Clinical trial results:
A Phase II Open-Label, Randomized, Multi-Centre Comparative Study of Bevacizumab-Based Therapy in Paediatric Patients with Newly Diagnosed Supratentorial, Infratentorial Cerebellar, or Peduncular High-Grade Glioma

Summary

EudraCT number	2010-022189-28
Trial protocol	BE AT CZ DE GB SE HU FR ES DK FI NL IT PL Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	17 September 2016
First version publication date	17 September 2016

Trial information

Trial identification

Sponsor protocol code	BO25041

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01390948
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. , F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. , F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000056-PIP03-10
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	Interim
Date of interim/final analysis	05 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the benefit in terms of event-free survival (EFS) of the addition of bevacizumab to postoperative radiotherapy with concomitant and adjuvant temozolomide (TMZ).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	124
EEA total number of subjects	111

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)	2
Children (2-11 years)	71
Adolescents (12-17 years)	51
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Chemoradiation + temozolomide (TMZ) and Chemoradiation + Bevacizumab + TMZ arms: 174 subjects were screened; 121 were randomised; 116 received study treatment.

Young Patient Cohort: 4 subjects were screened; 3 were enrolled and received study treatment (these subjects were not randomised and are not included in efficacy analyses).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Main Cohort: Chemoradiation + TMZ

Arm description:

Subjects received a total dose of 54 Grey (Gy) units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 milligrams per meter squared (mg/m^2) TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Arm type	Active comparator
Investigational medicinal product name	Temozolomide (TMZ)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 milligrams per square meter (mg/m^2) daily continuous starting concomitantly with the first radiation fraction and ending with the last radiation fraction for a maximum number of treatment days = 49 days. During the TMZ adjuvant treatment phase and for subjects from YPC: TMZ (150 to 200 mg/m^2/day) x 12 cycles, 1st cycle 150 mg/m^2 on Days 1-5, escalated to 200 mg/m^2 on Days 1-5 from the 2nd cycle onwards depending on the tolerance during the 1st cycle. Cycle length = 28 days.

Arm title	Main Cohort: Chemoradiation + Bevacizumab + TMZ

Arm description:

Subjects received a total dose of 54 Gy units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 mg/m^2 TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle. Bevacizumab was given concomitantly at a dose of 10 milligrams per kilogram (mg/kg) every 2 weeks throughout the entire treatment period.

Arm type	Experimental

Investigational medicinal product name	Temozolomide (TMZ)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 milligrams per square meter (mg/m^2) daily continuous starting concomitantly with the first radiation fraction and ending with the last radiation fraction for a maximum number of treatment days = 49 days. During the TMZ adjuvant treatment phase and for subjects from YPC: TMZ (150 to 200 mg/m^2/day) x 12 cycles, 1st cycle 150 mg/m^2 on Days 1-5, escalated to 200 mg/m^2 on Days 1-5 from the 2nd cycle onwards depending on the tolerance during the 1st cycle. Cycle length = 28 days.

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:

10 milligrams per kilogram every 2 weeks during the study for up to 12 cycles, each cycle length of 28 days

Arm title	Bevacizumab + TMZ Young Patient Cohort (YPC)

Arm description:

Subjects aged >/= 6 months and < 3 years received 10 mg/kg Bevacizumab every 2 weeks and 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Arm type	Experimental
Investigational medicinal product name	Temozolomide (TMZ)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 milligrams per square meter (mg/m^2) daily continuous starting concomitantly with the first radiation fraction and ending with the last radiation fraction for a maximum number of treatment days = 49 days. During the TMZ adjuvant treatment phase and for subjects from YPC: TMZ (150 to 200 mg/m^2/day) x 12 cycles, 1st cycle 150 mg/m^2 on Days 1-5, escalated to 200 mg/m^2 on Days 1-5 from the 2nd cycle onwards depending on the tolerance during the 1st cycle. Cycle length = 28 days.

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:

10 milligrams per kilogram every 2 weeks during the study for up to 12 cycles, each cycle length of 28 days

Number of subjects in period 1	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ	Bevacizumab + TMZ Young Patient Cohort (YPC)
Started	59	62	3
Treated	56	60	3
Completed	0	0	0
Not completed	59	62	3
Withdrew consent from survival follow-up	3	5	-
Death	30	34	2
Ongoing	6	6	-
Alive in follow-up	20	17	1

Baseline characteristics

Reporting groups

Reporting group title	Main Cohort: Chemoradiation + TMZ

Reporting group description:

Subjects received a total dose of 54 Grey (Gy) units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 milligrams per meter squared (mg/m^2) TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Reporting group title	Main Cohort: Chemoradiation + Bevacizumab + TMZ

Reporting group description:

Subjects received a total dose of 54 Gy units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 mg/m^2 TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle. Bevacizumab was given concomitantly at a dose of 10 milligrams per kilogram (mg/kg) every 2 weeks throughout the entire treatment period.

Reporting group title	Bevacizumab + TMZ Young Patient Cohort (YPC)

Reporting group description:

Subjects aged >/= 6 months and < 3 years received 10 mg/kg Bevacizumab every 2 weeks and 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Reporting group values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ	Bevacizumab + TMZ Young Patient Cohort (YPC)
Number of subjects	59	62	3
Age categorical Units: Subjects			
< 3 years	0	0	3
>/= 3 years and < 6 years	6	10	0
>/= 6 years and < 13 years	30	35	0
>/= 13 years and < 18 years	23	17	0
Gender categorical Units: Subjects			
Female	23	28	0
Male	36	34	3

Reporting group values	Total		
Number of subjects	124		
Age categorical Units: Subjects			
< 3 years	3		
>/= 3 years and < 6 years	16		
>/= 6 years and < 13 years	65		
>/= 13 years and < 18 years	40		

Gender categorical Units: Subjects			
Female	51		
Male	73		

End points

End points reporting groups

Reporting group title	Main Cohort: Chemoradiation + TMZ

Reporting group description:

Subjects received a total dose of 54 Grey (Gy) units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 milligrams per meter squared (mg/m^2) TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Reporting group title	Main Cohort: Chemoradiation + Bevacizumab + TMZ

Reporting group description:

Subjects received a total dose of 54 Gy units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 mg/m^2 TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle. Bevacizumab was given concomitantly at a dose of 10 milligrams per kilogram (mg/kg) every 2 weeks throughout the entire treatment period.

Reporting group title	Bevacizumab + TMZ Young Patient Cohort (YPC)

Reporting group description:

Subjects aged >/= 6 months and < 3 years received 10 mg/kg Bevacizumab every 2 weeks and 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Primary: Event-Free Survival (EFS) as Assessed by the Central Radiology Review Committee (CRRC)

End point title	Event-Free Survival (EFS) as Assessed by the Central Radiology Review Committee (CRRC)[1]

End point description:

EFS was defined as the time from diagnosis to the earliest occurrence of any of the following: tumor progression, tumor recurrence, second primary non-high-grade glioma (HGG) malignancy or death attributable to any cause. Tumor assessments were conducted using magnetic resonance imaging (MRI) and reviewed by the site-independent CRRC using RANO criteria. Tumor progression was defined as clear clinical progression or >/= 25% increase in the sum of the products of perpendicular diameters of the contrast enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease was observed) or best response and with the subject on stable or increasing doses of corticosteroids. Tumor recurrence was defined as recurrence after tumor was completely resected (no disease present at baseline). EFS was estimated using the Kaplan-Meier method. Randomised subject population: all randomised subjects regardless of whether they received study treatment.

End point type	Primary

End point timeframe:

From the time of randomisation to the date of clinical cutoff (up to approximately 52 months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 95%)	11.79 (7.85 to 16.39)	8.21 (7.75 to 12.68)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Main Cohort: Chemoradiation + Bevacizumab + TMZ v Main Cohort: Chemoradiation + TMZ
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1292
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.3

Secondary: Overall Survival

End point title	Overall Survival[2]

End point description:

Overall Survival was defined as the time of diagnosis to the date of death due to any cause. Overall Survival was estimated using the Kaplan-Meier method. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

From the time of randomisation to the date of clinical cutoff (up to approximately 52 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 95%)	26.97 (14 to 33.77)	18.27 (16.2 to 28.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With 1-Year Survival

End point title	Percentage of Subjects With 1-Year Survival[3]

End point description:

1-year survival was estimated using the Kaplan-Meier method. Randomised subject population included all randomised subjects regardless of whether they received study treatment. Here, number of subjects analyzed signifies the subjects who were evaluable for the outcome measure.

End point type	Secondary

End point timeframe:

1 year

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of subjects				
number (confidence interval 95%)	67.69 (53.7 to 78.27)	74.59 (61.39 to 83.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With EFS as Determined by the CRRC at 6 Months

End point title	Percentage of Subjects With EFS as Determined by the CRRC at 6 Months[4]

End point description:

EFS was defined as the time from diagnosis to the earliest occurrence of any of the following: tumor progression, tumor recurrence, second primary non- HGG malignancy or death attributable to any cause. Tumor assessments were conducted using MRI and reviewed by the site-independent CRRC using

RANO criteria. Tumor progression was defined as clear clinical progression or >/= 25% increase in the sum of the products of perpendicular diameters of the contrast enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease was observed) or best response and with the subject on stable or increasing doses of corticosteroids. Tumor recurrence was defined as recurrence after tumor was completely resected (no disease present at baseline). EFS was estimated using the Kaplan-Meier method. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

6 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of participants				
number (confidence interval 95%)	66.46 (52.58 to 77.13)	68.43 (55.06 to 78.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With EFS as Determined by the CRRC at 1 Year

End point title	Percentage of Subjects With EFS as Determined by the CRRC at 1 Year[5]

End point description:

EFS was defined as the time from randomisation to the earliest occurrence of any of the following: tumor progression, tumor recurrence, second primary non- HGG malignancy or death attributable to any cause. Tumor assessments were conducted using MRI and reviewed by the site-independent CRRC using RANO criteria. Tumor progression was defined as clear clinical progression or >/= 25% increase in the sum of the products of perpendicular diameters of the contrast enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease was observed) or best response and with the subject on stable or increasing doses of corticosteroids. Tumor recurrence was defined as recurrence after tumor was completely resected (no disease present at baseline). EFS was estimated using the Kaplan-Meier method. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

1 year

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of subjects				
number (confidence interval 95%)	48.37 (34.82 to 60.65)	38.28 (25.79 to 50.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: EFS as Assessed by the Investigator

End point title	EFS as Assessed by the Investigator[6]

End point description:

EFS was defined as the time from diagnosis to the earliest occurrence of any of the following: tumor progression, tumor recurrence, second primary non-HGG malignancy or death attributable to any cause. Tumor assessments were conducted using MRI and reviewed by the investigator using RANO criteria. Tumor progression was defined as clear clinical progression or >/= 25% increase in the sum of the products of perpendicular diameters of the contrast enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease was observed) or best response and with the subject on stable or increasing doses of corticosteroids. Tumor recurrence was defined as recurrence after tumor was completely resected (no disease present at baseline). EFS was estimated using the Kaplan-Meier method. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

From the time of randomisation to the date of clinical cutoff (up to approximately 52 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 95%)	11.79 (8.51 to 20.53)	11.27 (8.11 to 14.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[7]

End point description:

ORR was defined as the percentage of subjects with a complete response (CR) or partial response (PR) determined on two consecutive occasions >/= 4 weeks apart. Tumor assessments were conducted using MRI and reviewed by the site-independent CRRC using RANO criteria. The following were needed to qualify as CR: complete disappearance of all measurable enhancing lesions sustained for at least 4 weeks by MRI, no steroids above physiological levels, clinical status stable or improved compared to baseline. The following were needed to qualify as PR: ≥ 50% decrease from baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks by MRI, steroid dose not increased compared to baseline, clinical status stable or improved compared to baseline. Randomised subject population with a measurable lesion at baseline.

End point type	Secondary

End point timeframe:

From the time of randomisation of the first subject to the date of clinical cutoff (up to approximately 52 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: percentage of subjects				
number (confidence interval 95%)	40 (19.09 to 66.77)	41.7 (18.1 to 70.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concordance between Structural Versus Multimodal Imaging for CRRC-Assessed Event-Free Survival

End point title	Concordance between Structural Versus Multimodal Imaging for CRRC-Assessed Event-Free Survival[8]

End point description:

Concordance is presented as the percentage of subjects with concordance between assessments. EFS concordance was defined as event Structural assessment and Diffusion Perfusion assessment occurs within 28 days or no event Structural and no Diffusion Perfusion. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

From the time of randomisation of the first subject to the date of clinical cutoff (approximately 52 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of subjects				
number (not applicable)				
EFS concordance	96.6	87.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Status as Measured by the Health Utility Index (HUI)

End point title	Health Status as Measured by the Health Utility Index (HUI)[9]

End point description:

HUI is a preference-based, multi-attitude, health-related instrument specifically developed for use with children. HUI consists of eight attributes of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Each attribute had 5 or 6 levels varying from highly impaired to normal. Each of the eight health dimensions was tested separately and a composite score ranging between 1 (perfect health) and 0 (death) was obtained for subjects aged 5 years or older. Randomised subject population aged 5 years or older with a measure at the specified time point. Here, 'n' represents the number of subjects with a measure at the specified time point. Here, '99999' represents that the confidence interval is not applicable because a single subject was analyzed.

End point type	Secondary

End point timeframe:

Baseline, Cycle 6 of the adjuvant phase, end of treatment (approximately 58 weeks post-baseline), and yearly during the follow-up period (maximum 5 years in follow-up)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	45		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Baseline (n=36,45)	0.713 (± 0.317)	0.73 (± 0.274)		
Cycle 6, Day 1 (n=30,39)	0.785 (± 0.239)	0.779 (± 0.232)		

End of Treatment (n=21,20)	0.832 (± 0.216)	0.822 (± 0.215)		
Yearly Follow-Up 1 (n=4,3)	0.895 (± 0.167)	0.887 (± 0.155)		
Yearly Follow-up 2 (n=1,1)	1 (± 99999)	0.67 (± 99999)		
End of Study (n=3,6)	0.647 (± 0.496)	0.79 (± 0.234)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neurological Psychological Function as Measured by the Wechsler Scale

End point title	Neurological Psychological Function as Measured by the Wechsler Scale[10]

End point description:

The Wechsler Intelligence Scale for Children version IV (WISC-IV) was used to generate a full scale IQ which represents a child's general intellectual ability. The average IQ score is 100, with lower scores representing lower intellectual ability. Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

End of treatment (approximately 58 weeks post-baseline)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: units on a scale				
geometric mean (standard deviation)	92 (± 9.8)	97 (± 18.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Completed >/= 90% of Planned Radiotherapy and TMZ Administrations

End point title	Percentage of Subjects Who Completed >/= 90% of Planned Radiotherapy and TMZ Administrations[11]

End point description:

Safety population included all subjects that received study treatment.

End point type	Secondary

End point timeframe:

From the time of randomisation of the first subject to the date of clinical cutoff (approximately 52 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	60		
Units: percentage of subjects				
number (not applicable)				
Radiotherapy	94.6	98.3		
TMZ	85.7	88.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Treatment Delay or Discontinuation

End point title	Percentage of Subjects With a Treatment Delay or Discontinuation[12]

End point description:

Randomised subject population included all randomised subjects regardless of whether they received study treatment.

End point type	Secondary

End point timeframe:

From the time of randomisation of the first subject to the date of clinical cutoff (approximately 52 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of subjects				
number (not applicable)				
AE leading to dose modification/interruption	60.7	71.7		

AE leading to withdrawal from treatment	5.4	21.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Duration in the Concurrent Phase

End point title	Treatment Duration in the Concurrent Phase[13]

End point description:

Treatment duration was assessed for the concurrent phase, which is the treatment period after both the initial treatment phase and the subsequent treatment break of approximately 4 weeks. Safety population included all subjects that received study drug. Here, '99999' represents that the data is not applicable because Bevacizumab was not administered for the arm.

End point type	Secondary

End point timeframe:

Beginning of the concurrent phase to end of treatment (48 weeks)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	60		
Units: number of dose administrations				
arithmetic mean (full range (min-max))				
Radiotherapy	28.6 (2 to 30)	29.5 (1 to 31)		
TMZ	40.5 (1 to 50)	41.6 (3 to 49)		
Bevacizumab	99999 (99999 to 99999)	5.1 (1 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Adverse Event (AE)

End point title	Percentage of Subjects With an Adverse Event (AE)[14]

End point description:

An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety population included all subjects that received study

drug.

End point type	Secondary

End point timeframe:

From the time of randomisation of the first subject to the date of clinical cutoff (approximately 52 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned to be performed between arm "Chemoradiation + TMZ" and arm "Chemoradiation + Bevacizumab + TMZ" only.

End point values	Main Cohort: Chemoradiation + TMZ	Main Cohort: Chemoradiation + Bevacizumab + TMZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	60		
Units: percentage of subjects				
number (not applicable)	100	98.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation/enrollment of the first subject to date of clinical cut off (approximately 52 months)

Adverse event reporting additional description:

An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Chemoradiation + TMZ

Reporting group description:

Subjects received a total dose of 54 Gy units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 mg/m^2 TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Reporting group title	Chemoradiation + Bevacizumab + TMZ

Reporting group description:

Subjects received a total dose of 54 Gy units delivered in 30 daily fractions of 1.8 Gy over 6 weeks with 75 mg/m^2 TMZ daily for up to 49 days followed by a treatment break of approximately 4 weeks. The treatment break was followed by an adjuvant treatment phase where subjects received 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle. Bevacizumab was given concomitantly at a dose of 10 milligrams per kilogram (mg/kg) every 2 weeks throughout the entire treatment period.

Reporting group title	Bevacizumab + TMZ Young Patient Cohort (YPC)

Reporting group description:

Subjects aged >/= 6 months and < 3 years received 10 mg/kg Bevacizumab every 2 weeks and 150 to 200 mg/m^2 of TMZ daily on Days 1-5 of each cycle. TMZ was given at a dose of 150 mg/m^2 on Days 1-5 of cycle 1 and then escalated to 200 mg/m^2 on days 1-5 from cycle 2 onwards depending on the tolerance during the 1st cycle.

Serious adverse events	Chemoradiation + TMZ	Chemoradiation + Bevacizumab + TMZ	Bevacizumab + TMZ Young Patient Cohort (YPC)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 56 (48.21%)	35 / 60 (58.33%)	0 / 3 (0.00%)
number of deaths (all causes)	28	33	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell type acute leukaemia			

subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Device occlusion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Hypothermia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Implant site dehiscence			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Influenza like illness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Pyrexia			
subjects affected / exposed	5 / 56 (8.93%)	12 / 60 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	3 / 6	6 / 17	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombosis in device			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Hypersensitivity			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 56 (0.00%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Lymphocyte count decreased			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Neutrophil count decreased			

subjects affected / exposed	1 / 56 (1.79%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 56 (0.00%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Haematuria traumatic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Radius fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Nervous system disorders			
Cerebral cyst			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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

Headache			
subjects affected / exposed	2 / 56 (3.57%)	4 / 60 (6.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Hydrocephalus			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Monoplegia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Nervous system disorder			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Presyncope			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Seizure			

subjects affected / exposed	7 / 56 (12.50%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Status epilepticus			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Febrile neutropenia			
subjects affected / exposed	0 / 56 (0.00%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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			
Constipation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Nausea			
subjects affected / exposed	0 / 56 (0.00%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 56 (5.36%)	6 / 60 (10.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 3	6 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Rash			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Urticaria			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Infections and infestations			
Catheter site infection			

subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Device related infection			
subjects affected / exposed	0 / 56 (0.00%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Gastroenteritis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Herpes zoster			
subjects affected / exposed	2 / 56 (3.57%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Klebsiella bacteraemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Lung infection			
subjects affected / exposed	1 / 56 (1.79%)	1 / 60 (1.67%)	0 / 3 (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
Pseudomonas infection			

subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Shunt infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 60 (1.67%)	0 / 3 (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
Skin infection			
subjects affected / exposed	1 / 56 (1.79%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Tonsillitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 60 (0.00%)	0 / 3 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 56 (1.79%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	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	Chemoradiation + TMZ	Chemoradiation + Bevacizumab + TMZ	Bevacizumab + TMZ Young Patient Cohort (YPC)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 56 (100.00%)	58 / 60 (96.67%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	3 / 56 (5.36%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 56 (1.79%)	7 / 60 (11.67%)	1 / 3 (33.33%)
occurrences (all)	1	10	2
Hypotension			
subjects affected / exposed	2 / 56 (3.57%)	4 / 60 (6.67%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 56 (7.14%)	6 / 60 (10.00%)	0 / 3 (0.00%)
occurrences (all)	7	6	0
Fatigue			
subjects affected / exposed	32 / 56 (57.14%)	26 / 60 (43.33%)	0 / 3 (0.00%)
occurrences (all)	44	36	0
Influenza like illness			
subjects affected / exposed	3 / 56 (5.36%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	4	2	0
Pyrexia			
subjects affected / exposed	16 / 56 (28.57%)	15 / 60 (25.00%)	1 / 3 (33.33%)
occurrences (all)	27	30	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 56 (21.43%)	19 / 60 (31.67%)	0 / 3 (0.00%)
occurrences (all)	17	29	0
Epistaxis			
subjects affected / exposed	4 / 56 (7.14%)	12 / 60 (20.00%)	0 / 3 (0.00%)
occurrences (all)	4	19	0
Oropharyngeal pain			

subjects affected / exposed	5 / 56 (8.93%)	7 / 60 (11.67%)	0 / 3 (0.00%)
occurrences (all)	11	8	0
Rhinorrhoea			
subjects affected / exposed	2 / 56 (3.57%)	7 / 60 (11.67%)	0 / 3 (0.00%)
occurrences (all)	2	7	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 56 (3.57%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences (all)	2	6	0
Insomnia			
subjects affected / exposed	7 / 56 (12.50%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	8	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 56 (10.71%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	6	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Neutrophil count decreased			
subjects affected / exposed	18 / 56 (32.14%)	16 / 60 (26.67%)	1 / 3 (33.33%)
occurrences (all)	34	29	1
Platelet count decreased			
subjects affected / exposed	19 / 56 (33.93%)	18 / 60 (30.00%)	1 / 3 (33.33%)
occurrences (all)	46	42	2
Weight decreased			
subjects affected / exposed	3 / 56 (5.36%)	6 / 60 (10.00%)	0 / 3 (0.00%)
occurrences (all)	3	8	0
White blood cell count decreased			
subjects affected / exposed	14 / 56 (25.00%)	16 / 60 (26.67%)	1 / 3 (33.33%)
occurrences (all)	28	32	1
Heart rate increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 60 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Radiation skin injury			
subjects affected / exposed	5 / 56 (8.93%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences (all)	5	5	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 56 (3.57%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	2	5	0
Dysgeusia			
subjects affected / exposed	4 / 56 (7.14%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Headache			
subjects affected / exposed	32 / 56 (57.14%)	34 / 60 (56.67%)	0 / 3 (0.00%)
occurrences (all)	66	63	0
Intracranial pressure increased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Paraesthesia			
subjects affected / exposed	4 / 56 (7.14%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Seizure			
subjects affected / exposed	5 / 56 (8.93%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	10	2	0
Somnolence			
subjects affected / exposed	3 / 56 (5.36%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 56 (10.71%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences (all)	13	9	0
Leukopenia			
subjects affected / exposed	6 / 56 (10.71%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	11	3	0
Lymphopenia			
subjects affected / exposed	3 / 56 (5.36%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Neutropenia			

subjects affected / exposed	12 / 56 (21.43%)	9 / 60 (15.00%)	0 / 3 (0.00%)
occurrences (all)	25	19	0
Thrombocytopenia			
subjects affected / exposed	8 / 56 (14.29%)	9 / 60 (15.00%)	0 / 3 (0.00%)
occurrences (all)	20	30	0
White blood count increased			
subjects affected / exposed	4 / 56 (7.14%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	4	2	0
Neutrophil count increased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 56 (3.57%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Eye disorders			
Eye pain			
subjects affected / exposed	5 / 56 (8.93%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 56 (17.86%)	12 / 60 (20.00%)	1 / 3 (33.33%)
occurrences (all)	17	18	1
Abdominal pain upper			
subjects affected / exposed	6 / 56 (10.71%)	7 / 60 (11.67%)	0 / 3 (0.00%)
occurrences (all)	7	9	0
Constipation			
subjects affected / exposed	12 / 56 (21.43%)	18 / 60 (30.00%)	0 / 3 (0.00%)
occurrences (all)	19	29	0
Dental caries			
subjects affected / exposed	0 / 56 (0.00%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	13 / 56 (23.21%)	14 / 60 (23.33%)	2 / 3 (66.67%)
occurrences (all)	19	22	2
Nausea			

subjects affected / exposed	24 / 56 (42.86%)	22 / 60 (36.67%)	0 / 3 (0.00%)
occurrences (all)	49	38	0
Oral pain			
subjects affected / exposed	0 / 56 (0.00%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Toothache			
subjects affected / exposed	3 / 56 (5.36%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	3	3	0
Vomiting			
subjects affected / exposed	29 / 56 (51.79%)	36 / 60 (60.00%)	2 / 3 (66.67%)
occurrences (all)	65	89	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	34 / 56 (60.71%)	19 / 60 (31.67%)	0 / 3 (0.00%)
occurrences (all)	34	20	0
Dermatitis			
subjects affected / exposed	5 / 56 (8.93%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Dry skin			
subjects affected / exposed	2 / 56 (3.57%)	4 / 60 (6.67%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
Erythema			
subjects affected / exposed	2 / 56 (3.57%)	7 / 60 (11.67%)	0 / 3 (0.00%)
occurrences (all)	2	9	0
Pruritus			
subjects affected / exposed	5 / 56 (8.93%)	5 / 60 (8.33%)	0 / 3 (0.00%)
occurrences (all)	5	6	0
Purpura			
subjects affected / exposed	0 / 56 (0.00%)	4 / 60 (6.67%)	0 / 3 (0.00%)
occurrences (all)	0	10	0
Rash			
subjects affected / exposed	1 / 56 (1.79%)	11 / 60 (18.33%)	2 / 3 (66.67%)
occurrences (all)	4	17	2
Skin striae			
subjects affected / exposed	5 / 56 (8.93%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0

Urticaria			
subjects affected / exposed	5 / 56 (8.93%)	8 / 60 (13.33%)	0 / 3 (0.00%)
occurrences (all)	8	10	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 56 (0.00%)	15 / 60 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	27	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 56 (5.36%)	6 / 60 (10.00%)	0 / 3 (0.00%)
occurrences (all)	4	6	0
Back pain			
subjects affected / exposed	3 / 56 (5.36%)	4 / 60 (6.67%)	0 / 3 (0.00%)
occurrences (all)	3	4	0
Musculoskeletal pain			
subjects affected / exposed	5 / 56 (8.93%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Neck pain			
subjects affected / exposed	3 / 56 (5.36%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	4	2	0
Pain in extremity			
subjects affected / exposed	4 / 56 (7.14%)	3 / 60 (5.00%)	1 / 3 (33.33%)
occurrences (all)	5	3	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	5 / 56 (8.93%)	1 / 60 (1.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Herpes zoster			
subjects affected / exposed	3 / 56 (5.36%)	2 / 60 (3.33%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Influenza			
subjects affected / exposed	1 / 56 (1.79%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Nasopharyngitis			
subjects affected / exposed	6 / 56 (10.71%)	10 / 60 (16.67%)	0 / 3 (0.00%)
occurrences (all)	6	10	0

Pharyngitis			
subjects affected / exposed	4 / 56 (7.14%)	0 / 60 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Rhinitis			
subjects affected / exposed	9 / 56 (16.07%)	8 / 60 (13.33%)	0 / 3 (0.00%)
occurrences (all)	10	9	0
Upper respiratory tract infection			
subjects affected / exposed	7 / 56 (12.50%)	3 / 60 (5.00%)	2 / 3 (66.67%)
occurrences (all)	7	6	4
Viral infection			
subjects affected / exposed	0 / 56 (0.00%)	3 / 60 (5.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Candida infection			
subjects affected / exposed	0 / 56 (0.00%)	0 / 60 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Otitis media acute			
subjects affected / exposed	0 / 56 (0.00%)	0 / 60 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 56 (37.50%)	17 / 60 (28.33%)	0 / 3 (0.00%)
occurrences (all)	28	22	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2012	Added a cohort of 10 younger patients below 3 years of age into a separate arm of the main study for treatment at the request of the EMA Pediatric Committee (PDCO). Added the availability of a baseline MRI scan to the inclusion criteria. Added EFS as determined by the CRRC as secondary endpoint. Added an interim pharmacokinetic (PK) analysis for the first 10 patients randomised to the bevacizumab arm in order to align with the paediatric investigation plan (PIP) requirement.
15 July 2013	Modified the primary endpoint to become a blinded site-independent central radiology committee reviewed EFS, and consequently implemented a site-independent central radiology review process for the primary endpoint. Clarified that assessment of efficacy and disease progression or recurrence evaluation were to be performed according to the Wen et al 2010 publication. Added secondary endpoints of ORR and functional changes in tumor diffusion/perfusion MRI (multi modal imaging) for correlative analysis with structural imaging and efficacy outcome measures. The endpoints of Health Utility Index (HUI) and intelligence quotient (IQ) measurements, which were previously exploratory endpoints, were redefined as secondary endpoints. Extended the study population to patients with selected tumors in the infratentorial region (i.e., cerebellar or peduncular localized HGG) characterized by relatively similar history of disease as supratentorial HGGs, similar treatment options and response, and prognostically and biologically distinct from the more aggressive brainstem tumors (i.e., diffuse intrinsic pontine gliomas, medulla oblongata, or other midbrain tumours).
12 September 2014	Added collection of safety data to ensure compliance to the PIP's key binding elements, risk management plan (RMP) and post marketing commitment (PMC) requirements: growth and development, including fertility and sexual development, health-related quality of life, neuropsychological function and bone toxicities. Updated sections "end of study" and "duration of study" to: Extend the follow-up duration from 3 to 5 years in order to collect long-term safety data and OS as per the agreed PIP. Clarified treatment options following independent data monitoring committee (iDMC) recommendations based on the futility analysis. The statistical section was also updated accordingly. Removed the minimum requirement of 10 patients to be enrolled in the Young Patient Cohort to align with PDCO in its positive opinion on a modification of a PIP. A positive PDCO Opinion was received in December 2013 and the EMA decision was issued on 22 January 2014 (P/0005/2014). Updated the duration of study of the Young Patient Cohort to align with the main study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported