ClinicalTrials.gov
Protocol Registration System

Protocol Registration Receipt
09/06/2013

Grantor: CDER IND/IDE Number: BB-7023 Serial Number: 1596

A Study of Avastin® (Bevacizumab) in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma

This study is ongoing, but not recruiting participants.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00943826

Purpose

This 2 arm study investigated the efficacy and safety of the addition of bevacizumab (Avastin®) to the current standard of care (multimodality therapy of concurrent radiotherapy plus temozolomide followed by adjuvant temozolomide) as compared to the current standard of care alone. Patients were randomly assigned to either the Avastin® (10 mg/kg iv q2w) or the placebo arm, in combination with radiation therapy (total dose 60 Gy, administered as 2 Gy fractions, 5 days/week)plus temozolomide (75 mg/m2 po daily) for 6 weeks. After a 4 week treatment break, patients continued to receive Avastin® (10 mg/kg iv q2w) or placebo, plus temozolomide (150-200 mg/m2 po daily on days 1-5 of each 4 week cycle) for 6 cycles of maintenance treatment. Following the maintenance phase, Avastin® (15 mg/kg iv q3w) or placebo monotherapy was continued. The anticipated time on study treatment was until disease progression/unacceptable

toxicity.

Condition	Intervention	Phase
Glioblastoma	Drug: bevacizumab [Avastin®] Drug: Placebo Drug: temozolomide Radiation: Radiation therapy	Phase 3

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator [Time Frame: Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]] [Designated as safety issue: No]

  PFS was defined as the time from randomization to disease progression or death due to any cause. Disease progression (PD) was assessed by the investigator using adapted Macdonald response criteria (modified World Health Organization (WHO) criteria) based on 3 components: radiological tumor assessments using Magnetic Resonance Imaging (MRI) scans, neurological assessment and changes in corticosteroid use. PD was determined as ≥ 25% increase in the sum of the products of the perpendicular longest diameters of all index lesions (enhancing, measurable) compared with the smallest recorded sum (nadir) during the study or unequivocal progression of existing non-index lesions (non-enhancing and enhancing, non-measurable) or unequivocal appearance of new lesions); or neurological worsening (if corticosteroid dose is stable or increased) with no need for a confirmatory scan. Data from the final analysis is presented.
- Co-Primary: Overall Survival (OS) [Time Frame: Randomization until Overall Survival Event] [Designated as safety issue: No]

  Overall Survival was defined as the time from randomization to death due to any cause.

Secondary Outcome Measures:

- Progression-free Survival (PFS) as Assessed by an Independent Review Facility [Time Frame: Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]] [Designated as safety issue: No]

  An Independent Review Facility reviewed the magnetic resonance imaging (MRI) scans used by the investigator to evaluate radiological tumor response. PFS was defined as the time from randomization to disease progression or death due to any cause.
- Percentage of Participants With One-Year Survival [Time Frame: 1 year] [Designated as safety issue: No]

  Percentage of participants who are still alive 1 year post randomization.
- Percentage of Participants With Two-year Survival [Time Frame: 2 years] [Designated as safety issue: No]

  Percentage of participants who are still alive 2 years post randomization.

- Duration of Stable/Improved Health Related Quality of Life (HRQoL) Using the European Organisation for Research and Treatment of Cancer Scales (EORTC) QLQ-C30 and BN20 [Time Frame: Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]] [Designated as safety issue: No]

  Stable and Improved HRQoL during PFS time was determined using the EORTC QLQ-C30 and BN20 questionnaires. The EORTC QLQ-C30 is a 30-item self-reported questionnaire in 5 functional scales (physical,role,emotional,cognitive,social), 3 symptoms scales, 6 single-item measures and a global health status/QoL scale.Patients rated the items on a 4-point scale: 1=not at all to 4=very much.Global health status/QoL items were rated on a 7-point scale: 1=very poor to 7=excellent. The BN20 consisted of 20 questions in 4 scales(future uncertainty,visual disorder,motor dysfunction,communication deficit) and 7 single-item measures rated on a 4-point scale: 1=not at all to 4=very much. A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100. Stable HRQoL was defined as a change from baseline within 10 points.Improved HRQoL is defined as an increase of at least 10 points for functioning/global health status and a decrease of at least 10 points for symptoms.
- Number of Participants With Adverse Events, Serious Adverse Events and Death [Time Frame: Until data cutoff= 31 March 2012 (up to 34 months)] [Designated as safety issue: No]

  An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events. A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.

Enrollment: 921
Study Start Date: June 2009
Estimated Study Completion Date: April 2014
Primary Completion Date: March 2012

Arms	Assigned Interventions
Experimental: Bevacizumab + RT+Temozolomide In the Concurrent Phase participants received radiotherapy (RT) in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then	Drug: bevacizumab [Avastin®] 10 mg/kg intravenously every 2 weeks in the Concurrent and Maintenance Phases. 15 mg/kg intravenously every 3 weeks in the Monotherapy Phase. Drug: temozolomide 75 mg/m2 once daily for 6 weeks, followed by 150-200 mg/m2 once daily on days 1-5 of each 6 x 4 week cycle.

Arms	Assigned Interventions
entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.	Radiation: Radiation therapy 30 fractions of 2 Gy delivered on days 1-5 per week for 6 weeks
Placebo Comparator: Placebo + RT+ Temozolomide In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.	Drug: Placebo Intravenously every 2 weeks in the Concurrent and Maintenance Phases and every 3 weeks in the Monotherapy Phase. Drug: temozolomide 75 mg/m2 once daily for 6 weeks, followed by 150-200 mg/m2 once daily on days 1-5 of each 6 x 4 week cycle. Radiation: Radiation therapy 30 fractions of 2 Gy delivered on days 1-5 per week for 6 weeks

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- adult patients, >=18 years of age;
- newly diagnosed glioblastoma;
- World Health Organization (WHO) performance status <=2;
- stable or decreasing corticosteroid dose within 5 days prior to randomization.

Exclusion Criteria:

- evidence of recent hemorrhage or postoperative magnetic resonance imaging (MRI) of brain;
- any prior chemotherapy or immunotherapy for glioblastomas and low grade astrocytomas;
- any prior radiotherapy to brain;
- clinically significant cardiovascular disease;
- history of >=grade 2 hemoptysis within 1 month prior to randomization;
- previous centralized screening for Methylguanine-DNA methyltransferase (MGMT) status for enrollment into a clinical trial.

Contacts and Locations

Locations

United States, Alabama

Birmingham, Alabama, United States, 35294

United States, California

Los Angeles, California, United States, 90095

United States, Colorado

Aurora, Colorado, United States, 80045

United States, Florida

Tampa, Florida, United States, 33612-9497

United States, Illinois

Evanston, Illinois, United States, 60201

United States, Michigan

Detroit, Michigan, United States, 48202

United States, North Carolina

Charlottesville, North Carolina, United States, 22903

United States, Ohio

Cincinnati, Ohio, United States, 45220

United States, Tennessee

Nashville, Tennessee, United States, 37203

Australia

Nedlands, Australia, 6009

North Adelaide, Australia, 5006

Parkville, Australia, 3052

Randwick, Australia, 2031

St Leonards, Australia, 2065

St. Leonards, Australia, 2065

Woolloongabba, Australia, 4102

Belgium

Bruxelles, Belgium, 1200

Bruxelles, Belgium, 1070

Edegem, Belgium, 2650

Gent, Belgium, 9000

Liège, Belgium, 4000

Roeselare, Belgium, 8800

Canada, Alberta

Calgary, Alberta, Canada, T2N 4N2

Edmonton, Alberta, Canada, T6G 1Z2

Canada, British Columbia

Vancouver, British Columbia, Canada, V5Z 4E6

Canada, Manitoba

Winnipeg, Manitoba, Canada, R3E 0V9

Canada, Ontario

Hamilton, Ontario, Canada, L8V 5C2

Kingston, Ontario, Canada, K7L 5P9

London, Ontario, Canada, N6A 5A5

Ottawa, Ontario, Canada, K1H 1C4

Toronto, Ontario, Canada, M5G 2M9

Toronto, Ontario, Canada, M4N 3M5

Canada, Quebec

Montreal, Quebec, Canada, H3A 2B4

Montreal, Quebec, Canada, H2L 4M1

Quebec City, Quebec, Canada, G1R 2J6

Canada, Saskatchewan

Saskatoon, Saskatchewan, Canada, S7N 4H4

Denmark

Aalborg, Denmark, 9000

Copenhagen, Denmark, 2100

Odense, Denmark, 5000

France

Bobigny, France, 93009

Bordeaux, France, 33075

Bordeaux, France, 33076

Bron, France, 69677

Clermont Ferrand, France, 63011

Clichy, France, 92118

Dijon, France, 21079

Marseille, France, 13385

Montpellier, France, 34298

Nancy, France, 54000

Paris, France, 75651

Germany

Dresden, Germany, 01307

Giessen, Germany, 35385

Hamburg, Germany, 20246

Heidelberg, Germany, 69120

Mainz, Germany, 55131

Muenchen, Germany, 81377

Velen, Germany, 46342

Greece

Heraklion, Greece, 71110

Larissa, Greece, 41110
Thessaloniki, Greece, 56429

Hong Kong

Hong Kong, Hong Kong
Hong Kong, Hong Kong
Hong Kong, Hong Kong

Hungary

Budapest, Hungary, 1062
Miskolc, Hungary, 3526
Pecs, Hungary, 7624
Szeged, Hungary, 6725

Israel

Haifa, Israel, 31096
Jerusalem, Israel, 91120
Petach Tikva, Israel, 49100
Tel Hashomer, Israel, 52621

Italy

Bologna, Italy, 40139
Forli, Italy, 47023
Milano, Italy, 20133
Terni, Italy, 05100
Torino, Italy, 10126
Treviso, Italy, 31100

Japan

Hiroshima, Japan, 734-8551
Ibaraki, Japan, 305-8576
Kumamoto, Japan, 860-8556
Osaka, Japan, 530-8480
Saitama, Japan, 350-1298
Tokyo, Japan, 104-0045
Tokyo, Japan, 181-8611
Tokyo, Japan, 113-8677

Korea, Republic of

Busan, Korea, Republic of, 602-739

Daegu, Korea, Republic of, 700-721
Goyang-si, Korea, Republic of, 410-769
Hwasun, Korea, Republic of, 519-809
Seoul, Korea, Republic of, 120-752
Seoul, Korea, Republic of, 138-736
Seoul, Korea, Republic of, 110-744
Seoul, Korea, Republic of, 135-170

Netherlands

Amsterdam, Netherlands, 1081 HV
Eindhoven, Netherlands, 5623 EJ
Utrecht, Netherlands, 3584 CX

New Zealand

Auckland, New Zealand, 100
Christchurch, New Zealand
Hamilton, New Zealand

Poland

Bialystok, Poland, 15-027
Bydgoszcz, Poland, 85-796
Lublin, Poland, 20-954

Portugal

Coimbra, Portugal, 3000-075
Lisboa, Portugal, 1099-023
Lisboa, Portugal, 1649-035
Porto, Portugal, 4200-319

Romania

Bucharest, Romania, 022328
Cluj-napoca, Romania, 400015
Targu Mures, Romania, 540142

Russian Federation

Moscow, Russian Federation, 115478
Moscow, Russian Federation, 125047
Moscow, Russian Federation, 105229
St. Petersburg, Russian Federation, 194175

Spain

Barcelona, Spain, 08907
Barcelona, Spain, 08036
Barcelona, Spain, 08916
Madrid, Spain, 28034
Madrid, Spain, 28046
Malaga, Spain, 29010
Valencia, Spain, 46010

Sweden

Göteborg, Sweden, 413 45
Lund, Sweden, 22185
Umea, Sweden, 901 85
Uppsala, Sweden, 751 85

Switzerland

Geneve, Switzerland, 1211

United Kingdom

Birmingham, United Kingdom, B15 2TT
Bristol, United Kingdom, BS1 3NU
London, United Kingdom, SW3 6JJ
Merseyside, United Kingdom, CH63 45Y
Newcastle Upon Tyne, United Kingdom, NE7 7DN
Nottingham, United Kingdom, NG5 1PB
Romford, United Kingdom, RM7 0AG
Sheffield, United Kingdom, S1O 2SJ
Sutton, United Kingdom, SM2 5PT

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO21990
	2008-006146-26
Health Authority:	United States: Food and Drug Administration

Participant Flow

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy (RT) in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression//unacceptable toxicity.

Concurrent Phase

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
STARTED	458	463
Received Randomized Treatment	452	459
COMPLETED	397	421
Not Completed	61	42
Adverse Event	50	27
Withdrew consent	4	8
Refused treatment/Did not cooperate	4	6
Administrative reasons	2	1
Protocol Violation	1	0

Maintenance Phase

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
STARTED	396	370
COMPLETED	353	329
Not Completed	43	41
Adverse Event	31	30
Withdrew consent	4	5
Refused treatment/Did not cooperate	4	3

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Administrative reasons	4	2
Failure to return	0	1

Monotherapy Phase

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
STARTED	269	159
COMPLETED	218	146
Not Completed	51	13
Adverse Event	33	3
Administrative reasons	8	4
Refused treatment/ Did not cooperate	5	2
Withdrew Consent	3	3
Failure to return	2	1

Baseline Characteristics

Analysis Population Description

Intent to treat population included all randomized participants.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Baseline Measures

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomid	Total
Number of Participants	458	463	921
Age, Continuous [units: years] Mean (Full Range)	55.9 (20 to 84)	55.9 (18 to 79)	55.9 (18 to 84)
Gender, Male/Female [units: participants]			

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomid	Total
Female	176	165	341
Male	282	298	580

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator
Measure Description	PFS was defined as the time from randomization to disease progression or death due to any cause. Disease progression (PD) was assessed by the investigator using adapted Macdonald response criteria (modified World Health Organization (WHO) criteria) based on 3 components: radiological tumor assessments using Magnetic Resonance Imaging (MRI) scans, neurological assessment and changes in corticosteroid use. PD was determined as ≥ 25% increase in the sum of the products of the perpendicular longest diameters of all index lesions (enhancing, measurable) compared with the smallest recorded sum (nadir) during the study or unequivocal progression of existing non-index lesions (non-enhancing and enhancing, non-measurable) or unequivocal appearance of new lesions); or neurological worsening (if corticosteroid dose is stable or increased) with no need for a confirmatory scan. Data from the final analysis is presented.
Time Frame	Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]

Safety Issue?	No

Analysis Population Description

Intent to treat population included all randomized participants.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Measured Values

	Bevacizumab + RT+Temozolomide	Placebo + RT+Temozolomide
Number of Participants Analyzed	458	463

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator [units: Months] Median (95% Confidence Interval)	10.6 (10.0 to 11.4)	6.2 (6.0 to 7.5)

Statistical Analysis 1 for Co-Primary: Progression-free Survival (PFS) as Assessed by Investigator

Groups	Bevacizumab + RT+Temozolomide, Placebo + RT+Temozolomide
Method	Log Rank
P-Value	<.0001
Hazard Ratio (HR)	0.64
95% Confidence Interval	0.55 to 0.74

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Stratified by Region and Recursive partitioning analysis (RPA) Class

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

Stratified by Region and RPA Class.

2. Primary Outcome Measure:

Measure Title	Co-Primary: Overall Survival (OS)

Measure Description	Overall Survival was defined as the time from randomization to death due to any cause.
Time Frame	Randomization until Overall Survival Event
Safety Issue?	No

Data Not Posted

Anticipated Posting Date: February 2014

3. Secondary Outcome Measure:

Measure Title	Progression-free Survival (PFS) as Assessed by an Independent Review Facility
Measure Description	An Independent Review Facility reviewed the magnetic resonance imaging (MRI) scans used by the investigator to evaluate radiological tumor response. PFS was defined as the time from randomization to disease progression or death due to any cause.
Time Frame	Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]
Safety Issue?	No

Analysis Population Description

Intent to treat population included all randomized participants.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance

	Description
	Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Measured Values

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Number of Participants Analyzed	458	463
Progression-free Survival (PFS) as Assessed by an Independent Review Facility [units: Months] Median (95% Confidence Interval)	8.4 (7.9 to 9.7)	4.3 (4.1 to 5.1)

Statistical Analysis 1 for Progression-free Survival (PFS) as Assessed by an Independent Review Facility

Groups	Bevacizumab + RT+Temozolomide, Placebo + RT+Temozolomide

Method	Log Rank
P-Value	<.0001
Hazard Ratio (HR)	0.61
95% Confidence Interval	0.53 to 0.71

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Stratified by Region and RPA Class.

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

Stratified by Region and RPA Class.

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With One-Year Survival
Measure Description	Percentage of participants who are still alive 1 year post randomization.
Time Frame	1 year
Safety Issue?	No

Analysis Population Description

Intent to treat participants included all randomized participants.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Measured Values

	Bevacizumab + RT+Temozolomide	Placebo + RT+Temozolomide
Number of Participants Analyzed	458	463
Percentage of Participants With One-Year Survival [units: Percentage of participants]	72	66

5. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Two-year Survival
Measure Description	Percentage of participants who are still alive 2 years post randomization.
Time Frame	2 years
Safety Issue?	No

Data Not Posted

Anticipated Posting Date: February 2014

6. Secondary Outcome Measure:

Measure Title	Duration of Stable/Improved Health Related Quality of Life (HRQoL) Using the European Organisation for Research and Treatment of Cancer Scales (EORTC) QLQ-C30 and BN20
Measure Description	Stable and Improved HRQoL during PFS time was determined using the EORTC QLQ-C30 and BN20 questionnaires. The EORTC QLQ-C30 is a 30-item self-reported questionnaire in 5 functional scales (physical,role,emotional,cognitive,social), 3 symptoms scales, 6 single-item measures and a global health status/QoL scale.Patients rated the items on a 4-point scale: 1=not at all to 4=very much.Global health status/QoL items were rated on a 7-point scale: 1=very poor to 7=excellent. The BN20 consisted of 20 questions in 4 scales(future uncertainty,visual disorder,motor dysfunction,communication deficit) and 7 single-item measures rated on a 4-point scale: 1=not at all to 4=very much. A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100. Stable HRQoL was defined as a change from baseline within 10 points.Improved HRQoL is defined as an increase of at least 10 points for functioning/global health

	status and a decrease of at least 10 points for symptoms.
Time Frame	Randomization until Progressive Free Survival Event [Until data cutoff= 31 March 2012 (up to 34 months)]
Safety Issue?	No

Analysis Population Description

Intent to treat population included all randomized participants.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Measured Values

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Number of Participants Analyzed	458	463
Duration of Stable/Improved Health Related Quality of Life (HRQoL) Using the European Organisation for Research and Treatment of Cancer Scales (EORTC) QLQ-C30 and BN20 [units: Months] Median (Full Range)		
Global health status	8 (0 to 26)	4 (1 to 29)
Physical functioning	7 (0 to 27)	5 (1 to 29)
Social functioning	8 (0 to 26)	4 (0 to 27)
Motor dysfunction	7 (1 to 27)	4 (0 to 26)
Communication deficit	8 (0 to 27)	4 (1 to 24)

7. Secondary Outcome Measure:

Measure Title	Number of Participants With Adverse Events, Serious Adverse Events and Death
Measure Description	An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events. A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of

	existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.
Time Frame	Until data cutoff= 31 March 2012 (up to 34 months)
Safety Issue?	No

Analysis Population Description

Safety Population included all randomized participants who received study treatment during the study treatment period. Twelve of the patients randomized to the Placebo + RT + Temozolomide arm received at least one dose of bevacizumab and were added to the Bevacizumab + RT + Temozolomide arm for Safety.

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every

	Description
	3 weeks until disease progression/unacceptable toxicity.

Measured Values

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Number of Participants Analyzed	464	447
Number of Participants With Adverse Events, Serious Adverse Events and Death [units: Participants]		
Adverse Events	455	428
Serious Adverse Events	170	115
Death	258	253

Reported Adverse Events

Reporting Groups

	Description
Bevacizumab + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and bevacizumab 10 mg/kg intravenous (IV) every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of bevacizumab 10 mg/kg IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the

	Description
	Monotherapy Phase where they received bevacizumab 15 mg/kg IV every 3 weeks until disease progression/unacceptable toxicity.
Placebo + RT+Temozolomide	In the Concurrent Phase participants received radiotherapy in daily fractions of 2 Gy given 5 days per week for 6 week and temozolomide 75 mg/m^2 daily for a maximum of 49 days and placebo IV every 2 weeks for 6 weeks. There was a 4 week treatment break. Participants then entered the Maintenance Phase where they received six 28-day cycle of placebo IV every 2 weeks and temozolomide 150 to 200 mg/m^2 daily in the first 5 days of each cycle. The participants then entered the Monotherapy Phase where they received placebo IV every 3 weeks until disease progression/unacceptable toxicity.

Additional Description

Safety Population included all randomized participants who received study treatment during the study treatment period. Twelve of the patients randomized to the Placebo + RT + Temozolomide arm received at least one dose of bevacizumab and were added to the Bevacizumab + RT + Temozolomide arm for Safety.

Serious Adverse Events

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Total # participants affected/at risk	170/464 (36.64%)	115/447 (25.73%)
Blood and lymphatic system disorders		
Anaemia † [A]		
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Eosinophilia †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Febrile bone marrow aplasia †[A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Febrile neutropenia †[A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Leukopenia †[A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		
Neutropenia †[A]		
# participants affected/at risk	4/464 (0.86%)	2/447 (0.45%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Pancytopenia †[A]		
# participants affected/at risk	5/464 (1.08%)	1/447 (0.22%)
# events		
Thrombocytopenia †[A]		
# participants affected/at risk	17/464 (3.66%)	8/447 (1.79%)
# events		
Thrombotic microangiopathy †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cardiac disorders		
Angina pectoris †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Atrial fibrillation †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Cardiac arrest †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cardiac failure congestive †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cardio-respiratory arrest †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Cardiovascular disorder †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Coronary artery stenosis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Myocardial infarction †[A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)
# events		
Myocardial ischaemia † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Tachyarrhythmia † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Ear and labyrinth disorders		
Vertigo † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Vertigo positional † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Endocrine disorders		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Diabetes insipidus †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Eye disorders		
Vision blurred †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Gastrointestinal disorders		
Abdominal pain †[A]		
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)
# events		
Anal prolapse †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Colitis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Diarrhoea †[A]		
# participants affected/at risk	2/464 (0.43%)	1/447 (0.22%)
# events		
Dyspepsia †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Faecaloma †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Gastrointestinal haemorrhage †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Gastrooesophageal reflux disease †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Haematemesis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Intestinal perforation † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Large intestine perforation † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Nausea † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Oesophageal ulcer † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Pancreatitis † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Rectal perforation †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Stomatitis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Subileus †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Vomiting †[A]		
# participants affected/at risk	5/464 (1.08%)	5/447 (1.12%)
# events		
General disorders		
Cyst †[A]		
# participants affected/at	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Death †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Fatigue †[A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		
General physical health deterioration †[A]		
# participants affected/at risk	3/464 (0.65%)	2/447 (0.45%)
# events		
Impaired healing †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Pyrexia †[A]		
# participants affected/at risk	8/464 (1.72%)	3/447 (0.67%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Hepatobiliary disorders		
Cholangitis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cholecystitis †[A]		
# participants affected/at risk	2/464 (0.43%)	0/447 (0%)
# events		
Cholelithiasis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Hepatic function abnormal †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Hepatotoxicity †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Hyperbilirubinaemia † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Infections and infestations		
Abscess † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Acute tonsillitis † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Anal abscess † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Bacteraemia † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Brain abscess † [A]		
# participants affected/at risk	1/464 (0.22%)	2/447 (0.45%)
# events		
Bronchopneumonia † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Cellulitis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Central nervous system abscess † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cytomegalovirus infection † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Diverticulitis †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Encephalitis herpes †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Erysipelas †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Gastroenteritis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Gastroenteritis viral †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Graft infection †[A]		
# participants affected/at	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Helicobacter infection † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Hepatitis B † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Herpes simplex † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Herpes zoster † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Infection † [A]		
# participants affected/at risk	2/464 (0.43%)	0/447 (0%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Infectious pleural effusion † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Lobar pneumonia † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Lower respiratory tract infection † [A]		
# participants affected/at risk	0/464 (0%)	3/447 (0.67%)
# events		
Lung infection † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Meningitis † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Neutropenic sepsis † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Oesophageal candidiasis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Oral fungal infection † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Parotitis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Pneumocystis jiroveci pneumonia † [A]		
# participants affected/at risk	1/464 (0.22%)	2/447 (0.45%)
# events		
Pneumonia † [A]		
# participants affected/at	10/464	6/447 (1.34%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk	(2.16%)	
# events		
Pneumonia respiratory syncytial viral † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Post procedural infection † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Postoperative wound infection † [A]		
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)
# events		
Respiratory tract infection † [A]		
# participants affected/at risk	1/464 (0.22%)	2/447 (0.45%)
# events		
Sepsis † [A]		
# participants affected/at	6/464 (1.29%)	1/447 (0.22%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Septic shock † [A]		
# participants affected/at risk	2/464 (0.43%)	1/447 (0.22%)
# events		
Sinusitis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Streptococcal sepsis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Upper respiratory tract infection † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Urinary tract infection † [A]		
# participants affected/at risk	1/464 (0.22%)	3/447 (0.67%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Urosepsis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Viral infection † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Wound infection † [A]		
# participants affected/at risk	2/464 (0.43%)	0/447 (0%)
# events		
Wound infection staphylococcal † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Injury, poisoning and procedural complications		
Fall † [A]		
# participants affected/at	1/464 (0.22%)	0/447 (0%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Femur fracture † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Head injury † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Incision site haemorrhage † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Lumbar vertebral fracture † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Post procedural complication † [A]		
# participants affected/at	0/464 (0%)	1/447 (0.22%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Radiation necrosis † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Spinal compression fracture † [A]		
# participants affected/at risk	1/464 (0.22%)	2/447 (0.45%)
# events		
Spinal fracture † [A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		
Toxicity to various agents † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Wound complication † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Wound dehiscence † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Wound secretion † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Wrist fracture † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Investigations		
Troponin increased † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Metabolism and nutrition disorders		
Decreased appetite † [A]		
# participants affected/at	0/464 (0%)	3/447 (0.67%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk		
# events		
Dehydration † [A]		
# participants affected/at risk	2/464 (0.43%)	3/447 (0.67%)
# events		
Diabetes mellitus † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Hyperglycaemia † [A]		
# participants affected/at risk	1/464 (0.22%)	5/447 (1.12%)
# events		
Hypoalbuminaemia † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Musculoskeletal and connective tissue disorders		
Back pain † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Muscular weakness †[A]		
# participants affected/at risk	2/464 (0.43%)	0/447 (0%)
# events		
Musculoskeletal chest pain †[A]		
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)
# events		
Myopathy †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Synovial cyst †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
and polyps)		
Bladder cancer † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Intracranial tumour haemorrhage † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Prostate cancer † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Thyroid adenoma † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Tumour haemorrhage † [A]		
# participants affected/at risk	3/464 (0.65%)	1/447 (0.22%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Nervous system disorders		
Balance disorder † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Basal ganglia stroke † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Brain oedema † [A]		
# participants affected/at risk	2/464 (0.43%)	4/447 (0.89%)
# events		
Cerebral haemorrhage † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Cerebral ischaemia † [A]		
# participants affected/at risk	3/464 (0.65%)	2/447 (0.45%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Cerebral thrombosis † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Cerebrovascular accident † [A]		
# participants affected/at risk	6/464 (1.29%)	2/447 (0.45%)
# events		
Convulsion † [A]		
# participants affected/at risk	5/464 (1.08%)	6/447 (1.34%)
# events		
Dizziness † [A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		
Encephalitis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Encephalopathy † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Epilepsy † [A]		
# participants affected/at risk	3/464 (0.65%)	2/447 (0.45%)
# events		
Grand mal convulsion † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Haemorrhage intracranial † [A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		
Haemorrhagic stroke † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Headache † [A]		
# participants affected/at risk	4/464 (0.86%)	2/447 (0.45%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Hemiparesis † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Hydrocephalus † [A]		
# participants affected/at risk	2/464 (0.43%)	0/447 (0%)
# events		
Intracranial pressure increased † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Ischaemic stroke † [A]		
# participants affected/at risk	2/464 (0.43%)	1/447 (0.22%)
# events		
Leukoencephalopathy † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Nervous system disorder † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Neurological decompensation † [A]		
# participants affected/at risk	1/464 (0.22%)	1/447 (0.22%)
# events		
Paraesthesia † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Partial seizures † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Pyramidal tract syndrome † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Somnolence †[A]		
# participants affected/at risk	3/464 (0.65%)	0/447 (0%)
# events		
Speech disorder †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Syncope †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Psychiatric disorders		
Acute psychosis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Anxiety †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Confusional state †[A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Delirium † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Delirium tremens † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Mania † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Renal and urinary disorders		
Nephrolithiasis † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Nephrotic syndrome † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Proteinuria †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Renal failure acute †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Urinary retention †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Reproductive system and breast disorders		
Scrotal cyst †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Respiratory, thoracic and		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
mediastinal disorders		
Acute respiratory distress syndrome †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Aspiration †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Chronic obstructive pulmonary disease †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Epistaxis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Lung disorder †[A]		
# participants affected/at risk	2/464 (0.43%)	1/447 (0.22%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Pleural effusion †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Pulmonary embolism †[A]		
# participants affected/at risk	13/464 (2.8%)	12/447 (2.68%)
# events		
Sleep apnoea syndrome †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Skin and subcutaneous tissue disorders		
Drug eruption †[A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Rash †[A]		
# participants affected/at risk	2/464 (0.43%)	1/447 (0.22%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Skin ulcer † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Toxic skin eruption † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Vascular disorders		
Deep vein thrombosis † [A]		
# participants affected/at risk	11/464 (2.37%)	6/447 (1.34%)
# events		
Embolism † [A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Embolism venous † [A]		
# participants affected/at risk	0/464 (0%)	1/447 (0.22%)
# events		
Hypertension † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	3/464 (0.65%)	1/447 (0.22%)
# events		
Peripheral arterial occlusive disease †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Thrombophlebitis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Thrombosis †[A]		
# participants affected/at risk	1/464 (0.22%)	0/447 (0%)
# events		
Venous thrombosis †[A]		
# participants affected/at risk	0/464 (0%)	2/447 (0.45%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (15.0)

Other Adverse Events

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

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Total # participants affected/at risk	438/464 (94.4%)	409/447 (91.5%)
Blood and lymphatic system disorders		
Anaemia †[A]		
# participants affected/at risk	27/464 (5.82%)	33/447 (7.38%)
# events		
Leukopenia †[A]		
# participants affected/at risk	55/464 (11.85%)	39/447 (8.72%)
# events		
Lymphopenia †[A]		
# participants affected/at risk	33/464 (7.11%)	37/447 (8.28%)
# events		
Neutropenia †[A]		
# participants affected/at risk	66/464 (14.22%)	52/447 (11.63%)
# events		
Thrombocytopenia †[A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	145/464 (31.25%)	119/447 (26.62%)
# events		
Gastrointestinal disorders		
Abdominal pain †[A]		
# participants affected/at risk	32/464 (6.9%)	15/447 (3.36%)
# events		
Abdominal pain upper †[A]		
# participants affected/at risk	35/464 (7.54%)	11/447 (2.46%)
# events		
Constipation †[A]		
# participants affected/at risk	177/464 (38.15%)	136/447 (30.43%)
# events		
Diarrhoea †[A]		
# participants affected/at risk	91/464 (19.61%)	70/447 (15.66%)
# events		
Dyspepsia †[A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	32/464 (6.9%)	15/447 (3.36%)
# events		
Gingival bleeding †[A]		
# participants affected/at risk	32/464 (6.9%)	6/447 (1.34%)
# events		
Nausea †[A]		
# participants affected/at risk	221/464 (47.63%)	190/447 (42.51%)
# events		
Vomiting †[A]		
# participants affected/at risk	139/464 (29.96%)	99/447 (22.15%)
# events		
General disorders		
Asthenia †[A]		
# participants affected/at risk	80/464 (17.24%)	63/447 (14.09%)
# events		
Fatigue †[A]		
# participants affected/at	189/464	179/447

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk	(40.73%)	(40.04%)
# events		
Oedema peripheral †[A]		
# participants affected/at risk	34/464 (7.33%)	33/447 (7.38%)
# events		
Pyrexia †[A]		
# participants affected/at risk	37/464 (7.97%)	25/447 (5.59%)
# events		
Infections and infestations		
Nasopharyngitis †[A]		
# participants affected/at risk	60/464 (12.93%)	26/447 (5.82%)
# events		
Upper respiratory tract infection †[A]		
# participants affected/at risk	30/464 (6.47%)	12/447 (2.68%)
# events		
Urinary tract infection †[A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	43/464 (9.27%)	25/447 (5.59%)
# events		
Injury, poisoning and procedural complications		
Radiation skin injury † [A]		
# participants affected/at risk	39/464 (8.41%)	41/447 (9.17%)
# events		
Investigations		
Alanine aminotransferase increased † [A]		
# participants affected/at risk	22/464 (4.74%)	25/447 (5.59%)
# events		
Weight decreased † [A]		
# participants affected/at risk	35/464 (7.54%)	18/447 (4.03%)
# events		
Metabolism and nutrition disorders		
Decreased appetite † [A]		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# participants affected/at risk	114/464 (24.57%)	73/447 (16.33%)
# events		
Musculoskeletal and connective tissue disorders		
Arthralgia †[A]		
# participants affected/at risk	68/464 (14.66%)	27/447 (6.04%)
# events		
Back pain †[A]		
# participants affected/at risk	36/464 (7.76%)	27/447 (6.04%)
# events		
Muscular weakness †[A]		
# participants affected/at risk	28/464 (6.03%)	33/447 (7.38%)
# events		
Musculoskeletal pain †[A]		
# participants affected/at risk	38/464 (8.19%)	11/447 (2.46%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Myalgia †[A]		
# participants affected/at risk	28/464 (6.03%)	11/447 (2.46%)
# events		
Pain in extremity †[A]		
# participants affected/at risk	47/464 (10.13%)	22/447 (4.92%)
# events		
Nervous system disorders		
Convulsion †[A]		
# participants affected/at risk	35/464 (7.54%)	36/447 (8.05%)
# events		
Dizziness †[A]		
# participants affected/at risk	46/464 (9.91%)	52/447 (11.63%)
# events		
Dysgeusia †[A]		
# participants affected/at risk	39/464 (8.41%)	33/447 (7.38%)
# events		

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
Headache †[A]		
# participants affected/at risk	168/464 (36.21%)	126/447 (28.19%)
# events		
Psychiatric disorders		
Anxiety †[A]		
# participants affected/at risk	29/464 (6.25%)	25/447 (5.59%)
# events		
Depression †[A]		
# participants affected/at risk	41/464 (8.84%)	28/447 (6.26%)
# events		
Insomnia †[A]		
# participants affected/at risk	52/464 (11.21%)	40/447 (8.95%)
# events		
Renal and urinary disorders		
Proteinuria †[A]		
# participants affected/at risk	65/464 (14.01%)	18/447 (4.03%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Respiratory, thoracic and mediastinal disorders		
Cough †[A]		
# participants affected/at risk	54/464 (11.64%)	39/447 (8.72%)
# events		
Dysphonia †[A]		
# participants affected/at risk	40/464 (8.62%)	7/447 (1.57%)
# events		
Dyspnoea †[A]		
# participants affected/at risk	25/464 (5.39%)	16/447 (3.58%)
# events		
Epistaxis †[A]		
# participants affected/at risk	94/464 (20.26%)	20/447 (4.47%)
# events		
Oropharyngeal pain †[A]		
# participants affected/at risk	28/464 (6.03%)	11/447 (2.46%)

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
# events		
Skin and subcutaneous tissue disorders		
Alopecia †[A]		
# participants affected/at risk	178/464 (38.36%)	158/447 (35.35%)
# events		
Dry skin †[A]		
# participants affected/at risk	34/464 (7.33%)	23/447 (5.15%)
# events		
Pruritus †[A]		
# participants affected/at risk	55/464 (11.85%)	35/447 (7.83%)
# events		
Rash †[A]		
# participants affected/at risk	74/464 (15.95%)	59/447 (13.2%)
# events		
Vascular disorders		
Hypertension †[A]		
# participants affected/at	168/464	51/447

	Bevacizumab + RT+Temozolomid	Placebo + RT+Temozolomide
risk	(36.21%)	(11.41%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA (15.0)

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 that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: Medical Communications

Organization: Hoffman-LaRoche or Genentech, Inc.

Phone: 800-821-8590

Email: