ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 12/03/2014

ClinicalTrials.gov ID: NCT01115491

Study Identification

Unique Protocol ID:	ML25152
Brief Title:	A Study of Bevacizumab and Extended Treatment of Temozolomide in Patients With Recurrent Glioblastoma Multiforme
Official Title:	A Single Arm Phase II Study of Bevacizumab and Extended Treatment of Temozolomide in Patients With Recurrent Glioblastoma Multiforme
Secondary IDs:	2010-019051-21

Study Status

Record Verification:	December 2014
Overall Status:	Completed
Study Start:	June 2010
Primary Completion:	July 2012 [Actual]
Study Completion:	July 2012 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No

	Delayed Posting?
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 05.05.2010 Board Name: CEIC area 7 - Hospital Clinico San Carlos Board Affiliation: unknown Phone: 0034 91 330 34 13 Email: ceic.hscs@salud.madrid.org
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Spain: Agencia Española del medicamento y productos sanitarios.

Study Description

Brief Summary:	This is a Phase II, national, multicenter, open-label, non-comparative study to investigate the efficacy and safety of bevacizumab and temozolomide in patients with recurrent glioblastoma multiforme (GBM) after a first treatment failure. Patients will receive bevacizumab 10 mg/kg intravenously every two weeks until disease progression, consent withdrawal, or unacceptable toxicity. Anticipated time on study treatment is 12-24 months.
Detailed Description:	

Conditions

Conditions:	Glioblastoma Multiforme
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study

Enrollment: 32 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: A	Drug: bevacizumab [Avastin] Bevacizumab 10 mg/kg body weight will be administered intravenously every two weeks Drug: temozolomide Daily by the oral route (dose, 150 mg/m2) on days 1 to 7 and 15 to 21 of each cycle

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Age >= 18 years
- Histological diagnosis of glioblastoma multiforme (GBM) documented by surgical resection or biopsy.
- They should be patients in a first relapse treated with radiotherapy and chemotherapy and chemotherapy based on temozolomide 150-200 mg/m2 on days 1 to 5 every 28 days (Stupp regimen) for at least three cycles. At least 4 weeks must have lapsed since previous chemotherapy and 3 months since the last dose of radiotherapy.
- Use of an effective contraceptive method by patients and their partners.
- Stable or decreasing corticosteroid dose for the five days prior to study entry
- Adequate hematological function
- Adequate liver function
- Adequate kidney function

Exclusion Criteria:

- Signs of recent bleeding at the MRI of the brain. However, patients with clinically asymptomatic presence of hemosiderin, resolving bleeding changes related to surgery, and presence of punctate hemorrhage in the tumor will be allowed to participate in the study.
- Prior treatment with bevacizumab
- Poorly controlled arterial hypertension

- History of hypertensive crises or hypertensive encephalopathy
- New York Health Association (NYHA) Class II or higher congestive heart failure
- History of myocardial infarction or unstable angina pectoris within six months of study entry
- History of stroke or TIA within six months of study entry
- Significant vascular disease within six months of study entry
- History of hemoptysis > grade 2 according to the NCI CTC criteria within one month of study entry
- Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- Major surgery, open biopsy, intracranial biopsy, ventriculoperitoneal shunt, or major traumatic lesion within 28 days of study entry.
- Core needle biopsy (excluding intracranial biopsy) or other minor surgery within seven days of randomization. Placement of a central vascular access device (CVAD) if performed in the two days prior to bevacizumab administration
- History of abdominal fistula or gastrointestinal perforation within six months of study entry
- History of intracranial abscess within six months of randomization
- Any prior malignant neoplasm treated with curative intent in the five years prior to study entry, except for adequately controlled limited basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix
- Patients with any other metabolic or psychological disease
- Hypersensitivity to products derived from Chinese hamster ovary cells or to other humanized or recombinant human antibodies

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: Spain

Madrid, Madrid, Spain, 28041

Madrid, Madrid, Spain, 28040

Barcelona, Barcelona, Spain, 08907

Valencia, Valencia, Spain, 46026

Barcelona, Barcelona, Spain, 08916

Madrid, Madrid, Spain, 28046

Valencia, Valencia, Spain, 41014

Barcelona, Barcelona, Spain, 08025

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 milligrams per kilogram (mg/kg) intravenously (IV) on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg per square meter (mg/m^2), orally (PO), on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Overall Study

	Bevacizumab + Temozolomide
Started	32
Completed	2
Not Completed	30
Death	22
Adverse Event	3
Lost to Follow-up	3
Withdrawal by Subject	1
Physician Decision	1

Baseline Characteristics

Analysis Population Description

Intent-to-treat (ITT) population: all enrolled participants.

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Baseline Measures

	Bevacizumab + Temozolomide
Number of Participants	32
Age, Continuous [units: years] Mean (Standard Deviation)	56.19 (10.58)
Gender, Male/Female [units: participants]	
Female	15
Male	17

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-Free Survival (PFS) - Percentage of Participants With an Event
Measure Description	PFS was defined as the time, in weeks, from the date of inclusion in the study to the date of the first documentation of disease progression or death of the participant due to any cause. Participants that did not have an event at the time the analysis was performed were censored at the date of last contact. Participants that began a treatment other than those planned in this study (bevacizumab or temozolomide) were censored on the start date of the new treatment.
Time Frame	Baseline (BL), every 28 days, until progression, death or end-of-study, an average of 32 weeks
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
Progression-Free Survival (PFS) - Percentage of Participants With an Event [units: percentage of participants]	96.88

2. Primary Outcome Measure:

Measure Title	PFS - Time to Event
Measure Description	PFS was defined as the time, in weeks, from the date of inclusion in the study to the date of the first documentation of disease progression or death of the participant due to any cause. Participants that did not have an event at the time the analysis was performed were censored at the date of last contact. Participants that began a treatment other than those planned in this study (bevacizumab or temozolomide) were censored on the start date of the new treatment. PFS was estimated using the Kaplan-Meier method.
Time Frame	BL, every 28 days, until progression, death or end-of-study, an average of 32 weeks
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
PFS - Time to Event [units: weeks] Median (95% Confidence Interval)	18.29 (15.43 to 23.57)

3. Primary Outcome Measure:

Measure Title	PFS: Probability of Remaining Progression Free at 24 Weeks After Beginning the Study
Measure Description	
Time Frame	BL, 24 weeks (after 6th cycle)
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
PFS: Probability of Remaining Progression Free at 24 Weeks After Beginning the Study [units: survival probability]	0.30000

4. Secondary Outcome Measure:

Measure Title	Overall Survival - Percentage of Participants With an Event
Measure Description	Overall survival was defined as the time transpired (in weeks) between the date of the participant's inclusion in the trial until the date of his/her death by any cause. Participants that were alive at the time the analysis was performed were censored on the date of last contact.
Time Frame	BL, every 28 days, until death or end-of-study, an average of 32 weeks
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
Overall Survival - Percentage of Participants With an Event [units: percentage of participants]	75.00

5. Secondary Outcome Measure:

Measure Title	Overall Survival - Time to Event
Measure Description	Overall survival was defined as the time transpired (in weeks) between the date of the participant's inclusion in the trial until the date of his/her death by any cause. Participants that were alive at the time the analysis was performed were censored on the date of last contact. Median overall survival was estimated using the Kaplan-Meier method.
Time Frame	BL, every 28 days, until death or end-of-study, an average of 32 weeks
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
Overall Survival - Time to Event [units: weeks] Median (95% Confidence Interval)	31.43 (25.14 to 38.29)

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants Achieving an Overall Response of Complete Response (CR) or Partial Response (PR)

Measure Description	Overall response was defined as the percentage of participants who obtained CR or PR using adapted MacDonald criteria. CR: disappearance of all index and non-index lesions, confirmed no less than 4 weeks after assessment, no evidence of disease progression; corticosteroid dosage at or below 20 mg hydrocortisone daily; no neurological changes or an improvement as compared to last disease assessment. PR was defined as: Fifty percent or greater decrease in the sum of products of the larger diameter and the larger perpendicular diameter of all index lesions confirmed no less than 4 weeks after assessment, no evidence of disease progression and the absence of progressive, or non-evaluable disease status for non-index legions; unchanged, or decreased corticosteroid dose as compared to the last disease assessment; no neurological changes or an improvement as compared to the neurological examination at last disease assessment.
Time Frame	BL, every 28 days, until progression, death or end-of-study, an average of 32 weeks
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Measured Values

	Bevacizumab + Temozolomide
Number of Participants Analyzed	32
Percentage of Participants Achieving an Overall Response of Complete Response (CR) or Partial Response (PR) [units: percentage of participants]	40.6

Reported Adverse Events

Time Frame	Adverse events (AEs) were collected from the date of start of study treatment to 90 days after the last dose of study treatment.
Additional Description	All participants who received at least 1 dose of study treatment were included in the safety population.

Reporting Groups

	Description
Bevacizumab + Temozolomide	Cycles 1-12 (4-week cycles): Participants received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off); temozolomide 150 mg/m^2, PO, on Days 1 through 7 and on Days 15 through 21 (followed by 1 week off). Cycle was repeated for a maximum of 12 cycles. Cycle 13 and beyond (4-week cycles): If the first 12 cycles were tolerated with no disease progression, participants then received bevacizumab 10 mg/kg IV on Days 1 and 15 (followed by 2 weeks off). This cycle was repeated every 28 days until disease progression.

Serious Adverse Events

	Bevacizumab + Temozolomide
	Affected/At Risk (%)
Total	8/32 (25%)
Blood and lymphatic system disorders	
Intracranial haemorrhage [A] *	1/32 (3.12%)
General disorders	
Fever [A] *	2/32 (6.25%)
Infections and infestations	
Lung (pneumonia) [A] *	2/32 (6.25%)
Upper respiratory tract infection [A] *	1/32 (3.12%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	1/32 (3.12%)
Nervous system disorders	
Neurological disorder NOS [A] *	1/32 (3.12%)
Seizures [A] *	1/32 (3.12%)

	Bevacizumab + Temozolomide
	Affected/At Risk (%)
Renal and urinary disorders	
Bladder haemorrhage [A] *	1/32 (3.12%)
Vascular disorders	
Thrombosis [A] *	1/32 (3.12%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.0)

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Bevacizumab + Temozolomide
	Affected/At Risk (%)
Total	32/32 (100%)
Blood and lymphatic system disorders	
Leukocyte count decreased [A] *	3/32 (9.38%)
Lymphocyte count decreased [A] *	16/32 (50%)
Neutrophil count decreased [A] *	6/32 (18.75%)
Oedema limbs [A] *	5/32 (15.62%)
Platelet count decreased [A] *	15/32 (46.88%)
Gastrointestinal disorders	
Abdominal pain [A] *	3/32 (9.38%)
Constipation [A] *	6/32 (18.75%)
Diarrhoea [A] *	5/32 (15.62%)
Heartburn/dyspepsia [A] *	2/32 (6.25%)
Nausea [A] *	11/32 (34.38%)
Taste alteration (dysgeusia) [A] *	2/32 (6.25%)

	Bevacizumab + Temozolomide
	Affected/At Risk (%)
Vomiting [A] *	6/32 (18.75%)
General disorders	
Fatigue [A] *	18/32 (56.25%)
Fever [A] *	4/32 (12.5%)
General symptom [A] *	3/32 (9.38%)
Haemorrhage [A] *	4/32 (12.5%)
Infections and infestations	
Bronchitis [A] *	2/32 (6.25%)
Lung (pneumonia) [A] *	2/32 (6.25%)
Upper aerodigestive tract infection [A] *	2/32 (6.25%)
Upper respiratory infection [A] *	8/32 (25%)
Urinary tract infection [A] *	5/32 (15.62%)
Metabolism and nutrition disorders	
Anorexia [A] *	8/32 (25%)
Glucose, serum-high (hyperglycaemia) [A] *	5/32 (15.62%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	3/32 (9.38%)
Musculoskeletal disorder [A] *	2/32 (6.25%)
Nervous system disorders	
Ataxia [A] *	5/32 (15.62%)
Central nervous system necrosis [A] *	4/32 (12.5%)
Cognitive disturbance [A] *	2/32 (6.25%)
Depressed level of consciousness [A] *	5/32 (15.62%)

	Bevacizumab + Temozolomide
	Affected/At Risk (%)
Dizziness [A] *	3/32 (9.38%)
Headache [A] *	9/32 (28.12%)
Memory impairment [A] *	3/32 (9.38%)
Mood alteration [A] *	2/32 (6.25%)
Neurological disorder NOS [A] *	5/32 (15.62%)
Olfactory nerve disorder [A] *	9/32 (28.12%)
Peripheral motor neuropathy [A] *	3/32 (9.38%)
Peripheral sensory neuropathy [A] *	3/32 (9.38%)
Seizures [A] *	4/32 (12.5%)
Speech disorder [A] *	4/32 (12.5%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	3/32 (9.38%)
Skin and subcutaneous tissue disorders	
Pruritus [A] *	2/32 (6.25%)
Rash [A] *	2/32 (6.25%)
Vascular disorders	
Hypertension [A] *	7/32 (21.88%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request the Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Results Point of Contact:

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