percentage of Participants with 2L Disease Control as CR, PR, or Stable Disease (SD) Assessed According to Modified RANO Criteria

End point description:

2L disease control was defined as CR, PR, or SD recorded from the date of randomization/PD1 until PD2, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 2L-treatment, whichever occurred first. Tumor response was assessed according to modified RANO criteria. CR: complete disappearance of all enhancing disease, sustained >/=4 weeks; no new lesions; stable/improved non-enhancing lesions; no corticosteroids; and clinical status of stable or improved. PR: >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained >/=4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions; and clinical status of stable or improved. SD: absence of CR, PR, or progression; stable non-enhancing lesions; and clinical status of stable or improved. The 95% CI was computed using Clopper-Pearson approach. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From randomization/PD1 until PD2, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 2L-treatment, whichever occurred first (approximately 18 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[9]	57[10]		
Units: percentage of participants				
number (confidence interval 95%)	10.9 (4.1 to 22.2)	21.1 (11.4 to 33.9)		

Notes:

[9] - Participants with a valid response assessment

[10] - Participants with a valid response assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with 3L Disease Control as CR, PR, or SD Assessed According to Modified RANO Criteria

End point title	Percentage of Participants with 3L Disease Control as CR, PR, or SD Assessed According to Modified RANO Criteria

End point description:

3L disease control was defined as a CR, PR, or SD recorded from first administration of randomized treatment after PD2 until PD3, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 3L-treatment, whichever occurred first. According to modified RANO criteria, CR: complete disappearance of all enhancing disease, sustained >/=4 weeks; no new lesions; stable/improved non-enhancing lesions; no corticosteroids; and clinical status of stable or improved. PR: >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained >/=4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions; and clinical status of stable or improved. SD: absence of CR, PR, or progression; stable non-enhancing lesions; and clinical status of stable or improved. The 95% CI was computed using Clopper-Pearson approach. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

From PD2/start of 3L-treatment until PD3, death, subsequent anticancer therapy, operation/re-operation for glioblastoma, or 13 weeks after last administration of 3L-treatment, whichever occurred first (approximately 26 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21[11]	21[12]		
Units: percentage of participants				
number (confidence interval 95%)	14.3 (3.0 to 36.3)	9.5 (1.2 to 30.4)		

Notes:

[11] - Participants with PD2, start of 3L treatment, and valid response assessment

[12] - Participants with PD2, start of 3L treatment, and valid response assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of 2L Objective Response (DOR2) Assessed According to Modified RANO Criteria

End point title	Duration of 2L Objective Response (DOR2) Assessed According to Modified RANO Criteria

End point description:

Duration of 2L objective response was defined as the time interval from the first assessment of CR or PR after randomization/PD1 until PD2, death from any cause, subsequent anticancer therapy, whichever occurred first. Tumor response was assessed according to modified RANO criteria. CR: complete disappearance of all enhancing disease, sustained >/=4 weeks; no new lesions; stable/improved non-enhancing lesions; no corticosteroids; and clinical status of stable or improved. PR: >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained >/=4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions; and clinical status of stable or improved. Median DOR2 and 95% CI were assessed using Kaplan-Meier method. Analysis was performed on ITT Population. The data '99999 (99999 to 99999)' in the results signifies that median and corresponding CI could not be calculated as no participants experienced a CR or PR.

End point type	Secondary

End point timeframe:

From first occurrence of CR/PR after randomization/PD1 until PD2, death from any cause, subsequent anticancer therapy, whichever occurred first (approximately 18 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of 3L Objective Response (DOR3) Assessed According to Modified RANO Criteria

End point title	Duration of 3L Objective Response (DOR3) Assessed According to Modified RANO Criteria

End point description:

Duration of 3L objective response was defined as the time interval from the first assessment of CR or PR after PD2 until PD3, death from any cause, subsequent anticancer therapy, whichever occurred first. Tumor response was assessed according to modified RANO criteria. CR: complete disappearance of all enhancing disease, sustained >/=4 weeks; no new lesions; stable/improved non-enhancing lesions; no corticosteroids; and clinical status of stable or improved. PR: >/=50% decrease compared with baseline in all measurable enhancing lesions, sustained >/=4 weeks; no progression of non-measurable T1-enhancing disease; no new lesions; stable/improved non-enhancing lesions; and clinical status of stable or improved. Median DOR3 and 95% CI were assessed using Kaplan-Meier method. Analysis was performed on ITT Population. '99999 (99999 to 99999)' = median and corresponding CI could not be calculated as insufficient number of participants (<50%) experienced a CR or PR.

End point type	Secondary

End point timeframe:

From first occurrence of CR/PR after PD2 until PD3, subsequent anticancer therapy, or death from any cause, whichever occurred first (approximately 26 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) Global Health Status/Global QoL Scale Score

End point title	1L Treatment: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 (C30) Global Health Status/Global QoL Scale Score

End point description:

The EORTC QLQ-C30 is a validated self-report measure consisting of 30 questions incorporated into five functional scales (Physical, Role, Cognitive, Emotional, and Social scales), three symptom scales (fatigue, pain, nausea and vomiting scales), a global health status/global quality-of-life (QoL) scale, and single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact). Most questions used 4-point scale (1='Not at all' to 4='Very much'), while 2 questions used 7-point scale (1='very poor' to 7='Excellent'). Scores were averaged, transformed to 0-100 scale; where higher score for global health status/global QoL = better health related quality of life (HRQoL). Analysis was performed on enrolled analysis set, which included all participants enrolled in the study regardless of whether they received any trial drug. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Baseline;Week(Wk)3,5;end of Wk6;Maintenance:Day(D)1 (Visit[V]1), D15(V2) Cycles(C)1-6 Q4W;Monotherapy:V1-V44 Q3W;Safety Follow-up(FU) (30 days after last 1L dose);PD FUs(8 Wk after Safety FU [PD FU1],then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	279[13]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=279)	67.1 (± 22.09)			
Change at Beginning of Wk 3 (n=245)	2.4 (± 18.69)			
Change at Beginning of Wk 5 (n=257)	2.5 (± 19.52)			
Change at end of Wk 6 (n=245)	-1.2 (± 22.04)			
Change at Maintenance C1V1 (n=200)	1.7 (± 21.43)			
Change at Maintenance C1V2 (n=221)	0.1 (± 21.38)			
Change at Maintenance C2V1 (n=223)	-0.2 (± 21.25)			
Change at Maintenance C2V2 (n=204)	-1.6 (± 22.99)			
Change at Maintenance C3V1 (n=201)	-1.0 (± 22.20)			
Change at Maintenance C3V2 (n=205)	1.3 (± 20.66)			
Change at Maintenance C4V1 (n=196)	1.0 (± 19.19)			
Change at Maintenance C4V2 (n=194)	1.9 (± 19.35)			
Change at Maintenance C5V1 (n=185)	1.6 (± 21.17)			
Change at Maintenance C5V2 (n=181)	2.3 (± 21.58)			
Change at Maintenance C6V1 (n=171)	0.8 (± 22.00)			
Change at Maintenance C6V2 (n=168)	1.6 (± 20.04)			
Change at Monotherapy V1 (n=161)	0.7 (± 20.27)			
Change at Monotherapy V2 (n=147)	1.6 (± 19.47)			
Change at Monotherapy V3 (n=135)	2.0 (± 22.52)			
Change at Monotherapy V4 (n=118)	2.4 (± 22.54)			
Change at Monotherapy V5 (n=109)	0 (± 21.52)			
Change at Monotherapy V6 (n=99)	0.7 (± 21.55)			
Change at Monotherapy V7 (n=91)	0.8 (± 23.18)			
Change at Monotherapy V8 (n=77)	2.8 (± 21.74)			
Change at Monotherapy V9 (n=75)	5.1 (± 22.47)			
Change at Monotherapy V10 (n=72)	5.0 (± 22.28)			
Change at Monotherapy V11 (n=71)	3.8 (± 19.10)			
Change at Monotherapy V12 (n=66)	2.3 (± 21.86)			
Change at Monotherapy V13 (n=58)	1.4 (± 22.08)			

Change at Monotherapy V14 (n=58)	4.9 (± 21.00)			
Change at Monotherapy V15 (n=56)	2.5 (± 21.26)			
Change at Monotherapy V16 (n=50)	4.8 (± 23.03)			
Change at Monotherapy V17 (n=48)	3.3 (± 23.87)			
Change at Monotherapy V18 (n=44)	2.5 (± 23.54)			
Change at Monotherapy V19 (n=41)	2.4 (± 21.35)			
Change at Monotherapy V20 (n=36)	3.5 (± 21.40)			
Change at Monotherapy V21 (n=31)	3.0 (± 24.01)			
Change at Monotherapy V22 (n=32)	5.7 (± 22.64)			
Change at Monotherapy V23 (n=30)	3.6 (± 27.13)			
Change at Monotherapy V24 (n=25)	8.3 (± 23.94)			
Change at Monotherapy V25 (n=23)	7.2 (± 23.48)			
Change at Monotherapy V26 (n=21)	3.6 (± 23.95)			
Change at Monotherapy V27 (n=21)	8.3 (± 25.00)			
Change at Monotherapy V28 (n=17)	13.7 (± 26.67)			
Change at Monotherapy V29 (n=18)	13.4 (± 26.83)			
Change at Monotherapy V30 (n=15)	13.9 (± 24.93)			
Change at Monotherapy V31 (n=15)	15.0 (± 21.41)			
Change at Monotherapy V32 (n=10)	13.3 (± 31.72)			
Change at Monotherapy V33 (n=7)	15.5 (± 30.21)			
Change at Monotherapy V34 (n=7)	13.1 (± 32.58)			
Change at Monotherapy V35 (n=4)	-8.3 (± 15.21)			
Change at Monotherapy V36 (n=5)	5.0 (± 32.60)			
Change at Monotherapy V37 (n=4)	-8.3 (± 15.21)			
Change at Monotherapy V38 (n=3)	-11.1 (± 17.35)			
Change at Monotherapy V39 (n=2)	-20.8 (± 5.89)			
Change at Monotherapy V40 (n=3)	-11.1 (± 17.35)			
Change at Monotherapy V41 (n=3)	-11.1 (± 17.35)			
Change at Monotherapy V42 (n=2)	-20.8 (± 5.89)			
Change at Monotherapy V43 (n=3)	-11.1 (± 17.35)			
Change at Monotherapy V44 (n=2)	-4.2 (± 17.68)			
Change at Safety FU (n=51)	-0.5 (± 28.01)			
Change at PD FU1 (n=40)	4.2 (± 29.54)			
Change at PD FU2 (n=19)	4.8 (± 21.93)			
Change at PD FU3 (n=11)	4.5 (± 23.38)			
Change at PD FU4 (n=5)	3.3 (± 12.64)			
Change at PD FU5 (n=4)	2.1 (± 17.18)			
Change at PD FU6 (n=3)	11.1 (± 17.35)			
Change at PD FU7 (n=2)	4.2 (± 29.46)			
Change at PD FU8 (n=1)	25.0 (± 99999)			

Notes:

[13] - '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in EORTC QLQ C30 Global Health Status/Global QoL Scale Score

End point title	2L and 3L Treatment: Change From 2L Baseline in EORTC QLQ C30 Global Health Status/Global QoL Scale Score

End point description:

The EORTC QLQ-C30 is a validated self-report measure consisting of 30 questions incorporated into five functional scales (Physical, Role, Cognitive, Emotional, and Social scales), three symptom scales (fatigue, pain, nausea and vomiting scales), a global health status/global quality-of-life (QoL) scale, and single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact). Most questions used 4-point scale (1='Not at all' to 4='Very much'), while 2 questions used 7-point scale (1='very poor' to 7='Excellent'). Scores were averaged, transformed to 0-100 scale; where higher score for global health status/global QoL = better HRQoL. Analysis was performed on ITT population. 'n'=participants evaluable at specified time point for different arms, respectively. '99999'=either data were not available because no participant was evaluable or standard deviation (SD) was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline (2L treatment V1); 2L treatment: V2-V41 (Q2W) until PD2; 3L treatment: V1-V61 (Q2W) until PD3; Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	61		
Units: units on a scale				
arithmetic mean (standard deviation)				
2L Baseline (n=62,61)	65.6 (± 20.66)	57.5 (± 23.21)		
Change at 2L V2 (n=45,40)	-2.4 (± 13.49)	3.1 (± 17.37)		
Change at 2L V3 (n=41,39)	-6.1 (± 15.37)	-0.9 (± 19.19)		
Change at 2L V4 (n=29,31)	-6.0 (± 16.35)	-2.2 (± 18.25)		
Change at 2L V5 (n=22,19)	-8.3 (± 17.44)	5.7 (± 10.04)		
Change at 2L V6 (n=18,13)	-8.3 (± 18.96)	3.8 (± 16.88)		
Change at 2L V7 (n=7,9)	-3.6 (± 9.45)	-2.8 (± 11.79)		
Change at 2L V8 (n=4,6)	-4.2 (± 15.96)	18.1 (± 18.57)		
Change at 2L V9 (n=4,7)	0 (± 13.61)	-4.8 (± 6.56)		
Change at 2L V10 (n=4,7)	0 (± 13.61)	-9.5 (± 25.20)		
Change at 2L V11 (n=4,5)	-2.1 (± 4.17)	-5.0 (± 7.45)		
Change at 2L V12 (n=2,3)	-8.3 (± 11.79)	5.6 (± 9.62)		
Change at 2L V13 (n=3,1)	-2.8 (± 12.73)	-25.0 (± 99999)		
Change at 2L V14 (n=2,1)	-8.3 (± 11.79)	16.7 (± 99999)		
Change at 2L V15 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V16 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V17 (n=1,1)	0 (± 99999)	16.7 (± 99999)		
Change at 2L V19 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V20 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V21 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V22 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		

Change at 2L V24 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V26 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V27 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V28 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V29 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
Change at 2L V30 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V32 (n=1,0)	-33.3 (± 99999)	99999 (± 99999)		
Change at 2L V33 (n=1,0)	-33.3 (± 99999)	99999 (± 99999)		
Change at 2L V34 (n=1,0)	-33.3 (± 99999)	99999 (± 99999)		
Change at 2L V35 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V36 (n=1,0)	-33.3 (± 99999)	99999 (± 99999)		
Change at 2L V38 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
Change at 2L V40 (n=1,0)	-25.0 (± 99999)	99999 (± 99999)		
Change at 2L V41 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=19,17)	-6.6 (± 18.55)	0.5 (± 16.53)		
Change at 3L V2 (n=15,14)	-2.2 (± 12.39)	-6.5 (± 17.04)		
Change at 3L V3 (n=10,14)	0.8 (± 14.93)	-6.5 (± 17.96)		
Change at 3L V4 (n=12,13)	-8.3 (± 23.84)	-2.6 (± 18.13)		
Change at 3L V5 (n=9,8)	0 (± 16.67)	-9.4 (± 15.71)		
Change at 3L V6 (n=6,3)	-11.1 (± 12.55)	-13.9 (± 20.97)		
Change at 3L V7 (n=3,4)	-16.7 (± 28.87)	2.1 (± 23.94)		
Change at 3L V8 (n=3,3)	-2.8 (± 12.73)	19.4 (± 4.81)		
Change at 3L V9 (n=3,3)	-8.3 (± 22.05)	2.8 (± 12.73)		
Change at 3L V10 (n=3,1)	-13.9 (± 12.73)	0 (± 99999)		
Change at 3L V11 (n=1,1)	0 (± 99999)	16.7 (± 99999)		
Change at 3L V12 (n=2,2)	-8.3 (± 11.79)	12.5 (± 5.89)		
Change at 3L V13 (n=2,0)	-8.3 (± 11.79)	99999 (± 99999)		
Change at 3L V14 (n=2,0)	0 (± 0)	99999 (± 99999)		
Change at 3L V15 (n=2,0)	0 (± 0)	99999 (± 99999)		
Change at 3L V16 (n=2,0)	-8.3 (± 11.79)	99999 (± 99999)		
Change at 3L V17 (n=2,0)	0 (± 0)	99999 (± 99999)		
Change at 3L V18 (n=2,0)	-8.3 (± 11.79)	99999 (± 99999)		

Change at 3L V19 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V21 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V23 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V27 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V28 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V29 (n=1,0)	16.7 (± 99999)	99999 (± 99999)		
Change at 3L V30 (n=1,0)	16.7 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V32 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V33 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V34 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V35 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V36 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V39 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V41 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V42 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V43 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V44 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V45 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V46 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V47 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V48 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V51 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V52 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V53 (n=1,0)	0 (± 99999)	99999 (± 99999)		

Change at 3L V54 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V55 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V56 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V57 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V58 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V59 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V60 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=6,13)	-20.8 (± 11.49)	-11.5 (± 14.25)		
Change at PD FU1 (n=1,3)	-8.3 (± 99999)	-25.0 (± 0)		
Change at end of study (n=4,2)	-16.7 (± 22.57)	-12.5 (± 5.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in EORTC QLQ Brain Cancer Module 20 (BN20) Multiple Item Score

End point title	1L Treatment: Change From Baseline in EORTC QLQ Brain Cancer Module 20 (BN20) Multiple Item Score

End point description:

The BN20 consists of 4 multiple items scales (future uncertainty [FtUn], visual disorder [VsDr], motor dysfunction [MtDf], communication deficit [CmDf]) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). All questions used 4-point scale (1='Not at all' to 4='Very much'). Multiple item scores were transformed to a 0-100 scale, where higher score=more severe symptoms/poor QoL. The change from baseline in multiple items scales score at different time points is reported. Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Wk 3, 5; end of Wk6; Maintenance: D1(V1), D15(V2) of C1-6 (Q4W); Monotherapy: V1-V44 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	256			
Units: units on a scale				
arithmetic mean (standard deviation)				
FtUn: Baseline (n=256)	32.3 (± 24.08)			

FtUn: Change at Beginning of Wk 3 (n=230)	-8.9 (± 20.21)			
FtUn: Change at Beginning of Wk 5 (n=234)	-8.6 (± 21.32)			
FtUn: Change at end of Wk 6 (n=227)	-7.5 (± 22.88)			
FtUn: Change at Maintenance C1V1 (n=188)	-7.9 (± 26.64)			
FtUn: Change at Maintenance C1V2 (n=201)	-9.4 (± 24.31)			
FtUn: Change at Maintenance C2V1 (n=205)	-10.8 (± 25.27)			
FtUn: Change at Maintenance C2V2 (n=197)	-8.8 (± 27.05)			
FtUn: Change at Maintenance C3V1 (n=185)	-9.9 (± 24.82)			
FtUn: Change at Maintenance C3V2 (n=190)	-8.9 (± 23.56)			
FtUn: Change at Maintenance C4V1 (n=190)	-11.7 (± 21.91)			
FtUn: Change at Maintenance C4V2 (n=184)	-10.6 (± 24.55)			
FtUn: Change at Maintenance C5V1 (n=173)	-10.7 (± 22.30)			
FtUn: Change at Maintenance C5V2 (n=164)	-11.1 (± 23.70)			
FtUn: Change at Maintenance C6V1 (n=165)	-11.7 (± 23.52)			
FtUn: Change at Maintenance C6V2 (n=161)	-12.8 (± 23.65)			
FtUn: Change at Monotherapy V1 (n=154)	-10.7 (± 23.25)			
FtUn: Change at Monotherapy V2 (n=139)	-10.1 (± 25.22)			
FtUn: Change at Monotherapy V3 (n=131)	-9.1 (± 26.31)			
FtUn: Change at Monotherapy V4 (n=111)	-11.2 (± 23.90)			
FtUn: Change at Monotherapy V5 (n=101)	-11.5 (± 23.68)			
FtUn: Change at Monotherapy V6 (n=95)	-10.6 (± 26.12)			
FtUn: Change at Monotherapy V7 (n=86)	-10.7 (± 26.73)			
FtUn: Change at Monotherapy V8 (n=71)	-11.2 (± 27.68)			
FtUn: Change at Monotherapy V9 (n=70)	-14.0 (± 24.92)			
FtUn: Change at Monotherapy V10 (n=68)	-15.2 (± 23.81)			
FtUn: Change at Monotherapy V11 (n=66)	-15.0 (± 25.29)			
FtUn: Change at Monotherapy V12 (n=59)	-14.8 (± 23.57)			
FtUn: Change at Monotherapy V13 (n=53)	-16.3 (± 20.22)			
FtUn: Change at Monotherapy V14 (n=53)	-14.2 (± 22.88)			
FtUn: Change at Monotherapy V15 (n=56)	-17.2 (± 23.10)			
FtUn: Change at Monotherapy V16 (n=47)	-18.8 (± 21.17)			

FtUn: Change at Monotherapy V17 (n=43)	-18.2 (± 24.75)			
FtUn: Change at Monotherapy V18 (n=39)	-14.1 (± 23.27)			
FtUn: Change at Monotherapy V19 (n=36)	-18.3 (± 20.68)			
FtUn: Change at Monotherapy V20 (n=31)	-17.7 (± 21.05)			
FtUn: Change at Monotherapy V21 (n=28)	-18.8 (± 18.46)			
FtUn: Change at Monotherapy V22 (n=29)	-21.3 (± 18.17)			
FtUn: Change at Monotherapy V23 (n=27)	-19.4 (± 18.20)			
FtUn: Change at Monotherapy V24 (n=22)	-24.5 (± 20.17)			
FtUn: Change at Monotherapy V25 (n=22)	-20.8 (± 20.04)			
FtUn: Change at Monotherapy V26 (n=20)	-19.6 (± 17.16)			
FtUn: Change at Monotherapy V27 (n=20)	-22.9 (± 18.90)			
FtUn: Change at Monotherapy V28 (n=15)	-22.2 (± 18.54)			
FtUn: Change at Monotherapy V29 (n=16)	-20.8 (± 23.96)			
FtUn: Change at Monotherapy V30 (n=13)	-22.0 (± 23.42)			
FtUn: Change at Monotherapy V31 (n=13)	-23.7 (± 18.59)			
FtUn: Change at Monotherapy V32 (n=9)	-24.1 (± 19.30)			
FtUn: Change at Monotherapy V33 (n=6)	-36.1 (± 18.76)			
FtUn: Change at Monotherapy V34 (n=6)	-23.6 (± 26.57)			
FtUn: Change at Monotherapy V35 (n=4)	-16.7 (± 27.22)			
FtUn: Change at Monotherapy V36 (n=5)	-20.0 (± 22.52)			
FtUn: Change at Monotherapy V37 (n=4)	-18.8 (± 27.53)			
FtUn: Change at Monotherapy V38 (n=2)	-25.0 (± 11.79)			
FtUn: Change at Monotherapy V39 (n=2)	0 (± 23.57)			
FtUn: Change at Monotherapy V40 (n=3)	-13.9 (± 29.27)			
FtUn: Change at Monotherapy V41 (n=3)	-13.9 (± 29.27)			
FtUn: Change at Monotherapy V42 (n=2)	-4.2 (± 17.68)			
FtUn: Change at Monotherapy V43 (n=3)	-13.9 (± 29.27)			
FtUn: Change at Monotherapy V44 (n=2)	-29.2 (± 17.68)			
FtUn: Change at Safety FU (n=50)	-2.6 (± 26.92)			
FtUn: Change at PD FU1 (n=40)	-6.0 (± 32.26)			
FtUn: Change at PD FU2 (n=17)	-11.8 (± 19.56)			
FtUn: Change at PD FU3 (n=10)	-17.5 (± 21.32)			

FtUn: Change at PD FU4 (n=9)	-16.0 (± 20.59)			
FtUn: Change at PD FU5 (n=4)	-21.5 (± 3.50)			
FtUn: Change at PD FU6 (n=3)	-19.4 (± 20.97)			
FtUn: Change at PD FU7 (n=2)	-29.2 (± 17.68)			
FtUn: Change at PD FU8 (n=1)	-16.7 (± 99999)			
VsDr: Baseline (n=256)	13.4 (± 21.64)			
VsDr: Change at Beginning of Wk 3 (n=228)	-2.7 (± 15.76)			
VsDr: Change at Beginning of Wk 5 (n=234)	-2.8 (± 16.23)			
VsDr: Change at end of Wk 6 (n=226)	-0.5 (± 18.04)			
VsDr: Change at Maintenance C1V1 (n=186)	-1.8 (± 20.25)			
VsDr: Change at Maintenance C1V2 (n=200)	-1.6 (± 18.68)			
VsDr: Change at Maintenance C2V1 (n=204)	-2.2 (± 17.74)			
VsDr: Change at Maintenance C2V2 (n=197)	-2.8 (± 20.37)			
VsDr: Change at Maintenance C3V1 (n=185)	-1.3 (± 20.82)			
VsDr: Change at Maintenance C3V2 (n=189)	-2.3 (± 20.71)			
VsDr: Change at Maintenance C4V1 (n=190)	-2.1 (± 20.69)			
VsDr: Change at Maintenance C4V2 (n=184)	-1.4 (± 18.61)			
VsDr: Change at Maintenance C5V1 (n=172)	-1.6 (± 17.17)			
VsDr: Change at Maintenance C5V2 (n=164)	-1.2 (± 17.27)			
VsDr: Change at Maintenance C6V1 (n=165)	-1.8 (± 17.06)			
VsDr: Change at Maintenance C6V2 (n=158)	-0.9 (± 16.28)			
VsDr: Change at Monotherapy V1 (n=154)	-0.8 (± 18.31)			
VsDr: Change at Monotherapy V2 (n=140)	-2.3 (± 17.22)			
VsDr: Change at Monotherapy V3 (n=131)	-2.5 (± 17.35)			
VsDr: Change at Monotherapy V4 (n=111)	-0.7 (± 18.86)			
VsDr: Change at Monotherapy V5 (n=101)	0.2 (± 20.17)			
VsDr: Change at Monotherapy V6 (n=95)	-0.2 (± 20.05)			
VsDr: Change at Monotherapy V7 (n=85)	-2.8 (± 18.89)			
VsDr: Change at Monotherapy V8 (n=71)	-2.4 (± 14.60)			
VsDr: Change at Monotherapy V9 (n=70)	-0.6 (± 16.12)			
VsDr: Change at Monotherapy V10 (n=67)	-2.2 (± 12.76)			
VsDr: Change at Monotherapy V11 (n=66)	-1.6 (± 14.77)			

VsDr: Change at Monotherapy V12 (n=59)	-0.1 (± 17.94)			
VsDr: Change at Monotherapy V13 (n=54)	-3.5 (± 15.12)			
VsDr: Change at Monotherapy V14 (n=53)	-0.8 (± 15.84)			
VsDr: Change at Monotherapy V15 (n=55)	-2.1 (± 12.85)			
VsDr: Change at Monotherapy V16 (n=47)	-0.4 (± 14.30)			
VsDr: Change at Monotherapy V17 (n=43)	-1.6 (± 15.96)			
VsDr: Change at Monotherapy V18 (n=39)	0.4 (± 20.01)			
VsDr: Change at Monotherapy V19 (n=36)	-2.6 (± 14.21)			
VsDr: Change at Monotherapy V20 (n=31)	-3.8 (± 13.10)			
VsDr: Change at Monotherapy V21 (n=28)	-3.8 (± 11.52)			
VsDr: Change at Monotherapy V22 (n=29)	-4.0 (± 12.14)			
VsDr: Change at Monotherapy V23 (n=27)	-6.0 (± 14.69)			
VsDr: Change at Monotherapy V24 (n=22)	-3.8 (± 14.49)			
VsDr: Change at Monotherapy V25 (n=22)	-6.3 (± 11.41)			
VsDr: Change at Monotherapy V26 (n=20)	-4.4 (± 12.17)			
VsDr: Change at Monotherapy V27 (n=20)	-4.2 (± 13.35)			
VsDr: Change at Monotherapy V28 (n=25)	-2.6 (± 12.40)			
VsDr: Change at Monotherapy V29 (n=16)	-1.0 (± 12.87)			
VsDr: Change at Monotherapy V30 (n=13)	-3.0 (± 13.34)			
VsDr: Change at Monotherapy V31 (n=13)	-1.3 (± 12.03)			
VsDr: Change at Monotherapy V32 (n=9)	-0.6 (± 7.05)			
VsDr: Change at Monotherapy V33 (n=6)	1.9 (± 4.54)			
VsDr: Change at Monotherapy V34 (n=6)	1.9 (± 4.54)			
VsDr: Change at Monotherapy V35 (n=4)	0 (± 0)			
VsDr: Change at Monotherapy V36 (n=5)	0 (± 0)			
VsDr: Change at Monotherapy V37 (n=4)	0 (± 0)			
VsDr: Change at Monotherapy V38 (n=2)	0 (± 0)			
VsDr: Change at Monotherapy V39 (n=2)	0 (± 0)			
VsDr: Change at Monotherapy V40 (n=3)	0 (± 0)			
VsDr: Change at Monotherapy V41 (n=3)	0 (± 0)			
VsDr: Change at Monotherapy V42 (n=2)	0 (± 0)			

VsDr: Change at Monotherapy V43 (n=3)	0 (± 0)			
VsDr: Change at Monotherapy V44 (n=2)	0 (± 0)			
VsDr: Change at Safety FU (n=51)	-1.2 (± 21.27)			
VsDr: Change at PD FU1 (n=40)	1.5 (± 20.94)			
VsDr: Change at PD FU2 (n=17)	0 (± 17.12)			
VsDr: Change at PD FU3 (n=10)	1.1 (± 19.21)			
VsDr: Change at PD FU4 (n=9)	0 (± 22.91)			
VsDr: Change at PD FU5 (n=4)	-11.1 (± 22.22)			
VsDr: Change at PD FU6 (n=3)	0 (± 40.06)			
VsDr: Change at PD FU7 (n=2)	-16.7 (± 39.28)			
VsDr: Change at PD FU8 (n=1)	-44.4 (± 99999)			
MtDf: Baseline (n=256)	15.4 (± 22.75)			
MtDf: Change at Beginning of Wk 3 (n=228)	-1.2 (± 15.75)			
MtDf: Change at Beginning of Wk 5 (n=233)	-2.0 (± 19.50)			
MtDf: Change at end of Wk 6 (n=227)	-1.3 (± 17.99)			
MtDf: Change at Maintenance C1V1 (n=187)	-2.3 (± 20.89)			
MtDf: Change at Maintenance C1V2 (n=201)	-0.3 (± 20.02)			
MtDf: Change at Maintenance C2V1 (n=204)	-2.4 (± 20.42)			
MtDf: Change at Maintenance C2V2 (n=197)	-1.6 (± 19.22)			
MtDf: Change at Maintenance C3V1 (n=185)	-3.2 (± 19.11)			
MtDf: Change at Maintenance C3V2 (n=189)	-2.9 (± 18.23)			
MtDf: Change at Maintenance C4V1 (n=190)	-2.9 (± 19.34)			
MtDf: Change at Maintenance C4V2 (n=184)	-1.4 (± 19.65)			
MtDf: Change at Maintenance C5V1 (n=174)	-1.0 (± 17.96)			
MtDf: Change at Maintenance C5V2 (n=162)	-1.6 (± 20.14)			
MtDf: Change at Maintenance C6V1 (n=164)	-2.6 (± 19.53)			
MtDf: Change at Maintenance C6V2 (n=161)	-1.9 (± 19.08)			
MtDf: Change at Monotherapy V1 (n=153)	-0.9 (± 19.81)			
MtDf: Change at Monotherapy V2 (n=140)	-1.2 (± 19.42)			
MtDf: Change at Monotherapy V3 (n=131)	-0.4 (± 21.19)			
MtDf: Change at Monotherapy V4 (n=111)	-1.2 (± 20.54)			
MtDf: Change at Monotherapy V5 (n=99)	1.3 (± 22.52)			
MtDf: Change at Monotherapy V6 (n=95)	-0.2 (± 23.52)			
MtDf: Change at Monotherapy V7 (n=85)	-0.2 (± 24.16)			

MtDf: Change at Monotherapy V8 (n=71)	-3.0 (± 21.76)			
MtDf: Change at Monotherapy V9 (n=70)	-4.2 (± 20.51)			
MtDf: Change at Monotherapy V10 (n=68)	-4.4 (± 22.34)			
MtDf: Change at Monotherapy V11 (n=66)	-1.5 (± 18.99)			
MtDf: Change at Monotherapy V12 (n=59)	-3.4 (± 20.45)			
MtDf: Change at Monotherapy V13 (n=53)	-2.9 (± 25.73)			
MtDf: Change at Monotherapy V14 (n=53)	-2.4 (± 22.69)			
MtDf: Change at Monotherapy V15 (n=56)	-5.4 (± 22.82)			
MtDf: Change at Monotherapy V16 (n=47)	-4.3 (± 21.30)			
MtDf: Change at Monotherapy V17 (n=43)	-2.1 (± 23.66)			
MtDf: Change at Monotherapy V18 (n=39)	1.9 (± 24.86)			
MtDf: Change at Monotherapy V19 (n=36)	-4.0 (± 20.60)			
MtDf: Change at Monotherapy V20 (n=31)	-2.2 (± 23.38)			
MtDf: Change at Monotherapy V21 (n=28)	-3.2 (± 20.48)			
MtDf: Change at Monotherapy V22 (n=29)	-6.5 (± 24.94)			
MtDf: Change at Monotherapy V23 (n=27)	-0.6 (± 22.98)			
MtDf: Change at Monotherapy V24 (n=22)	-4.0 (± 26.46)			
MtDf: Change at Monotherapy V25 (n=22)	-4.0 (± 26.46)			
MtDf: Change at Monotherapy V26 (n=20)	-5.6 (± 24.58)			
MtDf: Change at Monotherapy V27 (n=20)	-5.0 (± 25.10)			
MtDf: Change at Monotherapy V28 (n=15)	-5.2 (± 30.82)			
MtDf: Change at Monotherapy V29 (n=16)	-6.9 (± 27.78)			
MtDf: Change at Monotherapy V30 (n=13)	0 (± 25.26)			
MtDf: Change at Monotherapy V31 (n=13)	-3.4 (± 28.10)			
MtDf: Change at Monotherapy V32 (n=9)	-4.9 (± 28.39)			
MtDf: Change at Monotherapy V33 (n=6)	-7.4 (± 35.60)			
MtDf: Change at Monotherapy V34 (n=6)	-9.3 (± 28.47)			
MtDf: Change at Monotherapy V35 (n=4)	0 (± 0)			
MtDf: Change at Monotherapy V36 (n=5)	-15.6 (± 34.78)			
MtDf: Change at Monotherapy V37 (n=4)	0 (± 0)			
MtDf: Change at Monotherapy V38 (n=2)	0 (± 0)			

MtDf: Change at Monotherapy V39 (n=2)	0 (± 0)			
MtDf: Change at Monotherapy V40 (n=3)	0 (± 0)			
MtDf: Change at Monotherapy V41 (n=3)	0 (± 0)			
MtDf: Change at Monotherapy V42 (n=2)	0 (± 0)			
MtDf: Change at Monotherapy V43 (n=3)	0 (± 0)			
MtDf: Change at Monotherapy V44 (n=2)	0 (± 0)			
MtDf: Change at Safety FU (n=49)	-2.4 (± 23.30)			
MtDf: Change at PD FU1 (n=40)	5.8 (± 28.99)			
MtDf: Change at PD FU2 (n=17)	12.7 (± 15.44)			
MtDf: Change at PD FU3 (n=10)	-3.3 (± 20.32)			
MtDf: Change at PD FU4 (n=9)	1.2 (± 35.33)			
MtDf: Change at PD FU5 (n=4)	2.8 (± 40.95)			
MtDf: Change at PD FU6 (n=3)	3.7 (± 16.97)			
MtDf: Change at PD FU7 (n=2)	11.1 (± 15.71)			
MtDf: Change at PD FU8 (n=1)	0 (± 99999)			
CmDf: Baseline (n=255)	17.2 (± 24.37)			
CmDf: Change at Beginning of Wk 3 (n=228)	-4.0 (± 21.50)			
CmDf: Change at Beginning of Wk 5 (n=233)	-4.6 (± 21.86)			
CmDf: Change at end of Wk 6 (n=227)	-2.8 (± 20.43)			
CmDf: Change at Maintenance C1V1 (n=186)	-2.0 (± 22.83)			
CmDf: Change at Maintenance C1V2 (n=200)	-2.9 (± 22.04)			
CmDf: Change at Maintenance C2V1 (n=203)	-4.2 (± 19.14)			
CmDf: Change at Maintenance C2V2 (n=196)	-2.7 (± 21.17)			
CmDf: Change at Maintenance C3V1 (n=183)	-2.9 (± 19.87)			
CmDf: Change at Maintenance C3V2 (n=187)	-3.4 (± 19.48)			
CmDf: Change at Maintenance C4V1 (n=189)	-3.0 (± 20.70)			
CmDf: Change at Maintenance C4V2 (n=184)	-3.6 (± 20.23)			
CmDf: Change at Maintenance C5V1 (n=173)	-3.5 (± 20.27)			
CmDf: Change at Maintenance C5V2 (n=162)	-3.2 (± 21.11)			
CmDf: Change at Maintenance C6V1 (n=163)	-3.1 (± 20.56)			
CmDf: Change at Maintenance C6V2 (n=158)	-3.9 (± 20.39)			
CmDf: Change at Monotherapy V1 (n=153)	-1.3 (± 21.70)			
CmDf: Change at Monotherapy V2 (n=139)	-1.0 (± 19.82)			
CmDf: Change at Monotherapy V3 (n=131)	-3.3 (± 19.42)			
CmDf: Change at Monotherapy V4 (n=111)	-2.8 (± 20.53)			

CmDf: Change at Monotherapy V5 (n=99)	-2.2 (± 20.69)			
CmDf: Change at Monotherapy V6 (n=95)	0.1 (± 23.57)			
CmDf: Change at Monotherapy V7 (n=85)	0.1 (± 24.70)			
CmDf: Change at Monotherapy V8 (n=71)	0.4 (± 26.47)			
CmDf: Change at Monotherapy V9 (n=70)	-3.1 (± 21.23)			
CmDf: Change at Monotherapy V10 (n=68)	-4.1 (± 23.97)			
CmDf: Change at Monotherapy V11 (n=66)	-3.0 (± 22.52)			
CmDf: Change at Monotherapy V12 (n=59)	-1.0 (± 22.64)			
CmDf: Change at Monotherapy V13 (n=52)	-1.6 (± 26.14)			
CmDf: Change at Monotherapy V14 (n=53)	-2.5 (± 22.92)			
CmDf: Change at Monotherapy V15 (n=56)	-0.6 (± 26.33)			
CmDf: Change at Monotherapy V16 (n=47)	0.2 (± 27.26)			
CmDf: Change at Monotherapy V17 (n=42)	-0.5 (± 26.76)			
CmDf: Change at Monotherapy V18 (n=39)	2.6 (± 31.16)			
CmDf: Change at Monotherapy V19 (n=36)	-2.2 (± 28.09)			
CmDf: Change at Monotherapy V20 (n=31)	-1.1 (± 29.73)			
CmDf: Change at Monotherapy V21 (n=28)	-4.0 (± 17.69)			
CmDf: Change at Monotherapy V22 (n=28)	-4.4 (± 28.90)			
CmDf: Change at Monotherapy V23 (n=27)	-6.6 (± 31.16)			
CmDf: Change at Monotherapy V24 (n=21)	-11.1 (± 28.97)			
CmDf: Change at Monotherapy V25 (n=21)	-3.2 (± 36.20)			
CmDf: Change at Monotherapy V26 (n=20)	-4.4 (± 33.70)			
CmDf: Change at Monotherapy V27 (n=20)	-8.6 (± 29.86)			
CmDf: Change at Monotherapy V28 (n=15)	-5.9 (± 38.00)			
CmDf: Change at Monotherapy V29 (n=15)	-14.8 (± 30.19)			
CmDf: Change at Monotherapy V30 (n=13)	-17.1 (± 31.95)			
CmDf: Change at Monotherapy V31 (n=13)	-5.1 (± 40.98)			
CmDf: Change at Monotherapy V32 (n=9)	-6.2 (± 21.60)			
CmDf: Change at Monotherapy V33 (n=6)	-7.4 (± 16.73)			
CmDf: Change at Monotherapy V34 (n=6)	-6.5 (± 18.06)			
CmDf: Change at Monotherapy V35 (n=4)	-13.9 (± 16.67)			

CmDf: Change at Monotherapy V36 (n=5)	-6.7 (± 21.66)			
CmDf: Change at Monotherapy V37 (n=4)	-13.9 (± 16.67)			
CmDf: Change at Monotherapy V38 (n=2)	-27.8 (± 7.86)			
CmDf: Change at Monotherapy V39 (n=2)	-11.1 (± 15.71)			
CmDf: Change at Monotherapy V40 (n=3)	-18.5 (± 16.97)			
CmDf: Change at Monotherapy V41 (n=3)	-18.5 (± 16.97)			
CmDf: Change at Monotherapy V42 (n=2)	-11.1 (± 15.71)			
CmDf: Change at Monotherapy V43 (n=3)	-18.5 (± 16.97)			
CmDf: Change at Monotherapy V44 (n=2)	-27.8 (± 7.86)			
CmDf: Change at Safety FU (n=50)	-2.9 (± 25.67)			
CmDf: Change at PD FU1 (n=40)	2.4 (± 28.10)			
CmDf: Change at PD FU2 (n=17)	0.3 (± 21.02)			
CmDf: Change at PD FU3 (n=10)	0 (± 14.81)			
CmDf: Change at PD FU4 (n=9)	8.6 (± 15.49)			
CmDf: Change at PD FU5 (n=4)	11.1 (± 15.71)			
CmDf: Change at PD FU6 (n=3)	14.8 (± 16.97)			
CmDf: Change at PD FU7 (n=2)	5.6 (± 7.86)			
CmDf: Change at PD FU8 (n=1)	0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in EORTC QLQ BN20 Multiple Item Score

End point title	2L and 3L Treatment: Change From 2L Baseline in EORTC QLQ BN20 Multiple Item Score

End point description:

The BN20 consists of 4 multiple items scales (future uncertainty [FtUn], visual disorder [VsDr], motor dysfunction [MtDf], communication deficit [CmDf]) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). All questions used 4-point scale (1='Not at all' to 4='Very much'). Multiple item scores were transformed to a 0-100 scale, where higher score=more severe symptoms/poor QoL. The change from baseline in multiple items scales score at different time points is reported. Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline (2L treatment V1); 2L treatment: V2-V41 (Q2W) until PD2; 3L treatment: V1-V61 (Q2W) until PD3; Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	59		
Units: units on a scale				
arithmetic mean (standard deviation)				
FtUn: 2L Baseline (n=57,59)	28.9 (± 25.90)	37.2 (± 26.69)		
FtUn: Change at 2L V2 (n=44,38)	0.7 (± 19.32)	-0.9 (± 16.19)		
FtUn: Change at 2L V3 (n=39,37)	3.8 (± 17.08)	-3.9 (± 22.89)		
FtUn: Change at 2L V4 (n=28,31)	3.3 (± 12.49)	-2.4 (± 20.66)		
FtUn: Change at 2L V5 (n=21,19)	0.8 (± 11.76)	-12.3 (± 18.50)		
FtUn: Change at 2L V6 (n=17,14)	14.1 (± 19.78)	-8.3 (± 17.60)		
FtUn: Change at 2L V7 (n=7,10)	-4.8 (± 13.49)	-5.0 (± 17.21)		
FtUn: Change at 2L V8 (n=4,7)	-2.1 (± 4.17)	-4.4 (± 18.69)		
FtUn: Change at 2L V9 (n=5,8)	1.7 (± 12.36)	-4.9 (± 22.80)		
FtUn: Change at 2L V10 (n=4,6)	-6.3 (± 12.50)	-15.3 (± 18.57)		
FtUn: Change at 2L V11 (n=4,6)	4.2 (± 4.81)	-8.8 (± 24.18)		
FtUn: Change at 2L V12 (n=2,4)	12.5 (± 17.68)	-16.7 (± 20.41)		
FtUn: Change at 2L V13 (n=3,3)	8.3 (± 16.67)	-22.2 (± 17.35)		
FtUn: Change at 2L V14 (n=2,1)	8.3 (± 11.79)	-8.3 (± 99999)		
FtUn: Change at 2L V15 (n=1,1)	8.3 (± 99999)	-8.3 (± 99999)		
FtUn: Change at 2L V16 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V17 (n=1,1)	8.3 (± 99999)	-8.3 (± 99999)		
FtUn: Change at 2L V18 (n=0,1)	99999 (± 99999)	0 (± 99999)		
FtUn: Change at 2L V19 (n=1,0)	16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V20 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V21 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V22 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V24 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V25 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V26 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V27 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V28 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V29 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V30 (n=1,0)	16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V31 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V32 (n=1,0)	33.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V33 (n=1,0)	33.3 (± 99999)	99999 (± 99999)		

FtUn: Change at 2L V34 (n=1,0)	33.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V35 (n=1,0)	41.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V36 (n=1,0)	50.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V38 (n=1,0)	16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V39 (n=1,0)	25.0 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V40 (n=1,0)	41.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 2L V41 (n=1,0)	33.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V1 (n=17,17)	10.3 (± 19.66)	7.2 (± 19.89)		
FtUn: Change at 3L V2 (n=13,14)	7.1 (± 14.77)	6.9 (± 19.48)		
FtUn: Change at 3L V3 (n=11,13)	4.5 (± 15.53)	7.1 (± 19.50)		
FtUn: Change at 3L V4 (n=12,13)	12.5 (± 22.33)	4.5 (± 21.41)		
FtUn: Change at 3L V5 (n=9,8)	2.8 (± 17.18)	-2.1 (± 15.27)		
FtUn: Change at 3L V6 (n=6,3)	7.4 (± 19.38)	2.8 (± 17.35)		
FtUn: Change at 3L V7 (n=3,4)	13.9 (± 24.06)	8.3 (± 28.87)		
FtUn: Change at 3L V8 (n=3,3)	0 (± 0)	-11.1 (± 19.25)		
FtUn: Change at 3L V9 (n=3,3)	0 (± 14.43)	-11.1 (± 19.25)		
FtUn: Change at 3L V10 (n=3,1)	16.7 (± 25.00)	8.3 (± 99999)		
FtUn: Change at 3L V11 (n=2,1)	-8.3 (± 23.57)	-33.3 (± 99999)		
FtUn: Change at 3L V12 (n=2,2)	4.2 (± 17.68)	-16.7 (± 23.57)		
FtUn: Change at 3L V13 (n=2,0)	0 (± 23.57)	99999 (± 99999)		
FtUn: Change at 3L V14 (n=2,0)	0 (± 11.79)	99999 (± 99999)		
FtUn: Change at 3L V15 (n=2,0)	8.3 (± 23.57)	99999 (± 99999)		
FtUn: Change at 3L V16 (n=2,0)	0 (± 11.79)	99999 (± 99999)		
FtUn: Change at 3L V17 (n=2,0)	8.3 (± 23.57)	99999 (± 99999)		
FtUn: Change at 3L V18 (n=2,0)	0 (± 11.79)	99999 (± 99999)		
FtUn: Change at 3L V19 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V21 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V23 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V25 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V26 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V27 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V28 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		

FtUn: Change at 3L V30 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V32 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V33 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V34 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V35 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V36 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V37 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V39 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V41 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V42 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V43 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V44 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V45 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V46 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V47 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V48 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V49 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V51 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V52 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V53 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V54 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V55 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V56 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V57 (n=1,0)	0 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V58 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V59 (n=1,0)	-16.7 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V60 (n=1,0)	-8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at 3L V61 (n=1,0)	8.3 (± 99999)	99999 (± 99999)		
FtUn: Change at Safety FU (n=6,12)	23.6 (± 14.35)	0.7 (± 17.93)		
FtUn: Change at PD FU1 (n=1,3)	0 (± 99999)	11.1 (± 4.81)		

FtUn: Change at end of study (n=3,2)	22.2 (± 9.62)	-8.3 (± 11.79)		
VsDr: 2L Baseline (n=57,59)	11.8 (± 17.63)	18.6 (± 25.72)		
VsDr: Change at 2L V2 (n=44,38)	0.8 (± 10.55)	-0.7 (± 12.53)		
VsDr: Change at 2L V3 (n=39,37)	1.7 (± 10.05)	-6.3 (± 20.54)		
VsDr: Change at 2L V4 (n=28,31)	1.2 (± 7.76)	0.7 (± 21.07)		
VsDr: Change at 2L V5 (n=21,19)	2.6 (± 9.88)	-8.8 (± 18.36)		
VsDr: Change at 2L V6 (n=17,14)	4.6 (± 17.15)	-11.9 (± 27.72)		
VsDr: Change at 2L V7 (n=7,10)	0 (± 6.42)	-11.1 (± 24.57)		
VsDr: Change at 2L V8 (n=4,7)	-2.8 (± 5.56)	-9.5 (± 26.00)		
VsDr: Change at 2L V9 (n=5,7)	6.7 (± 9.94)	-11.1 (± 24.85)		
VsDr: Change at 2L V10 (n=4,6)	2.8 (± 5.56)	-11.1 (± 27.22)		
VsDr: Change at 2L V11 (n=4,6)	2.8 (± 5.56)	-8.3 (± 20.41)		
VsDr: Change at 2L V12 (n=2,4)	5.6 (± 7.86)	-16.7 (± 33.33)		
VsDr: Change at 2L V13 (n=3,3)	11.1 (± 11.11)	-16.7 (± 28.87)		
VsDr: Change at 2L V14 (n=2,1)	11.1 (± 15.71)	0 (± 99999)		
VsDr: Change at 2L V15 (n=1,1)	0 (± 99999)	0 (± 99999)		
VsDr: Change at 2L V16 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V17 (n=1,1)	0 (± 99999)	0 (± 99999)		
VsDr: Change at 2L V18 (n=0,1)	99999 (± 99999)	0 (± 99999)		
VsDr: Change at 2L V19 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V21 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V22 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V24 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V25 (n=1,0)	5.6 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V26 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V27 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V28 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V29 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V30 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V32 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V33 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V34 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V35 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		

VsDr: Change at 2L V36 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V38 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V39 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V40 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 2L V41 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V1 (n=17,16)	7.8 (± 25.39)	5.6 (± 21.47)		
VsDr: Change at 3L V2 (n=13,14)	5.6 (± 14.34)	14.3 (± 17.12)		
VsDr: Change at 3L V3 (n=11,14)	-1.0 (± 3.35)	9.5 (± 17.89)		
VsDr: Change at 3L V4 (n=12,13)	1.9 (± 13.26)	12.8 (± 16.88)		
VsDr: Change at 3L V5 (n=9,8)	0 (± 5.56)	6.9 (± 15.64)		
VsDr: Change at 3L V6 (n=6,3)	0 (± 7.03)	18.5 (± 23.13)		
VsDr: Change at 3L V7 (n=3,4)	0 (± 11.11)	2.8 (± 5.56)		
VsDr: Change at 3L V8 (n=3,3)	-3.7 (± 6.42)	0 (± 0)		
VsDr: Change at 3L V9 (n=3,3)	0 (± 11.11)	0 (± 0)		
VsDr: Change at 3L V10 (n=3,1)	0 (± 11.11)	0 (± 99999)		
VsDr: Change at 3L V11 (n=2,1)	0 (± 0)	0 (± 99999)		
VsDr: Change at 3L V12 (n=2,2)	0 (± 0)	0 (± 0)		
VsDr: Change at 3L V13 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
VsDr: Change at 3L V14 (n=2,0)	0 (± 0)	99999 (± 99999)		
VsDr: Change at 3L V15 (n=2,0)	0 (± 0)	99999 (± 99999)		
VsDr: Change at 3L V16 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
VsDr: Change at 3L V17 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
VsDr: Change at 3L V18 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
VsDr: Change at 3L V19 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V21 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V23 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V26 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V27 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V28 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V30 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V32 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V33 (n=1,0)	0 (± 99999)	99999 (± 99999)		

VsDr: Change at 3L V34 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V35 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V36 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V37 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V39 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V41 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V42 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V43 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V44 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V45 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V46 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V47 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V48 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V49 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V51 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V52 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V53 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V54 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V55 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V56 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V57 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V58 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V59 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V60 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at 3L V61 (n=1,0)	0 (± 99999)	99999 (± 99999)		
VsDr: Change at Safety FU (n=6,12)	11.1 (± 24.34)	-2.8 (± 26.85)		
VsDr: Change at PD FU1 (n=1,3)	0 (± 99999)	-7.4 (± 6.42)		
VsDr: Change at end of study (n=3,2)	27.8 (± 25.46)	0 (± 0)		
MtDf: 2L Baseline (n=57,59)	17.5 (± 23.75)	19.3 (± 25.49)		
MtDf: Change at 2L V2 (n=44,38)	3.3 (± 14.49)	3.4 (± 15.04)		
MtDf: Change at 2L V3 (n=39,37)	3.7 (± 12.83)	3.0 (± 21.97)		
MtDf: Change at 2L V4 (n=27,30)	7.2 (± 15.39)	11.9 (± 19.78)		
MtDf: Change at 2L V5 (n=20,19)	10.0 (± 17.99)	8.2 (± 14.27)		

MtDf: Change at 2L V6 (n=17,14)	13.7 (± 20.98)	10.3 (± 15.39)		
MtDf: Change at 2L V7 (n=7,10)	12.7 (± 22.62)	8.9 (± 20.15)		
MtDf: Change at 2L V8 (n=4,7)	11.1 (± 20.29)	11.1 (± 25.66)		
MtDf: Change at 2L V9 (n=5,8)	6.7 (± 14.91)	8.3 (± 33.99)		
MtDf: Change at 2L V10 (n=4,6)	0 (± 0)	0 (± 7.03)		
MtDf: Change at 2L V11 (n=4,6)	0 (± 0)	0.9 (± 7.38)		
MtDf: Change at 2L V12 (n=2,4)	0 (± 0)	0 (± 0)		
MtDf: Change at 2L V13 (n=3,3)	0 (± 0)	11.1 (± 11.11)		
MtDf: Change at 2L V14 (n=2,1)	0 (± 0)	0 (± 99999)		
MtDf: Change at 2L V15 (n=1,1)	0 (± 99999)	-11.1 (± 99999)		
MtDf: Change at 2L V16 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V17 (n=1,1)	0 (± 99999)	0 (± 99999)		
MtDf: Change at 2L V18 (n=0,1)	99999 (± 99999)	0 (± 99999)		
MtDf: Change at 2L V19 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V21 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V24 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V26 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V27 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V28 (n=1,0)	-22.2 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V29 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V30 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V32 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V33 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V34 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V35 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V36 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V39 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V40 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 2L V41 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V1 (n=17,16)	5.2 (± 20.83)	27.1 (± 37.18)		
MtDf: Change at 3L V2 (n=13,14)	6.8 (± 16.69)	15.9 (± 27.81)		

MtDf: Change at 3L V3 (n=11,14)	1.0 (± 3.35)	20.6 (± 30.46)		
MtDf: Change at 3L V4 (n=12,13)	3.7 (± 13.68)	29.1 (± 35.00)		
MtDf: Change at 3L V5 (n=9,8)	2.5 (± 9.26)	21.5 (± 29.46)		
MtDf: Change at 3L V6 (n=6,3)	3.7 (± 9.07)	22.2 (± 19.25)		
MtDf: Change at 3L V7 (n=3,4)	7.4 (± 12.83)	19.4 (± 38.89)		
MtDf: Change at 3L V8 (n=3,3)	0 (± 0)	0 (± 0)		
MtDf: Change at 3L V9 (n=3,3)	7.4 (± 12.83)	0 (± 0)		
MtDf: Change at 3L V10 (n=3,1)	0 (± 0)	11.1 (± 99999)		
MtDf: Change at 3L V11 (n=2,1)	0 (± 0)	0 (± 99999)		
MtDf: Change at 3L V12 (n=2,2)	0 (± 0)	0 (± 0)		
MtDf: Change at 3L V13 (n=2,0)	0 (± 0)	99999 (± 99999)		
MtDf: Change at 3L V14 (n=2,0)	0 (± 0)	99999 (± 99999)		
MtDf: Change at 3L V15 (n=2,0)	-11.1 (± 15.71)	99999 (± 99999)		
MtDf: Change at 3L V16 (n=2,0)	0 (± 0)	99999 (± 99999)		
MtDf: Change at 3L V17 (n=2,0)	-11.1 (± 15.71)	99999 (± 99999)		
MtDf: Change at 3L V18 (n=2,0)	0 (± 0)	99999 (± 99999)		
MtDf: Change at 3L V19 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V21 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V23 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V26 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V27 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V28 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V30 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V32 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V33 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V34 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V35 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V36 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V37 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V39 (n=1,0)	0 (± 99999)	99999 (± 99999)		

MtDf: Change at 3L V41 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V42 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V43 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V44 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V45 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V46 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V47 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V48 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V49 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V51 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V52 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V53 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V54 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V55 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V56 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V57 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V58 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V59 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V60 (n=1,0)	0 (± 99999)	99999 (± 99999)		
MtDf: Change at 3L V61 (n=1,0)	-11.1 (± 99999)	99999 (± 99999)		
MtDf: Change at Safety FU (n=6,12)	7.4 (± 19.46)	11.6 (± 12.19)		
MtDf: Change at PD FU1 (n=1,3)	0 (± 99999)	22.2 (± 11.11)		
MtDf: Change at end of study (n=3,2)	29.6 (± 33.95)	11.1 (± 15.71)		
CmDf: 2L Baseline (n=57,59)	17.3 (± 22.62)	24.1 (± 25.45)		
CmDf: Change at 2L V2 (n=44,38)	1.0 (± 14.54)	-1.5 (± 12.43)		
CmDf: Change at 2L V3 (n=39,38)	2.8 (± 12.67)	2.6 (± 18.53)		
CmDf: Change at 2L V4 (n=27,30)	-0.4 (± 13.60)	1.1 (± 13.79)		
CmDf: Change at 2L V5 (n=21,19)	-3.2 (± 15.37)	-0.3 (± 11.78)		
CmDf: Change at 2L V6 (n=17,14)	4.6 (± 18.03)	-1.6 (± 15.63)		
CmDf: Change at 2L V7 (n=7,10)	-1.6 (± 10.00)	2.2 (± 12.61)		
CmDf: Change at 2L V8 (n=4,7)	0 (± 0)	0.8 (± 15.85)		
CmDf: Change at 2L V9 (n=5,8)	-2.2 (± 4.97)	6.9 (± 17.76)		
CmDf: Change at 2L V10 (n=4,6)	2.8 (± 5.56)	7.4 (± 21.85)		
CmDf: Change at 2L V11 (n=4,6)	-2.8 (± 5.56)	-1.9 (± 8.36)		
CmDf: Change at 2L V12 (n=2,4)	0 (± 0)	8.3 (± 18.98)		
CmDf: Change at 2L V13 (n=3,3)	0 (± 0)	3.7 (± 25.66)		
CmDf: Change at 2L V14 (n=2,1)	5.6 (± 7.86)	-16.7 (± 99999)		

CmDf: Change at 2L V15 (n=1,1)	11.1 (± 99999)	-11.1 (± 99999)		
CmDf: Change at 2L V16 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V17 (n=1,1)	11.1 (± 99999)	-11.1 (± 99999)		
CmDf: Change at 2L V18 (n=0,1)	99999 (± 99999)	-11.1 (± 99999)		
CmDf: Change at 2L V19 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V20 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V21 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V22 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V24 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V25 (n=1,0)	5.6 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V26 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V27 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V28 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V29 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V30 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V31 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V32 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V33 (n=1,0)	11.1 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V34 (n=1,0)	33.3 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V35 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V36 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V39 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V40 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 2L V41 (n=1,0)	22.2 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V1 (n=17,16)	3.9 (± 19.62)	9.0 (± 19.55)		
CmDf: Change at 3L V2 (n=13,13)	0.9 (± 15.36)	3.4 (± 16.60)		
CmDf: Change at 3L V3 (n=11,14)	-2.0 (± 10.91)	5.6 (± 19.85)		
CmDf: Change at 3L V4 (n=12,13)	2.8 (± 10.73)	8.5 (± 24.91)		
CmDf: Change at 3L V5 (n=9,8)	1.2 (± 15.16)	5.6 (± 26.56)		
CmDf: Change at 3L V6 (n=6,3)	-1.9 (± 24.76)	0 (± 11.11)		
CmDf: Change at 3L V7 (n=3,4)	-11.1 (± 19.25)	-2.8 (± 13.98)		
CmDf: Change at 3L V8 (n=3,3)	-14.8 (± 16.97)	-7.4 (± 12.83)		

CmDf: Change at 3L V9 (n=3,3)	-22.2 (± 29.40)	-7.4 (± 12.83)		
CmDf: Change at 3L V10 (n=3,1)	-7.4 (± 12.83)	0 (± 99999)		
CmDf: Change at 3L V11 (n=2,1)	-5.6 (± 7.86)	-22.2 (± 99999)		
CmDf: Change at 3L V12 (n=2,2)	5.6 (± 7.86)	-11.1 (± 15.71)		
CmDf: Change at 3L V13 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
CmDf: Change at 3L V14 (n=2,0)	-5.6 (± 7.86)	99999 (± 99999)		
CmDf: Change at 3L V15 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
CmDf: Change at 3L V16 (n=2,0)	-5.6 (± 7.86)	99999 (± 99999)		
CmDf: Change at 3L V17 (n=2,0)	5.6 (± 7.86)	99999 (± 99999)		
CmDf: Change at 3L V18 (n=2,0)	11.1 (± 15.71)	99999 (± 99999)		
CmDf: Change at 3L V19 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V20 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V21 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V22 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V23 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V26 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V27 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V28 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V30 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V32 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V33 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V34 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V35 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V36 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V37 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V38 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V39 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V41 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V42 (n=1,0)	0 (± 99999)	99999 (± 99999)		

CmDf: Change at 3L V43 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V44 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V45 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V46 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V47 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V48 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V49 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V51 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V52 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V53 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V54 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V55 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V56 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V57 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V58 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V59 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V60 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at 3L V61 (n=1,0)	0 (± 99999)	99999 (± 99999)		
CmDf: Change at Safety FU (n=6,12)	1.9 (± 4.54)	8.3 (± 16.50)		
CmDf: Change at PD FU1 (n=1,3)	22.2 (± 99999)	44.4 (± 11.11)		
CmDf: Change at end of study (n=3,2)	7.4 (± 6.42)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Mini Mental Status Examination (MMSE) Score <27 or >/=27

End point title	Percentage of Participants with Mini Mental Status Examination (MMSE) Score <27 or >/=27

End point description:

The MMSE score measures general cognitive functioning (via following subscales: orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two intersecting polygons). It was used to screen for cognitive impairment at a given point in time. Total score is derived from sub-scores; total score ranged from 0 to 30, with higher score = better cognitive state. Percentage of participants with MMSE total score <27 or >/=27 is reported at Baseline and 2L-Baseline. Analysis was performed on enrolled analysis set for Baseline and on ITT population for 2L Baseline. 'Number of Subject Analysed'=participants evaluable for this outcome measure at Baseline/2L Baseline.

End point type	Secondary

End point timeframe:

Baseline [for 1L Bevacizumab] and 2L Baseline [for Placebo + Lomustine/SOC (ITT) and Bevacizumab + Lomustine/SOC (ITT)]

End point values	1L Bevacizumab	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	225	55	58	
Units: percentage of participants				
number (not applicable)				
MMSE total score <27	26.7	29.1	37.9	
MMSE total score >/=27	71.1	70.9	62.1	
Missing	2.2	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Part A (Immediate Recall) z-score

End point title	1L Treatment: Change From Baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) Part A (Immediate Recall) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, and C). In Part A (immediate recall), the participant was asked to learn and recall a list of 12 words over three trials. The Part A score ranges from 0 to 36, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant's age at enrollment. The change from Baseline in z-scores was then calculated for each time point and is reported here. Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	220			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline (n=220)	-1.60 (± 1.625)			
Change at Maintenance C1V1 (n=198)	0.03 (± 1.204)			

Change at Maintenance C3V1 (n=176)	-0.13 (± 1.416)			
Change at Maintenance C5V1 (n=154)	0.08 (± 1.400)			
Change at Monotherapy V1 (n=134)	0.01 (± 1.319)			
Change at Monotherapy V4 (n=96)	0.14 (± 1.489)			
Change at Monotherapy V7 (n=76)	0.33 (± 1.295)			
Change at Monotherapy V10 (n=66)	0.49 (± 1.316)			
Change at Monotherapy V13 (n=54)	0.53 (± 1.516)			
Change at Monotherapy V16 (n=42)	0.34 (± 1.379)			
Change at Monotherapy V19 (n=34)	0.23 (± 1.202)			
Change at Monotherapy V22 (n=21)	0.26 (± 0.969)			
Change at Monotherapy V25 (n=21)	0.20 (± 1.219)			
Change at Monotherapy V28 (n=14)	0.43 (± 1.404)			
Change at Monotherapy V31 (n=10)	0.79 (± 0.983)			
Change at Monotherapy V34 (n=6)	0.35 (± 1.086)			
Change at Monotherapy V37 (n=2)	-1.88 (± 0.688)			
Change at Monotherapy V40 (n=3)	-0.24 (± 1.200)			
Change at Monotherapy V43 (n=2)	-2.01 (± 0.874)			
Change at Safety FU (n=18)	0.44 (± 2.128)			
Change at PD FU1 (n=26)	0.30 (± 1.770)			
Change at PD FU2 (n=15)	-0.28 (± 1.355)			
Change at PD FU3 (n=7)	1.19 (± 2.203)			
Change at PD FU4 (n=4)	0.78 (± 0.506)			
Change at PD FU5 (n=2)	0.54 (± 0.764)			
Change at PD FU6 (n=2)	-0.47 (± 1.316)			
Change at PD FU7 (n=1)	1.35 (± 99999)			
Change at PD FU8 (n=1)	1.35 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part A (Immediate Recall) z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part A (Immediate Recall) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, and C). In Part A (immediate recall), the participant was asked to learn and recall a list of 12 words over three trials. The Part A score ranges from 0 to 36, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant's age at enrollment. The change from 2L Baseline in z-scores was then calculated for each time point and is reported here. Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	58		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=54,58)	-1.62 (± 1.871)	-2.03 (± 1.969)		
Change at 2L V7 (n=22,28)	-0.79 (± 1.513)	-0.41 (± 1.561)		
Change at 2L V13 (n=4,2)	-0.23 (± 0.327)	0.02 (± 0.351)		
Change at 2L V19 (n=1,0)	-0.47 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	-0.70 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	-1.86 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	-0.93 (± 99999)	99999 (± 99999)		
Change at 2L V43 (n=1,0)	-1.63 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=6,11)	-0.48 (± 1.141)	-0.48 (± 2.062)		
Change at 3L V7 (n=7,8)	0.20 (± 0.478)	0.18 (± 1.660)		
Change at 3L V13 (n=2,2)	-0.95 (± 0.965)	1.45 (± 0.186)		
Change at 3L V19 (n=2,0)	-0.33 (± 0.844)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	0.26 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	1.32 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	1.32 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	1.05 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	1.58 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,2)	99999 (± 99999)	0.28 (± 0.723)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	-2.76 (± 1.303)		
Change at end of study (n=1,0)	-0.93 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in HVLT-R Part B (Delayed Recall) z-score

End point title	1L Treatment: Change From Baseline in HVLT-R Part B (Delayed Recall) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, C). In Part B (delayed recall), the participant was asked to recall the words learned in Part A after a delay of 20 minutes. The Part B score ranged from 0 to 12, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant's age at enrollment. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	215			
Units: z-scores				
arithmetic mean (standard deviation)				
Baseline (n=215)	-1.85 (± 1.894)			
Change at Maintenance C1V1 (n=190)	0 (± 1.559)			
Change at Maintenance C3V1 (n=170)	-0.30 (± 1.611)			
Change at Maintenance C5V1 (n=150)	-0.08 (± 1.517)			
Change at Monotherapy V1 (n=131)	-0.11 (± 1.451)			
Change at Monotherapy V4 (n=94)	-0.07 (± 1.608)			
Change at Monotherapy V7 (n=74)	0.15 (± 1.419)			
Change at Monotherapy V10 (n=64)	0.21 (± 1.358)			
Change at Monotherapy V13 (n=51)	0.30 (± 1.247)			
Change at Monotherapy V16 (n=39)	0.02 (± 1.200)			
Change at Monotherapy V19 (n=31)	0.02 (± 1.254)			
Change at Monotherapy V22 (n=20)	-0.25 (± 1.350)			
Change at Monotherapy V25 (n=20)	-0.03 (± 1.210)			
Change at Monotherapy V28 (n=13)	-0.26 (± 1.604)			
Change at Monotherapy V31 (n=9)	0.44 (± 0.836)			
Change at Monotherapy V34 (n=6)	-0.10 (± 1.009)			
Change at Monotherapy V37 (n=2)	-1.19 (± 2.473)			
Change at Monotherapy V40 (n=3)	-0.57 (± 1.001)			
Change at Monotherapy V43 (n=2)	-2.60 (± 1.317)			

Change at Safety FU (n=17)	-0.18 (± 1.980)			
Change at PD FU1 (n=25)	-0.16 (± 1.529)			
Change at PD FU2 (n=15)	-0.63 (± 1.696)			
Change at PD FU3 (n=6)	0.95 (± 1.615)			
Change at PD FU4 (n=3)	0.20 (± 0.340)			
Change at PD FU5 (n=2)	-0.28 (± 0.393)			
Change at PD FU6 (n=2)	-1.11 (± 0)			
Change at PD FU7 (n=1)	0 (± 99999)			
Change at PD FU8 (n=1)	0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part B (Delayed Recall) z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part B (Delayed Recall) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, C). In Part B (delayed recall), the participant was asked to recall the words learned in Part A after a delay of 20 minutes. The Part B score ranged from 0 to 12, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant's age at enrollment. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit starting from V1 to V37, V49, V61 (Q2W); Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	58		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=53,58)	-1.96 (± 1.778)	-2.52 (± 2.033)		
Change at 2L V7 (n=22,28)	-0.51 (± 1.866)	-0.49 (± 1.646)		
Change at 2L V13 (n=4,2)	-0.50 (± 1.646)	0.0 (± 0.0)		
Change at 2L V19 (n=1,0)	-1.11 (± 99999)	99999 (± 99999)		

Change at 2L V25 (n=1,0)	-1.67 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	-2.22 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	-1.11 (± 99999)	99999 (± 99999)		
Change at 2L V43 (n=1,0)	-2.78 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=6,11)	0.30 (± 1.303)	-0.44 (± 1.432)		
Change at 3L V7 (n=7,7)	-0.15 (± 1.549)	-0.71 (± 2.172)		
Change at 3L V13 (n=2,2)	-2.48 (± 4.344)	0.29 (± 1.248)		
Change at 3L V19 (n=2,0)	-1.41 (± 1.155)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	-1.18 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	0.59 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	0.59 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,3)	99999 (± 99999)	-1.15 (± 1.520)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	-1.76 (± 0)		
Change at end of study (n=1,0)	-1.11 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in HVLT-R Part C (Delayed Recognition) z-score

End point title	1L Treatment: Change From Baseline in HVLT-R Part C (Delayed Recognition) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, C). In Part C (delayed recognition), the participant was asked to identify the list of 12 words learned in Part A from distractors. The Part C score ranged from -12 to 12, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant’s age at enrollment. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; ‘99999’=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: z-score				
arithmetic mean (standard deviation)				
Baseline (n=222)	-1.06 (± 1.952)			
Change at Maintenance C1V1 (n=198)	-0.05 (± 1.972)			
Change at Maintenance C3V1 (n=177)	0.44 (± 2.093)			
Change at Maintenance C5V1 (n=155)	0.04 (± 1.911)			
Change at Monotherapy V1 (n=135)	0.04 (± 1.932)			
Change at Monotherapy V4 (n=96)	0.01 (± 2.101)			
Change at Monotherapy V7 (n=76)	0.20 (± 1.793)			
Change at Monotherapy V10 (n=66)	0.23 (± 2.064)			
Change at Monotherapy V13 (n=53)	0.38 (± 2.089)			
Change at Monotherapy V16 (n=41)	0.21 (± 1.756)			
Change at Monotherapy V19 (n=33)	-0.05 (± 1.515)			
Change at Monotherapy V22 (n=21)	0.43 (± 1.059)			
Change at Monotherapy V25 (n=20)	0.13 (± 1.389)			
Change at Monotherapy V28 (n=14)	-0.29 (± 2.085)			
Change at Monotherapy V31 (n=10)	-0.32 (± 0.904)			
Change at Monotherapy V34 (n=6)	0.63 (± 0.844)			
Change at Monotherapy V37 (n=2)	0.36 (± 0.505)			
Change at Monotherapy V40 (n=3)	1.08 (± 0.957)			
Change at Monotherapy V43 (n=2)	0.26 (± 1.653)			
Change at Safety FU (n=17)	0.40 (± 2.692)			
Change at PD FU1 (n=25)	0.33 (± 2.817)			
Change at PD FU2 (n=15)	-0.85 (± 2.100)			
Change at PD FU3 (n=6)	1.64 (± 3.950)			
Change at PD FU4 (n=4)	-0.21 (± 2.979)			
Change at PD FU5 (n=2)	0.36 (± 0.505)			
Change at PD FU6 (n=2)	-0.71 (± 2.020)			
Change at PD FU7 (n=1)	0 (± 99999)			
Change at PD FU8 (n=1)	0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part C

(Delayed Recognition) z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in HVLT-R Part C (Delayed Recognition) z-score

End point description:

The HVLT-R is a test of learning and memory consisting of 3 parts (Part A, B, C). In Part C (delayed recognition), the participant was asked to identify the list of 12 words learned in Part A from distractors. The Part C score ranged from -12 to 12, with higher scores = better memory. The raw scores were normalized into standardized z-scores for each time point using participant's age at enrollment. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit starting from V1 to V37, V49, V61 (Q2W); Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	58		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=53,58)	-1.27 (± 2.071)	-1.25 (± 2.261)		
Change at 2L V7 (n=22,28)	0.08 (± 1.621)	-0.74 (± 1.837)		
Change at 2L V13 (n=4,2)	-0.63 (± 0.859)	0.36 (± 0.505)		
Change at 2L V19 (n=1,0)	-2.14 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	0.71 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	-0.71 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	-0.71 (± 99999)	99999 (± 99999)		
Change at 2L V43 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=7,11)	0.24 (± 2.066)	-0.43 (± 2.125)		
Change at 3L V7 (n=7,7)	0.66 (± 3.076)	-0.41 (± 1.128)		
Change at 3L V13 (n=2,2)	-1.27 (± 0.781)	0.91 (± 1.286)		
Change at 3L V19 (n=2,0)	-1.07 (± 1.515)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	-5.45 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	-0.91 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	-0.91 (± 99999)	99999 (± 99999)		

Change at 3L V49 (n=1,0)	-1.82 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	0.91 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,3)	99999 (± 99999)	-3.31 (± 2.852)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	0 (± 0)		
Change at end of study (n=1,0)	2.14 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in Controlled Oral Word Association (COWA) z-score

End point title	1L Treatment: Change From Baseline in Controlled Oral Word Association (COWA) z-score

End point description:

COWA is a test of phonemic verbal fluency. The participant was asked to produce as many words as possible in 60 seconds beginning with a specified letter (for 3 pre-specified letters). The total COWA score was calculated as the sum of acceptable words generated for each letter tested, with higher score indicating lower cognitive impairment. The raw scores were normalized into standardized z-scores for each time point using participant's gender. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: z-scores				
arithmetic mean (standard deviation)				
Baseline (n=219)	-1.50 (± 1.214)			
Change at Maintenance C1V1 (n=196)	0.16 (± 0.763)			
Change at Maintenance C3V1 (n=175)	0.18 (± 0.840)			
Change at Maintenance C5V1 (n=152)	0.31 (± 0.925)			
Change at Monotherapy V1 (n=134)	0.45 (± 1.022)			
Change at Monotherapy V4 (n=98)	0.33 (± 1.187)			
Change at Monotherapy V7 (n=77)	0.47 (± 0.943)			
Change at Monotherapy V10 (n=65)	0.69 (± 0.840)			
Change at Monotherapy V13 (n=54)	0.61 (± 0.995)			
Change at Monotherapy V16 (n=42)	0.88 (± 1.029)			

Change at Monotherapy V19 (n=34)	1.19 (± 1.190)			
Change at Monotherapy V22 (n=21)	0.95 (± 1.066)			
Change at Monotherapy V25 (n=21)	0.98 (± 0.891)			
Change at Monotherapy V28 (n=14)	1.27 (± 0.838)			
Change at Monotherapy V31 (n=10)	1.23 (± 1.166)			
Change at Monotherapy V34 (n=6)	1.12 (± 0.688)			
Change at Monotherapy V37 (n=2)	0.71 (± 0.253)			
Change at Monotherapy V40 (n=3)	0.23 (± 0.294)			
Change at Monotherapy V43 (n=2)	0.58 (± 0.821)			
Change at Safety FU (n=18)	0.36 (± 1.236)			
Change at PD FU1 (n=27)	0.46 (± 1.125)			
Change at PD FU2 (n=16)	0.17 (± 1.374)			
Change at PD FU3 (n=7)	0.93 (± 0.610)			
Change at PD FU4 (n=4)	-0.09 (± 0.531)			
Change at PD FU5 (n=2)	0.36 (± 1.660)			
Change at PD FU6 (n=2)	-1.67 (± 0.090)			
Change at PD FU7 (n=1)	0.92 (± 99999)			
Change at PD FU8 (n=1)	2.04 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in COWA z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in COWA z-score

End point description:

COWA is a test of phonemic verbal fluency. The participant was asked to produce as many words as possible in 60 seconds beginning with a specified letter (for 3 pre-specified letters). The total COWA score was calculated as the sum of acceptable words generated for each letter tested, with higher score indicating lower cognitive impairment. The raw scores were normalized into standardized z-scores for each time point using participant’s gender. The change from Baseline in z-score was then calculated for each time point and is reported here. Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; ‘99999’=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit starting from V1 to V37, V49, V61 (Q2W); Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	58		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=53,58)	-1.17 (± 1.425)	-1.35 (± 1.657)		
Change at 2L V7 (n=22,29)	-0.27 (± 0.824)	-0.28 (± 0.775)		
Change at 2L V13 (n=4,2)	0.26 (± 0.395)	-0.26 (± 0.361)		
Change at 2L V19 (n=1,0)	0.10 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	0.10 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	0.71 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	0.31 (± 99999)	99999 (± 99999)		
Change at 2L V43 (n=1,0)	0.31 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=6,11)	-0.13 (± 0.701)	-0.63 (± 0.896)		
Change at 3L V7 (n=7,8)	-0.19 (± 0.673)	-0.59 (± 0.923)		
Change at 3L V13 (n=2,2)	0.51 (± 0.433)	-0.46 (± 1.371)		
Change at 3L V19 (n=2,0)	0.46 (± 0.216)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	0.10 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	0.92 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	0.41 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	0 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,2)	99999 (± 99999)	-0.51 (± 1.010)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	-0.19 (± 0.018)		
Change at end of study (n=1,0)	-0.82 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in Trail-Making Test (TMT) Part A z-score

End point title	1L Treatment: Change From Baseline in Trail-Making Test (TMT) Part A z-score

End point description:

TMT Part A test required the participant to connect circles numbered 1 - 25 in numerical order from 1 to 25, as fast as possible. The Part A score was the total time-to-completion, in seconds (higher scores reveal greater impairment), if the test was completed. If the test was not completed, the Part A score was adjusted based on the last number correctly reached on the test, as follows: Part A score = 25*(total time-to-completion/last number correctly reached). The raw scores were normalized into standardized z-scores for each time point using participant's age and education at enrollment. The z-scores were multiplied by -1 (negative values=performance below the mean). Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; '99999'=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	216			
Units: z-scores				
arithmetic mean (standard deviation)				
Baseline (n=216)	-6.40 (± 32.420)			
Change at Maintenance C1V1 (n=191)	2.37 (± 34.329)			
Change at Maintenance C3V1 (n=171)	2.73 (± 33.993)			
Change at Maintenance C5V1 (n=151)	3.17 (± 35.703)			
Change at Monotherapy V1 (n=131)	1.52 (± 12.429)			
Change at Monotherapy V4 (n=92)	-0.76 (± 9.295)			
Change at Monotherapy V7 (n=73)	1.86 (± 12.680)			
Change at Monotherapy V10 (n=64)	2.82 (± 17.302)			
Change at Monotherapy V13 (n=52)	3.16 (± 19.286)			
Change at Monotherapy V16 (n=42)	1.06 (± 3.666)			
Change at Monotherapy V19 (n=34)	1.35 (± 3.943)			
Change at Monotherapy V22 (n=21)	1.67 (± 4.715)			
Change at Monotherapy V25 (n=21)	1.77 (± 4.470)			
Change at Monotherapy V28 (n=14)	2.66 (± 5.365)			
Change at Monotherapy V31 (n=10)	2.82 (± 4.920)			
Change at Monotherapy V34 (n=6)	1.60 (± 1.874)			
Change at Monotherapy V37 (n=2)	0.69 (± 2.257)			
Change at Monotherapy V40 (n=3)	1.09 (± 2.155)			
Change at Monotherapy V43 (n=2)	1.07 (± 2.230)			
Change at Safety FU (n=17)	-0.75 (± 8.737)			
Change at PD FU1 (n=24)	-0.73 (± 3.243)			
Change at PD FU2 (n=15)	0.56 (± 2.636)			

Change at PD FU3 (n=7)	1.03 (± 3.541)			
Change at PD FU4 (n=4)	2.20 (± 4.336)			
Change at PD FU5 (n=2)	3.38 (± 4.639)			
Change at PD FU6 (n=1)	-6.11 (± 99999)			
Change at PD FU7 (n=1)	7.00 (± 99999)			
Change at PD FU8 (n=1)	6.77 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in TMT Part A z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in TMT Part A z-score

End point description:

TMT Part A test required the participant to connect circles numbered 1-25 in numerical order from 1 to 25, as fast as possible. The Part A score = total time-to-completion, in seconds (higher scores reveal greater impairment), if the test was completed. Otherwise, the Part A score was adjusted based on the last number correctly reached, as follows: Part A score = 25*(total time-to-completion/last number correctly reached). The raw scores were normalized into standardized z-scores for each time point using participant's age and education. The z-scores were multiplied by -1 (negative values=performance below the mean). Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit starting from V1 to V37, V49, V61 (Q2W); Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	58		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=54,58)	-5.94 (± 14.103)	-4.62 (± 8.563)		
Change at 2L V7 (n=22,28)	-2.04 (± 4.304)	-2.48 (± 7.091)		
Change at 2L V13 (n=4,2)	0.39 (± 1.599)	0.92 (± 1.867)		
Change at 2L V19 (n=1,0)	-9.72 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	1.49 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	0.15 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	-4.63 (± 99999)	99999 (± 99999)		

Change at 2L V43 (n=1,0)	-1.35 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=6,11)	-6.32 (± 10.342)	-3.78 (± 4.640)		
Change at 3L V7 (n=7,7)	-1.02 (± 3.064)	-19.57 (± 32.309)		
Change at 3L V13 (n=2,2)	-1.91 (± 5.121)	-0.40 (± 0.419)		
Change at 3L V19 (n=2,0)	-2.36 (± 5.755)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	0.91 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	0.91 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	1.31 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	1.51 (± 99999)	99999 (± 99999)		
Change at 3L V61 (n=1,0)	0.60 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,2)	99999 (± 99999)	-0.18 (± 0.822)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	-1.70 (± 0.122)		
Change at end of study (n=1,0)	-52.64 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1L Treatment: Change From Baseline in TMT Part B z-score

End point title	1L Treatment: Change From Baseline in TMT Part B z-score

End point description:

TMT Part B required the participant to connect 25 circles numbered 1-13 and A-L in order (1-A-2-B...) as fast as possible. The Part B score was the total time-to-completion, in seconds (higher scores=greater impairment), if the test was completed. If the test was not completed, the Part B score was adjusted based on the number of circles correctly connected on the test, as follows: Part B score = 25*(total time-to-completion/last number of correctly connected circle). The raw scores were normalized into standardized z-scores for each time point using participant’s age and education. The z-scores were multiplied by -1 (negative values=performance below the mean). Analysis was performed on enrolled analysis set. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point; ‘99999’=SD could not be calculated as only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

Baseline; Maintenance: D1(V1) Cycles 1, 3, 5 (Q4W); Monotherapy: every 3rd visit starting from V1 to V43 (Q3W); Safety FU (30 days after last 1L dose); PD FUs (8 Wk after Safety FU [PD FU1], then every 12 Wk until PD1) (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: z-scores				
arithmetic mean (standard deviation)				
Baseline (n=203)	-9.38 (± 23.115)			
Change at Maintenance C1V1 (n=173)	1.18 (± 22.407)			
Change at Maintenance C3V1 (n=154)	1.44 (± 24.412)			
Change at Maintenance C5V1 (n=140)	-2.58 (± 55.685)			
Change at Monotherapy V1 (n=121)	1.74 (± 26.685)			
Change at Monotherapy V4 (n=82)	-1.14 (± 17.561)			
Change at Monotherapy V7 (n=66)	3.10 (± 20.006)			
Change at Monotherapy V10 (n=57)	4.69 (± 27.281)			
Change at Monotherapy V13 (n=46)	4.83 (± 21.081)			
Change at Monotherapy V16 (n=37)	2.42 (± 6.649)			
Change at Monotherapy V19 (n=31)	3.28 (± 7.420)			
Change at Monotherapy V22 (n=19)	3.76 (± 8.984)			
Change at Monotherapy V25 (n=18)	2.40 (± 3.161)			
Change at Monotherapy V28 (n=12)	2.37 (± 3.522)			
Change at Monotherapy V31 (n=8)	3.36 (± 3.053)			
Change at Monotherapy V34 (n=5)	2.77 (± 1.211)			
Change at Monotherapy V37 (n=1)	1.60 (± 99999)			
Change at Monotherapy V40 (n=2)	1.88 (± 0.792)			
Change at Monotherapy V43 (n=1)	1.73 (± 99999)			
Change at Safety FU (n=14)	-0.42 (± 6.000)			
Change at PD FU1 (n=22)	-1.65 (± 8.005)			
Change at PD FU2 (n=15)	0.79 (± 4.900)			
Change at PD FU3 (n=6)	-15.15 (± 39.732)			
Change at PD FU4 (n=3)	4.36 (± 3.270)			
Change at PD FU5 (n=1)	7.12 (± 99999)			
Change at PD FU6 (n=0)	99999 (± 99999)			
Change at PD FU7 (n=1)	7.04 (± 99999)			
Change at PD FU8 (n=1)	6.80 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2L and 3L Treatment: Change From 2L Baseline in TMT Part B z-score

End point title	2L and 3L Treatment: Change From 2L Baseline in TMT Part B

	z-score

End point description:

TMT Part B required the participant to connect 25 circles numbered 1-13 and A-L in order (1-A-2-B...) as fast as possible. The Part B score=total time-to-completion in seconds (higher scores=greater impairment), if the test was completed. Otherwise, Part B score was adjusted based on the number of circles correctly connected, as follows: Part B score=25*(total time-to-completion/last number of correctly connected circle). The raw scores were normalized into standardized z-scores for each time point using participant's age and education. The z-scores were multiplied by -1 (negative values=performance below the mean). Analysis was performed on ITT population. 'Number of Subject Analysed'=participants evaluable for this outcome measure; 'n'=participants evaluable at specified time point for different arms, respectively; '99999'=either data were not available because no participant was evaluable or SD was not available because only 1 participant was evaluable at indicated time point.

End point type	Secondary

End point timeframe:

2L Baseline; 2L treatment: every 6th visit starting from V7 to V43 (Q2W); 3L treatment: every 6th visit starting from V1 to V37, V49, V61 (Q2W); Safety FU (30 days after last 3L dose); PD FU1 (8 Wk after Safety FU); end of study (up to 41 months overall)

End point values	Placebo + Lomustine/SOC (ITT)	Bevacizumab + Lomustine/SOC (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	57		
Units: z-scores				
arithmetic mean (standard deviation)				
2L Baseline (n=54,57)	-12.51 (± 37.406)	-11.42 (± 20.524)		
Change at 2L V7 (n=22,27)	-3.33 (± 6.879)	-5.78 (± 14.211)		
Change at 2L V13 (n=4,2)	1.07 (± 5.508)	-0.09 (± 0.129)		
Change at 2L V19 (n=1,0)	4.40 (± 99999)	99999 (± 99999)		
Change at 2L V25 (n=1,0)	-2.15 (± 99999)	99999 (± 99999)		
Change at 2L V31 (n=1,0)	-7.62 (± 99999)	99999 (± 99999)		
Change at 2L V37 (n=1,0)	-0.43 (± 99999)	99999 (± 99999)		
Change at 2L V43 (n=1,0)	3.11 (± 99999)	99999 (± 99999)		
Change at 3L V1 (n=6,11)	-13.10 (± 21.948)	-59.93 (± 137.707)		
Change at 3L V7 (n=7,7)	-7.26 (± 8.449)	-14.44 (± 24.248)		
Change at 3L V13 (n=2,2)	-9.09 (± 13.148)	0.68 (± 1.392)		
Change at 3L V19 (n=2,0)	-26.24 (± 25.443)	99999 (± 99999)		
Change at 3L V25 (n=1,0)	-13.04 (± 99999)	99999 (± 99999)		
Change at 3L V31 (n=1,0)	-0.69 (± 99999)	99999 (± 99999)		
Change at 3L V37 (n=1,0)	-1.11 (± 99999)	99999 (± 99999)		
Change at 3L V49 (n=1,0)	-8.32 (± 99999)	99999 (± 99999)		

Change at 3L V61 (n=1,0)	-0.69 (± 99999)	99999 (± 99999)		
Change at Safety FU (n=0,3)	99999 (± 99999)	0.32 (± 6.517)		
Change at PD FU1 (n=0,2)	99999 (± 99999)	-8.21 (± 7.813)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Hospitalizations According to Type of Hospitalizations

End point title	Number of Participants with Hospitalizations According to Type of Hospitalizations

End point description:

Number of participants with hospitalizations according to type of hospitalizations (emergency room, normal hospital room, intensive care unit [ICU]/critical care unit [CCU]) was reported. One participant could have more than one type of hospitalization. Analysis was performed on safety set, which included all participants who received at least one dose of any study treatment. 'Number of Subject Analysed'=Number of participants hospitalized.

End point type	Secondary

End point timeframe:

From Baseline up to death or study withdrawal/study end (up to 41 months overall)

End point values	1L Bevacizumab	Placebo + Lomustine/SOC (Safety 2L+)	Bevacizumab + Lomustine/SOC (Safety 2L+)	Placebo + Lomustine/SOC (Safety 4L+)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	13	14	1
Units: participants				
Emergency room	37	2	7	1
normal hospital room	102	10	13	1
ICU/CCU	8	2	0	0

End point values	Bevacizumab + Lomustine/SOC (Safety 4L+)	Cross-over (Safety 4L+)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	0[14]		
Units: participants				
Emergency room	0			
normal hospital room	2			
ICU/CCU	0			

Notes:

[14] - No participant was hospitalized in this arm

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalizations According to Type of Hospitalizations

End point title	Duration of Hospitalizations According to Type of Hospitalizations

End point description:

Duration of hospitalization (in days) according to type of hospitalizations (emergency room, normal hospital room, ICU/CCU) was reported. Analysis was performed on safety set. 'Number of Subject Analysed'=Number of participants hospitalized; 'n'=participants evaluable for specified category for different arms, respectively.

End point type	Secondary

End point timeframe:

From Baseline up to death or study withdrawal/study end (up to 41 months overall)

End point values	1L Bevacizumab	Placebo + Lomustine/SOC (Safety 2L+)	Bevacizumab + Lomustine/SOC (Safety 2L+)	Placebo + Lomustine/SOC (Safety 4L+)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	13	14	1
Units: days				
median (full range (min-max))				
Emergency room (n=36,2,7,1,0,0)	1.0 (0 to 32)	1.0 (1 to 1)	1.0 (0 to 36)	0 (0 to 0)
Normal hospital room (n=100,10,12,1,2,0)	10.0 (0 to 108)	3.5 (1 to 22)	6.5 (1 to 49)	14.0 (14 to 14)
ICU/CCU (n=7,2,0,0,0,0)	4.0 (1 to 30)	12.0 (11 to 13)	99999 (99999 to 99999)	99999 (99999 to 99999)

End point values	Bevacizumab + Lomustine/SOC (Safety 4L+)	Cross-over (Safety 4L+)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	0[15]		
Units: days				
median (full range (min-max))				
Emergency room (n=36,2,7,1,0,0)	99999 (99999 to 99999)	(to)		
Normal hospital room (n=100,10,12,1,2,0)	6.5 (6 to 7)	(to)		
ICU/CCU (n=7,2,0,0,0,0)	99999 (99999 to 99999)	(to)		

Notes:

[15] - No participant was hospitalized in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol Five-Dimension Questionnaire (EQ-5D) Score

End point title	EuroQol Five-Dimension Questionnaire (EQ-5D) Score

End point description:

End point type	Secondary

End point timeframe:

From Baseline up to death or study withdrawal/study end (up to 41 months overall)

End point values	1L Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[16] - Because the study was terminated early, data were not summarized and only reported in listings.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to death or study withdrawal/study end (up to 41 months overall)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	1L Bevacizumab

Reporting group description:

Participants received 1L treatment with radiotherapy, temozolomide, and bevacizumab. All three treatments were given concurrently for the first 6 weeks, followed by 6 cycles (of 28 days each) of temozolomide plus bevacizumab, followed by bevacizumab monotherapy until PD1 or unacceptable toxicity.

Reporting group title	Placebo + Lomustine/SOC (Safety 2L+)

Reporting group description:

At PD1, eligible participants for 2L therapy were randomized and received bevacizumab-placebo plus lomustine until PD2. After PD2, eligible participants continued 3L treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and the participant. Analysis set included all participants who received at least one dose of 2L study treatment. Participants were analyzed as treated during 2L and 3L.

Reporting group title	Bevacizumab + Lomustine/SOC (Safety 2L+)

Reporting group description:

At PD1, eligible participants for 2L therapy were randomized and received bevacizumab plus lomustine until PD2. After PD2, eligible participants continued 3L treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and the participant. Analysis set included all participants who received at least one dose of 2L study treatment. Participants were analyzed as treated during 2L and 3L.

Reporting group title	Placebo + Lomustine/SOC (Safety 4L+)

Reporting group description:

After PD3, eligible participants continued 4L and later line of treatment with bevacizumab-placebo plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and the participant. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Reporting group title	Bevacizumab + Lomustine/SOC (Safety 4L+)

Reporting group description:

After PD3, eligible participants continued 4L and later line of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and the participant. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Reporting group title	Cross-over (Safety 4L+)

Reporting group description:

After PD3, eligible participants cross-over from bevacizumab-placebo treatment and received 4L and later line of treatment with bevacizumab plus the appropriate SOC treatment (generally used to treat recurrence) at the discretion of the investigator and the participant. Analysis set included all participants who received at least one dose of 4L study treatment. Participants were analyzed as treated during 4L and later lines.

Serious adverse events	1L Bevacizumab	Placebo + Lomustine/SOC (Safety 2L+)	Bevacizumab + Lomustine/SOC (Safety 2L+)
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 296 (34.80%)	5 / 59 (8.47%)	12 / 63 (19.05%)
number of deaths (all causes)	102	41	42
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 296 (1.01%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	9 / 296 (3.04%)	0 / 59 (0.00%)	2 / 63 (3.17%)
occurrences causally related to treatment / all	8 / 9	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	14 / 296 (4.73%)	1 / 59 (1.69%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 16	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	6 / 296 (2.03%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	3 / 296 (1.01%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 296 (0.00%)	1 / 59 (1.69%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Wound dehiscence			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic transfusion reaction			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin injury			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	15 / 296 (5.07%)	0 / 59 (0.00%)	3 / 63 (4.76%)
occurrences causally related to treatment / all	0 / 18	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	7 / 296 (2.36%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	4 / 296 (1.35%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Senile dementia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis transverse			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural effusion			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	14 / 296 (4.73%)	1 / 59 (1.69%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	3 / 14	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 296 (1.35%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	4 / 296 (1.35%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 296 (0.34%)	1 / 59 (1.69%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 296 (0.00%)	1 / 59 (1.69%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocrine disorders			
Secondary hypothyroidism			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	3 / 296 (1.01%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 296 (1.01%)	0 / 59 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 296 (0.68%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infected fistula			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella sepsis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 296 (0.34%)	1 / 59 (1.69%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + Lomustine/SOC (Safety 4L+)	Bevacizumab + Lomustine/SOC (Safety 4L+)	Cross-over (Safety 4L+)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
number of deaths (all causes)	3	9	2
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic transfusion reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Senile dementia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis transverse			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Secondary hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected fistula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	1L Bevacizumab	Placebo + Lomustine/SOC (Safety 2L+)	Bevacizumab + Lomustine/SOC (Safety 2L+)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	266 / 296 (89.86%)	47 / 59 (79.66%)	54 / 63 (85.71%)
Vascular disorders			
Hypertension			
subjects affected / exposed	112 / 296 (37.84%)	13 / 59 (22.03%)	17 / 63 (26.98%)
occurrences (all)	196	13	21
Deep vein thrombosis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis limb			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	93 / 296 (31.42%)	11 / 59 (18.64%)	13 / 63 (20.63%)
occurrences (all)	126	12	13
Asthenia			
subjects affected / exposed	69 / 296 (23.31%)	12 / 59 (20.34%)	14 / 63 (22.22%)
occurrences (all)	113	21	18
Pyrexia			
subjects affected / exposed	28 / 296 (9.46%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	31	0	0
Reproductive system and breast			

disorders			
Amenorrhoea			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	30 / 296 (10.14%)	3 / 59 (5.08%)	4 / 63 (6.35%)
occurrences (all)	35	3	5
Cough			
subjects affected / exposed	23 / 296 (7.77%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	25	0	0
Dysphonia			
subjects affected / exposed	21 / 296 (7.09%)	5 / 59 (8.47%)	1 / 63 (1.59%)
occurrences (all)	24	5	1
Pulmonary embolism			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 296 (6.08%)	3 / 59 (5.08%)	1 / 63 (1.59%)
occurrences (all)	21	3	1
Disorientation			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Bradyphrenia			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Investigations			
Platelet count decreased			
subjects affected / exposed	44 / 296 (14.86%)	7 / 59 (11.86%)	9 / 63 (14.29%)
occurrences (all)	73	10	15
Alanine aminotransferase increased			
subjects affected / exposed	23 / 296 (7.77%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	28	0	0
Weight decreased			

subjects affected / exposed	18 / 296 (6.08%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	18	0	0
Neutrophil count decreased			
subjects affected / exposed	16 / 296 (5.41%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	26	0	0
White blood cell count decreased			
subjects affected / exposed	15 / 296 (5.07%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	28	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	78 / 296 (26.35%)	9 / 59 (15.25%)	7 / 63 (11.11%)
occurrences (all)	144	9	9
Seizure			
subjects affected / exposed	21 / 296 (7.09%)	4 / 59 (6.78%)	3 / 63 (4.76%)
occurrences (all)	49	5	3
Dizziness			
subjects affected / exposed	15 / 296 (5.07%)	3 / 59 (5.08%)	3 / 63 (4.76%)
occurrences (all)	19	3	3
Epilepsy			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Dysarthria			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Presyncope			

subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	61 / 296 (20.61%)	10 / 59 (16.95%)	22 / 63 (34.92%)
occurrences (all)	113	18	30
Leukopenia			
subjects affected / exposed	30 / 296 (10.14%)	9 / 59 (15.25%)	8 / 63 (12.70%)
occurrences (all)	48	15	12
Neutropenia			
subjects affected / exposed	26 / 296 (8.78%)	5 / 59 (8.47%)	8 / 63 (12.70%)
occurrences (all)	33	7	13
Lymphopenia			
subjects affected / exposed	23 / 296 (7.77%)	3 / 59 (5.08%)	6 / 63 (9.52%)
occurrences (all)	33	3	6
Anaemia			
subjects affected / exposed	20 / 296 (6.76%)	3 / 59 (5.08%)	2 / 63 (3.17%)
occurrences (all)	25	3	2
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	99 / 296 (33.45%)	7 / 59 (11.86%)	8 / 63 (12.70%)
occurrences (all)	154	8	11
Constipation			
subjects affected / exposed	77 / 296 (26.01%)	8 / 59 (13.56%)	10 / 63 (15.87%)
occurrences (all)	111	10	14
Vomiting			
subjects affected / exposed	49 / 296 (16.55%)	2 / 59 (3.39%)	5 / 63 (7.94%)
occurrences (all)	75	2	7
Diarrhoea			
subjects affected / exposed	28 / 296 (9.46%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	39	0	0
Abdominal pain upper			

subjects affected / exposed	16 / 296 (5.41%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	18	0	0
Stomatitis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	25 / 296 (8.45%)	0 / 59 (0.00%)	4 / 63 (6.35%)
occurrences (all)	31	0	4
Alopecia			
subjects affected / exposed	56 / 296 (18.92%)	10 / 59 (16.95%)	11 / 63 (17.46%)
occurrences (all)	57	10	11
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	71 / 296 (23.99%)	10 / 59 (16.95%)	13 / 63 (20.63%)
occurrences (all)	113	14	18
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 296 (11.82%)	5 / 59 (8.47%)	5 / 63 (7.94%)
occurrences (all)	46	5	5
Pain in extremity			
subjects affected / exposed	17 / 296 (5.74%)	3 / 59 (5.08%)	5 / 63 (7.94%)
occurrences (all)	21	3	6
Musculoskeletal pain			
subjects affected / exposed	15 / 296 (5.07%)	3 / 59 (5.08%)	3 / 63 (4.76%)
occurrences (all)	15	4	3
Back pain			
subjects affected / exposed	0 / 296 (0.00%)	3 / 59 (5.08%)	1 / 63 (1.59%)
occurrences (all)	0	3	1
Muscular weakness			
subjects affected / exposed	0 / 296 (0.00%)	3 / 59 (5.08%)	0 / 63 (0.00%)
occurrences (all)	0	3	0
Neck pain			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	19 / 296 (6.42%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	23	0	0
Nasopharyngitis			
subjects affected / exposed	19 / 296 (6.42%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	21	0	0
Gingivitis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 296 (13.18%)	4 / 59 (6.78%)	9 / 63 (14.29%)
occurrences (all)	64	7	11
Hypokalaemia			
subjects affected / exposed	0 / 296 (0.00%)	0 / 59 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo + Lomustine/SOC (Safety 4L+)	Bevacizumab + Lomustine/SOC (Safety 4L+)	Cross-over (Safety 4L+)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	7 / 10 (70.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	2 / 4 (50.00%)
occurrences (all)	0	2	2
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis limb			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	5 / 10 (50.00%)	1 / 4 (25.00%)
occurrences (all)	1	5	1
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Disorientation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Bradyphrenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Investigations			

Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Epilepsy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hemiparesis			

subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 4 (50.00%)	4 / 10 (40.00%)	1 / 4 (25.00%)
occurrences (all)	2	4	1
Leukopenia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Lymphopenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Vomiting			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 10 (30.00%)	1 / 4 (25.00%)
occurrences (all)	2	3	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 4 (25.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			

subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2014	Limited 2L treatment to be given in combination with bevacizumab or bevacizumab/placebo from SOC to lomustine only, now provided as investigational medicinal product; Removed fotemustine as an option in 3L treatment; Adapted statistical analysis following suppression of stratification by SOC regimen. Changed definition of PFS3 to: 'from randomisation to PD3 or death; Permitted participants for whom operation or re-operation was clinically indicated at PD1 to enter the study as this reflected normal clinical practice; Amended sample size calculation based on more recent data showing median PFS had changed from 9.1 months to 10.6 months.
16 January 2015	Changed the study phase from IIIb to II; Reduced the number of participants enrolled from 510 to 300, the number of participants randomised from 300 to 200, and the number of study centres from 130 to 65; Reduced assumed drop-out rate prior to randomisation from 41% to 20% overall; Reduced the number of OS events required for final analysis from 250 to 130; Adjusted statistical analysis for the primary endpoint OS from one-sided alpha level = 5% with a power of 80% to one-side alpha = 10% with a power of 70%. This assumed a median survival time for participants randomised to receive bevacizumab of 9 months and of 6.57 months for participants randomised to receive non-bevacizumab treatment (corresponding to a HR of 0.73). Added that for HR, 80% CI would also be calculated, in addition to the 95% CI already stated; Removed interim analysis.
27 June 2016	Added details regarding participant management at the end of the study for ongoing participants still benefiting from bevacizumab and/or chemotherapy; Clarified 3L and later line treatment regarding the potential use of other investigational drugs to avoid confusion with the study investigational drugs.

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.

The study was terminated early because the primary endpoint (OS) could not be reached.

Notes: