CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125085Orig1s319

Trade Name:	AVASTIN
Generic or Proper Name:	bevacizumab
Sponsor:	Genentech, Inc.
Approval Date:	December 5, 2017
Indication:	AVASTIN is a vascular endothelial growth factor directed antibody indicated for the treatment of: • Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. • Metastatic colorectal cancer, in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer. • Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and

paclitaxel for the first-line treatment.

- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is:
    - platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan
    - platinum-sensitive in combination with carboplatin and paclitaxel or carboplatin and gemcitabine followed by Avastin as a single agent.

CENTER FOR DRUG EVALUATION AND RESEARCH

125085Orig1s319

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125085/S-319

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Genentech, Inc.
Attention: Kimberly Smith
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Smith:

Please refer to your supplemental Biologics License Application (sBLA) dated February 1, 2017, received February 1, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Avastin (bevacizumab) injection for intravenous use.

This Prior Approval supplemental biologics application provides for modifications to the indication approved under the provisions of 21 CFR 601.41 on May 5, 2009, for the treatment of adult patients with recurrent glioblastoma removing the following language (italicized) *Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.* In addition, the WARNINGS AND PRECAUTIONS section of the package insert was revised to add a new Warning subsection for congestive heart failure and the package insert was revised to comply with current regulations and guidances.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text, and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

SUBPART E FULFILLED

We approved BLA 125085/S-169 on May 5, 2009, under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this current supplement fulfills the postmarketing requirement (PMR #2680-1) required under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

Approval of this supplement fulfills the following postmarketing requirement listed in the May 5, 2009, approval letter for BLA 125085/S-169:

2680-1 To submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling based on the results of study AVF4396g/BO20990 entitled "A Randomized, Double Blind, Placebo Controlled,

Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma," which was accepted under a Request for Special Protocol Assessment on December 29, 2008.

You are no longer required to report on this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab) injection, for intravenous use
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Gastrointestinal Perforations: Discontinue for gastrointestinal perforation. (5.1)**
- **Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery and until the wound is fully healed. (5.2)**
- **Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Recurrent Glioblastoma (1.3)	12/2017
Dosage and Administration, Recurrent Glioblastoma (2.4)	12/2017
Warnings and Precautions, Congestive Heart Failure (5.12)	12/2017

----------INDICATIONS AND USAGE----------

Avastin is a vascular endothelial growth factor directed antibody indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is:
  - platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan
  - platinum-sensitive in combination with carboplatin and paclitaxel or carboplatin and gemcitabine followed by Avastin as a single agent (1.6)

----------DOSAGE AND ADMINISTRATION----------

Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
Metastatic colorectal cancer (2.2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen

First-Line Non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell cancer (2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Administer as an intravenous infusion. (2.8)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/4 mL or 400 mg/16 mL, single dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Perforation or Fistula: Discontinue for tracheoesophageal fistula, grade 4 fistula, or necrotizing fasciitis. (5.1)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion Reactions: Decrease rate for infusion reactions. Discontinue for severe infusion reactions and administer medical therapy. (5.9)
- Embryo-fetal Toxicity: Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue if CHF (5.12).

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breast feed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations: The incidence of gastrointestinal perforation, some fatal, in patients receiving Avastin ranges from 0.3% to 3%. Discontinue Avastin in patients who develop gastrointestinal perforation *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in patients receiving Avastin. Discontinue Avastin in patients who develop wound healing complications that require medical intervention. Withhold Avastin at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhages: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occur up to 5-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with a recent history of hemoptysis. Discontinue in patients who develop Grade 3-4 hemorrhage *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer.

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

Avastin, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer.

1.3 Recurrent Glioblastoma (GBM)

Avastin is indicated for the treatment of recurrent glioblastoma in adults.

1.4 Metastatic Renal Cell Carcinoma (mRCC)

Avastin, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.

1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

1.6 Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Do not administer Avastin until at least 28 days following surgery and the wound is fully healed.

2.2 Metastatic Colorectal Cancer (mCRC)

The recommended dose when Avastin is administered in combination with intravenous 5-fluorouracil-based chemotherapy is:

- 5 mg/kg every 2 weeks intravenously in combination with bolus-IFL.
- 10 mg/kg every 2 weeks intravenously in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line Avastin-containing regimen.

2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

The recommended dose is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

2.4 Recurrent Glioblastoma (GBM)

The recommended dose is 10 mg/kg intravenously every 2 weeks.

2.5 Metastatic Renal Cell Carcinoma (mRCC)

The recommended dose is 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dose of Avastin is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

2.7 Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Platinum Resistant

The recommended dose is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dose is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive
The recommended dose is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dose is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

2.8 Dose Modifications for Adverse Reactions
Table 1 describes dose modifications for specific adverse reactions *[see Warnings and Precautions (5)]*. No dose reductions for Avastin are recommended.

Table 1: Dose Modifications for Adverse Reactions

Adverse Reaction	**Severity**	**Dose Modification**
Gastrointestinal Perforation and fistulae *[see Warnings and Precautions (5.1)]*.	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Avastin
Wound Healing Complications *[see Warnings and Precautions (5.2)]*.	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue Avastin
Hemorrhage *[see Warnings and Precautions (5.3)]*.	• Grade 3 or 4	Discontinue Avastin
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Avastin
Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*.	• Arterial thromboembolism, severe	Discontinue Avastin
	• Venous thromboembolism, Grade 4	Discontinue Avastin
Hypertension *[see Warnings and Precautions (5.6)]*.	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Avastin
	• Hypertension, severe	Withhold Avastin if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*.	• Any	Discontinue Avastin
Renal Toxicity and Proteinuria *[see Warnings and Precautions (5.8)]*.	• Nephrotic syndrome	Discontinue Avastin
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Avastin until proteinuria less than 2 grams per 24 hours

Adverse Reaction	Severity	Dose Modification
Infusion Reaction *[see Warnings and Precautions (5.10)]*.	• Severe infusion reaction	Discontinue Avastin
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.	Any	Discontinue Avastin

2.9 Preparation and Administration

Administration

- Administer as an intravenous infusion.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated. Administer all subsequent infusions over 30 minutes if second infusion over 60 minutes is tolerated.

Preparation

- Use appropriate aseptic technique.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2–8°C (36–46°F) for up to 8 hours.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) as a clear to slightly opalescent, colorless to pale brown solution in single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious and sometimes fatal gastrointestinal perforation occur at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose.

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occur at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the

first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ *[see Adverse Reactions (6.1)]*.

5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

Discontinue Avastin in patients with wound healing complications requiring medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following surgery and until the wound is fully healed.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue in patients who develop necrotizing fasciitis *[see Adverse Reactions (6.3)]*.

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhage. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grade 3-4 hemorrhage.

5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤ 2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or greater than 65 years old *[see Use in Specific Populations (8.5)]*.

Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

5.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) was observed across clinical studies. In Study GOG-0240, Grade 3-4 VTE was reported in 11% of patients receiving Avastin with chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grade 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism *[see Adverse Reactions (6.1)]*.

5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grade 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.7 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

5.8 Renal Injury and Proteinuria

The incidence and severity of proteinuria is higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4

proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grade 2-4 proteinuria.

Nephrotic syndrome occurred in < 1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)].

5.9 Infusion Reactions

Infusion reactions reported across clinical studies and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.2% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion reactions. Interrupt the infusion in patients with clinically significant infusion reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

5.10 Embryo-Fetal Toxicity

Avastin may cause fetal harm based on its mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR 2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are

unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone. Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12).]*.

6.1 Clinical Trial Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with chemotherapy at a rate > 10%, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

The safety data below reflect exposure to Avastin in 2919 patients with mCRC, non-squamous NSCLC, glioblastoma, mRCC, cervical cancer, platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, including controlled studies

(AVF2107g, E3200, E4599, EORTC 26101, BO17705, GOG-0240, MO22224, AVF4095, GOG-0213) at the recommended dose and schedule for a median of 6 to 23 doses.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

Platinum-Resistant Recurrent Epithelia Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or chemotherapy alone in patients with platinum resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum based therapy. Patients were randomized to receive Avastin (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks). Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 2.

Table 2: Grade 2−4 Adverse Reactions Occurring at Higher Incidence (≥5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224

Adverse Reaction[a]	Avastin with Chemotherapy (N=179)	Chemotherapy (N=181)
Blood and lymphatic system disorders		
Neutropenia	31%	25%
General disorders		
Mucosal inflammation	13%	6%
Infections		
Infection	11%	4%
Nervous system disorders		
Peripheral sensory neuropathy	18%	7%
Renal and urinary disorders		
Proteinuria	12%	0.6%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	5%	0%
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia	11%	5%
Vascular disorders		
Hypertension	19%	6%

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Grade 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian,

fallopian tube or primary peritoneal cancer. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 3.

Table 3: Grade 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g

Adverse Reaction[a]	Avastin with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
Blood and lymphatic system disorders		
Thrombocytopenia	58%	51%
Gastrointestinal disorders		
Nausea	72%	66%
Diarrhea	38%	29%
Stomatitis	15%	7%
Hemorrhoids	8%	3%
Gingival bleeding	7%	0%
General disorders		
Fatigue	82%	75%
Mucosal inflammation	15%	10%
Infections		
Sinusitis	15%	9%
Injury and procedural complications		
Contusion	17%	9%
Musculoskeletal and connective tissue disorders		
Arthralgia	28%	19%
Back pain	21%	13%
Nervous system disorders		
Headache	49%	30%
Dizziness	23%	17%
Psychiatric disorders		
Insomnia	21%	15%
Renal and urinary disorders		
Proteinuria	20%	3%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	55%	14%
Dyspnea	30%	24%
Cough	26%	18%
Oropharyngeal pain	16%	10%
Dysphonia	13%	3%
Rhinorrhea	10%	4%
Sinus congestion	8%	2%

Adverse Reaction[a]	Avastin with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
Vascular disorders		
Hypertension	42%	9%

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Grade 3–4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%).

The safety of Avastin was evaluated in an open-label, controlled study, GOG-0213, in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 4.

Table 4: Grade 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Gastrointestinal disorders		
Diarrhea	39%	32%
Abdominal pain	33%	28%
Vomiting	33%	25%
Stomatitis	33%	16%
Metabolism and nutrition disorders		
Decreased appetite	35%	25%
Hyperglycemia	31%	24%
Hypomagnesemia	27%	17%
Hyponatremia	17%	6%
Weight decreased	15%	4%
Hypocalcemia	12%	5%
Hypoalbuminemia	11%	6%
Hyperkalemia	9%	3%
Musculoskeletal and connective tissue disorders		
Arthralgia	45%	30%
Myalgia	29%	18%
Pain in extremity	25%	14%
Back pain	17%	10%
Muscular weakness	13%	8%
Neck pain	9%	0%

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	33%	2%
Dyspnea	30%	25%
Cough	30%	17%
Rhinitis allergic	17%	4%
Nasal mucosal disorder	14%	3%
Nervous system disorders		
Headache	38%	20%
Dysarthria	14%	2%
Dizziness	13%	8%
Hepatic Disorders		
Aspartate aminotransferase increased	15%	9%
Skin and subcutaneous tissue disorders		
Exfoliative rash	23%	16%
Nail disorder	10%	2%
Dry skin	7%	2%
Vascular disorders		
Hypertension	42%	3%
Renal and urinary disorders		
Proteinuria	17%	1%
Blood creatinine increased	13%	5%
General disorders		
Chest pain	8%	2%
Infections		
Sinusitis	7%	2%

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Grade 3–4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).

Metastatic Renal Cell Carcinoma (mRCC)

The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with metastatic renal cell carcinoma. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grade 3-5 adverse reactions occurring at a higher incidence (>2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 5.

Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705

Adverse Reaction[a]	Avastin with Interferon Alfa (N=337)	Placebo with Interferon Alfa (N=304)
Gastrointestinal disorders		
Diarrhea	21%	16%
General disorders and administration site conditions		
Fatigue	33%	27%
Metabolism and nutrition disorders		
Decreased appetite	36%	31%
Weight decreased	20%	15%
Musculoskeletal and connective tissue disorders		
Myalgia	19%	14%
Back pain	12%	6%
Nervous system disorders		
Headache	24%	16%
Renal and urinary disorders		
Proteinuria	20%	3%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	27%	4%
Dysphonia	5%	0%
Vascular disorders		
Hypertension	28%	9%

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The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 6.

Table 6: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240

Adverse Reaction[a]	Avastin with Chemotherapy (N=218)	Chemotherapy (N=222)
Metabolism and nutrition disorders		
Decreased appetite	34%	26%
Hyperglycemia	26%	19%
Hypomagnesemia	24%	15%
Weight Decreased	21%	7%
Hyponatremia	19%	10%
Hypoalbuminemia	16%	11%
General disorders		
Fatigue	80%	75%
Edema Peripheral	15%	22%
Infections and infestations		
Urinary Tract Infection	22%	14%
Infection	10%	5%
Vascular disorders		
Hypertension	29%	6%
Thrombosis	10%	3%
Nervous system disorders		
Headache	22%	13%
Dysarthria	8%	1%
Gastrointestinal disorders		
Stomatitis	15%	10%
Proctalgia	6%	1%
Anal fistula	6%	0.0%
Blood and lymphatic system disorders		
Neutropenia	12%	6%
Lymphopenia	12%	5%
Psychiatric disorders		
Anxiety	17%	10%
Reproductive system and breast disorders		
Pelvic pain	14%	8%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	17%	1%
Renal and urinary disorders		
Blood Creatinine Increased	16%	10%
Proteinuria	10%	3%

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Grade 3–4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving Avastin with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%).

Metastatic Colorectal Cancer (mCRC)
The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus IFL in patients with mCRC. Patients were randomized (1:1:1) to placebo with bolus IFL, Avastin with bolus IFL, or Avastin with 5 fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population.

All Grade 3–4 adverse reactions and selected Grade 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 7.

Table 7: Grade 3–4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g

Adverse Reaction[a]	Avastin with IFL (N=392)	Placebo with IFL (N=396)
General disorders		
Asthenia	10%	7%
Pain	8%	5%
Vascular disorders		
Hypertension	12%	2%
Deep Vein Thrombosis	9%	5%
Intra-Abdominal Thrombosis	3%	1%
Syncope	3%	1%
Gastrointestinal disorders		
Diarrhea	34%	25%
Abdominal Pain	8%	5%
Constipation	4%	2%
Blood and lymphatic disorders		
Leukopenia	37%	31%
Neutropenia	21%	14%

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The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200). Patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic colorectal cancer. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population. The most frequent adverse reactions (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic) occurring at a higher incidence (≥2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms.

First-Line Non Squamous Non Small Cell Lung Cancer (NSCLC)
The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599). Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21 day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The demographics of the safety population were similar to the demographics of the efficacy population.

Only Grade 3-5 non hematologic and Grade 4-5 hematologic adverse reactions were collected. Grade 3-5 non hematologic and Grade 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma
EORTC 26101 was a multicenter, randomized, open-label study in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2323) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-bevacizumab antibodies is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis
Cardiovascular: Pulmonary hypertension, Mesenteric venous occlusion
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation

7 DRUG INTERACTIONS

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Avastin may cause fetal harm based on findings from animal studies and its mechanism of action. *[see Clinical Pharmacology (12.1)]*. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *[see Data]*. Furthermore, animal models link angiogenesis and VEGF and VEGFR-2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included:

reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, advise women not to breastfeed during treatment with Avastin and for 6 months following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Avastin may cause fetal harm when administered to a pregnant woman. *[see Use in Specific Populations (8.1).*] Advise female of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin.

Infertility

Females

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients. *[see Warnings and Precautions (5.11), Adverse Reactions (6.1*).]

8.4 Pediatric Use

The safety and effectiveness of Avastin in pediatric patients have not been established. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed glioblastoma receiving bevacizumab and irinotecan.

Animal Data

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In an exploratory, pooled analysis of 1745 patients from five randomized, controlled studies, 35% patients were ≥65 years old. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy

alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥ 65 years (8% vs. 3%) as compared to patients < 65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

No information is available concerning Avastin overdosage.

11 DESCRIPTION

Bevacizumab is vascular endothelial growth factor directed antibody. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Avastin (bevacizumab) Injection for intravenous use is a sterile, clear to slightly opalescent, colorless to pale brown solution. Avastin is supplied in 100 mg and 400 mg preservative-free, single-dose vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL).

The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP.

The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 (10^{th}, 90^{th} percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

Distribution

The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

Elimination
The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

Specific Populations
The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden. Based on data in specific populations, no dose adjustments for Avastin are needed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer (mCRC)

Study AVF2107g
In a double-blind, active-controlled study [AVF2107g (NCT00109070)], 923 patients were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2, 5-fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), Avastin (5 mg/kg every 2 weeks) with bolus-IFL, or Avastin (5 mg/kg every 2 weeks) with 5-fluorouracil and leucovorin. Enrollment to the Avastin with 5-fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Avastin was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

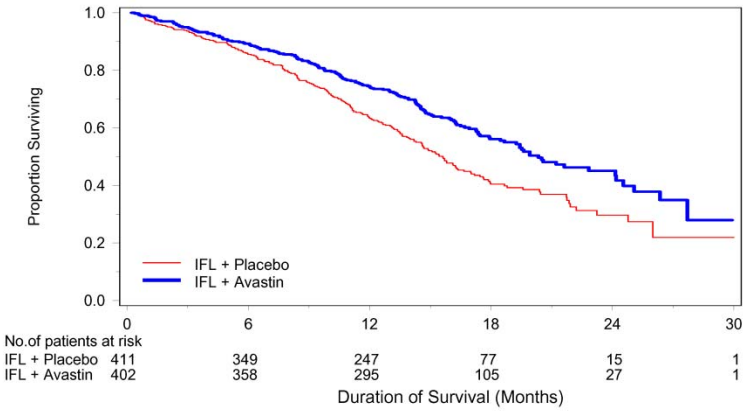
The addition of Avastin improved survival across subgroups defined by age (< 65 years, ≥ 65 years) and sex. Results are presented in Table 8 and Figure 1.

Table 8: Efficacy Results in Study AVF2107g

Efficacy Parameter	Avastin with bolus-IFL (N=402)	Placebo with bolus-IFL (N=411)
Overall Survival		
Median (months)	20.3	15.6
Hazard ratio (95% CI)	0.66 (0.54, 0.81)	
p-value[a]	< 0.001	
Progression Free Survival		
Median (months)	10.6	6.2
Hazard ratio (95% CI)	0.54 (0.45, 0.66)	
p-value[a]	< 0.0001	
Overall Response Rate		
Rate (%)	45%	35%
p-value[b]	< 0.01	
Duration of Response		
Median (months)	10.4	7.1

[a] by stratified log rank test.
[b] by χ^2 test

Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g



Among the 110 patients randomized to Avastin with 5-fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200
E3200 (NCT00025337) was a randomized, open-label, active-controlled study in 829 patients who were previously treated with irinotecan and 5-fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently, then 5-fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: leucovorin 200 mg/m^2, then 5-fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to

FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without 5-fluorouracil for metastatic disease, and 1% received prior irinotecan and 5-fluorouracil as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log rank test] with clinical benefit seen in subgroups defined by age (<65 years, ≥65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving Avastin with FOLFOX4.

Study TRC-0301
The activity of Avastin with 5-fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus 5-fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147
ML18147 (NCT00700102) was a prospective, randomized, open-label, multinational, controlled study in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line therapy to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line therapy was contingent upon first-line chemotherapy. Second-line therapy was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 9 and Figure 2.

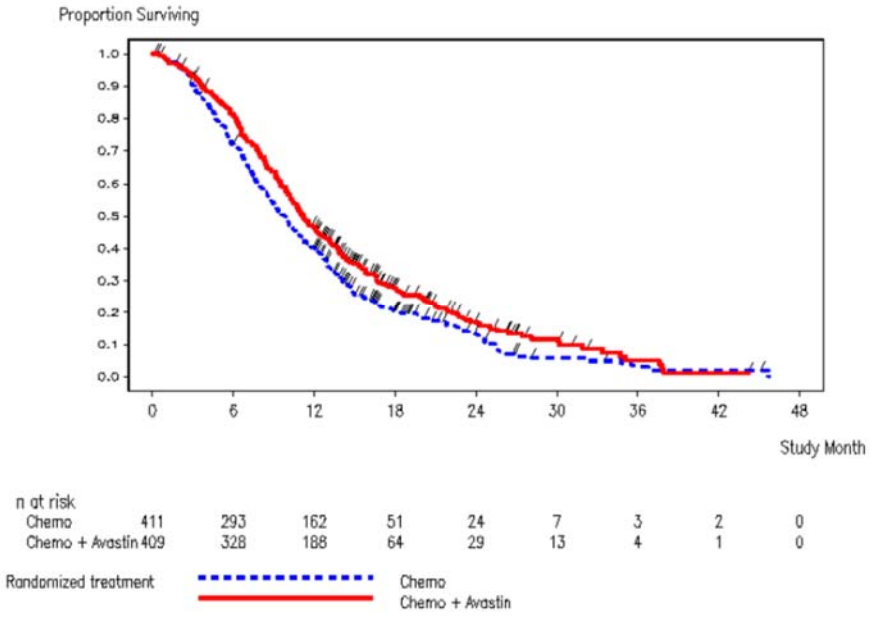
Table 9: Efficacy Results in Study ML18147

Efficacy Parameter	Avastin with Chemotherapy (N=409)	Chemotherapy (N=411)
Overall Survival[a]		
Median (months)	11.2	9.8
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median (months)	5.7	4.0
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] p = 0.0057 by unstratified log rank test.

[b] p-value < 0.0001 by unstratified log rank test.

Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies.

The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155), or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of Avastin to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS were observed in the Avastin-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main efficacy outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer (NSCLC)

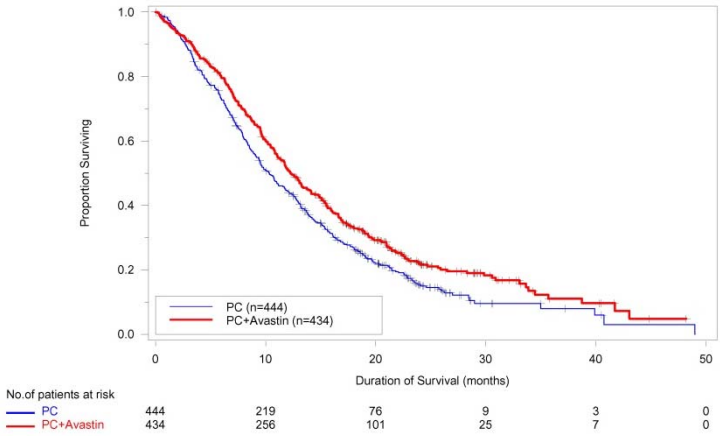
Study E4599

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with or without Avastin 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599



In an exploratory analysis across patient subgroups, the impact of Avastin on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704
The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

14.4 Recurrent Glioblastoma (GBM)
Study EORTC 26101
The safety and efficacy of Avastin were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment

in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or Avastin with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received Avastin following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E
One single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)] evaluated the efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

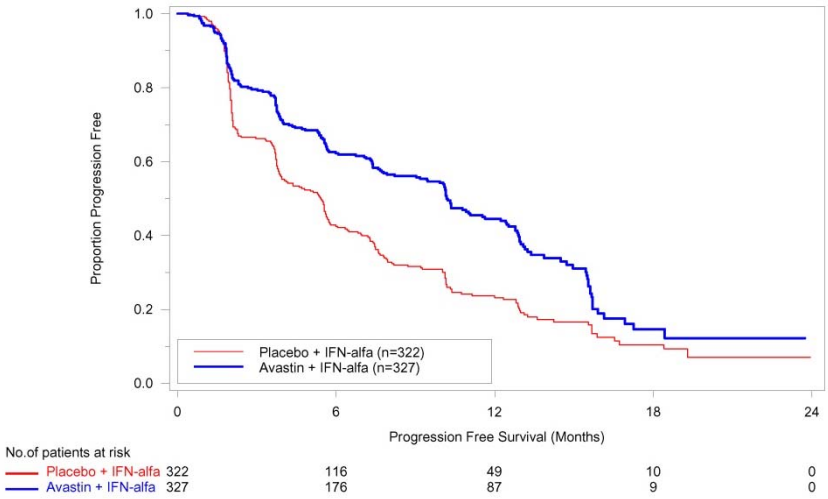
14.5 Metastatic Renal Cell Carcinoma (mRCC)

Study BO17705
Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa Avastin versus placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N=327) or placebo (every 2 weeks; N=322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value <0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI 0.72, 1.04)]. Results are presented in Figure 4.

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

Patients with persistent, recurrent, or metastatic cervical cancer were evaluated in a randomized, four-arm, multi-center study comparing Avastin with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

The dosing regimens for Avastin, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m^2 over 24 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with Avastin, Days 1-3: topotecan IV 0.75 mg/m^2 over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Table 10 and Figure 5.

Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240

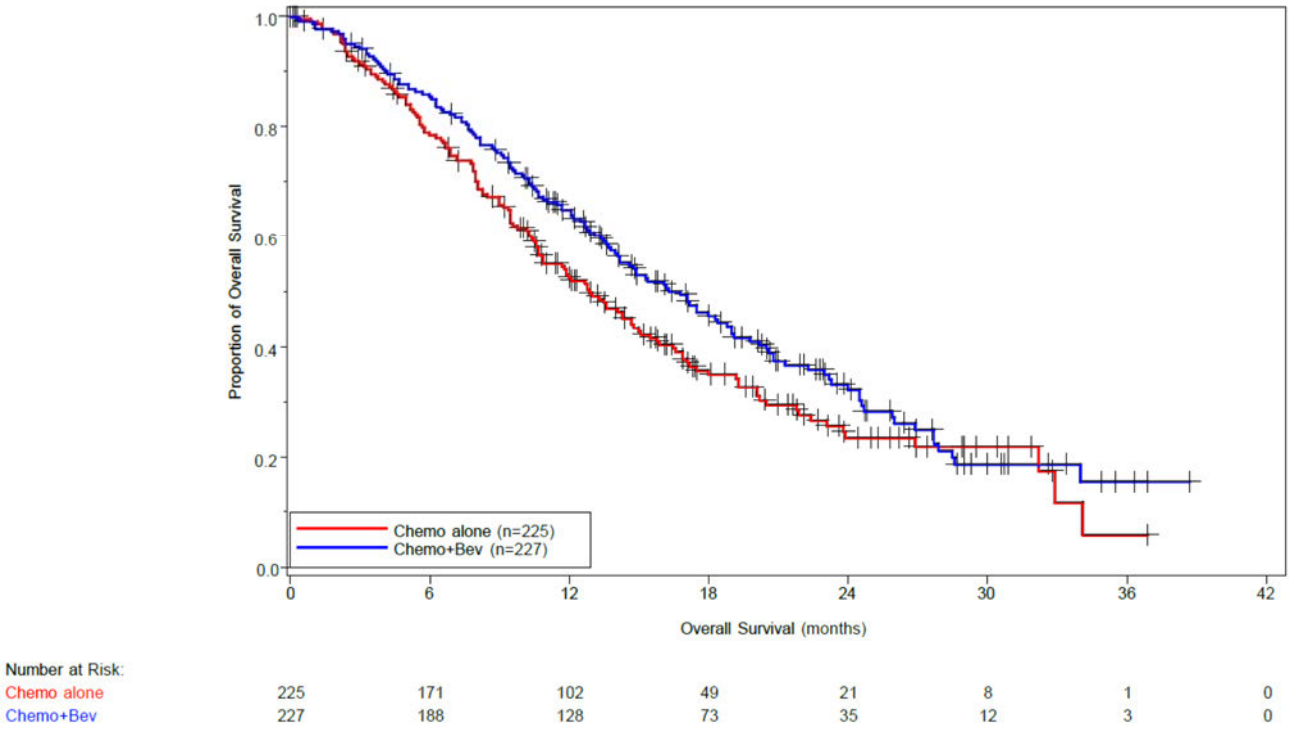


Table 10: Efficacy Results in Study GOG-0240

Efficacy Parameter	**Avastin with Chemotherapy (N=227)**	**Chemotherapy (N=225)**
Overall Survival		
Median (months)[a]	16.8	12.9
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value[b] = 0.0132)	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 11: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Avastin (N=223)	Cisplatin and Paclitaxel with or without Avastin (N=229)
Overall Survival		
Median (months)[a]	13.3	15.5
Hazard ratio [95% CI]	1.15 [0.91, 1.46] p-value=0.23	

[a] Kaplan-Meier estimates.

The HR for OS with Avastin with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

Avastin was evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m^2 on day 1 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 12 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 13.

Table 12: Efficacy Results in Study MO22224

Efficacy Parameter	Avastin with Chemotherapy (N=179)	Chemotherapy (N=182)
PFS per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI)[a]	0.38 (0.30, 0.49)	
p-value [b]	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI)[a]	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

[a] per stratified Cox proportional hazards model
[b] per stratified log rank test

Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224

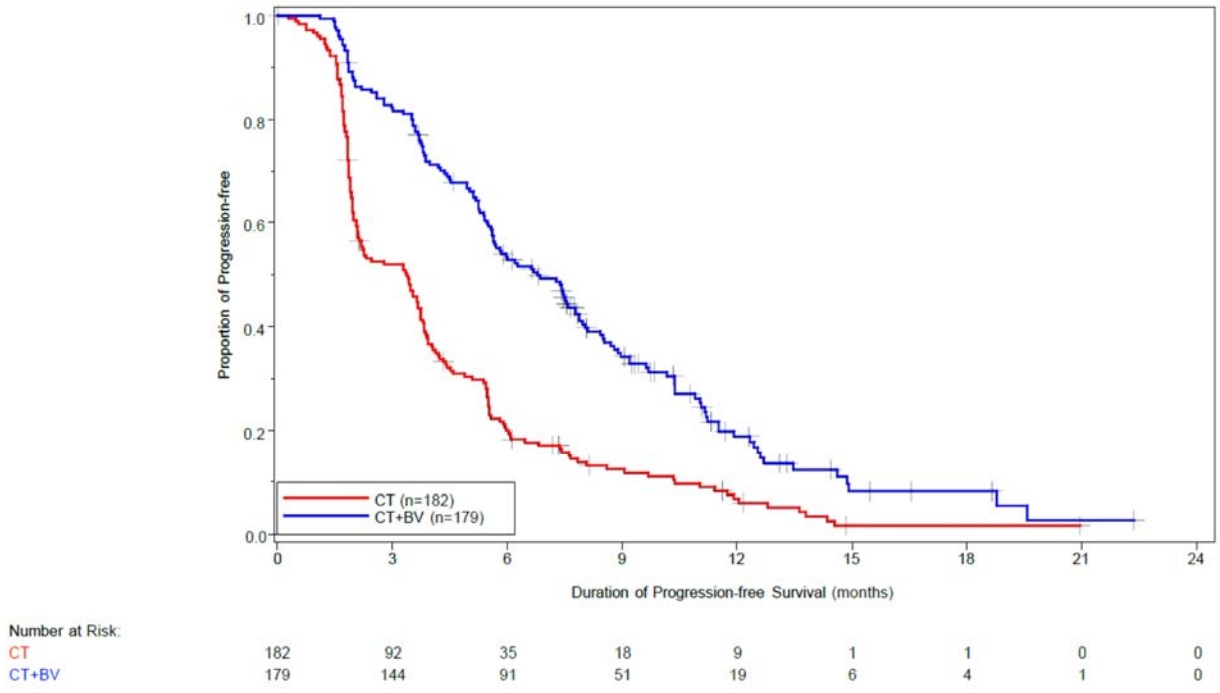


Table 13: Efficacy Results in Study MO22224 by Chemotherapy

Efficacy Parameter	Paclitaxel		Topotecan		Pegylated Liposomal Doxorubicin	
	Avastin with Chemotherapy (N=60)	Chemotherapy (N=55)	Avastin with Chemotherapy (N=57)	Chemotherapy (N=63)	Avastin with Chemotherapy (N=62)	Chemotherapy (N=64)
Progression-Free Survival *(per Investigator)*						
Median (months) (95% CI)	9.6 (7.8, 11.5)	3.9 (3.5, 5.5)	6.2 (5.3, 7.6)	2.1 (1.9, 2.3)	5.1 (3.9, 6.3)	3.5 (1.9, 3.9)
Hazard ratio[a] (95% CI)	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median (months) (95% CI)	22.4 (16.7, 26.7)	13.2 (8.2, 19.7)	13.8 (11.0, 18.3)	13.3 (10.4, 18.3)	13.7 (11.0, 18.3)	14.1 (9.9, 17.8)
Hazard ratio [a] (95% CI)	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Overall Response Rate						
Number of patients with measurable disease at baseline	45	43	46	50	51	51
Rate, % (95% CI)	53 (39, 68)	30 (17, 44)	17 (6, 28)	2 (0, 6)	16 (6, 26)	8 (0, 15)
Duration of Response						
Median (months)	11.6	6.8	5.2	NE	8.0	4.6

[a] per stratified Cox proportional hazards model
NE= Not Estimable

14.8 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g

AVF4095g (NCT00434642) was a randomized, double-blind, placebo-controlled study studying Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive Avastin (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) a for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity.
The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

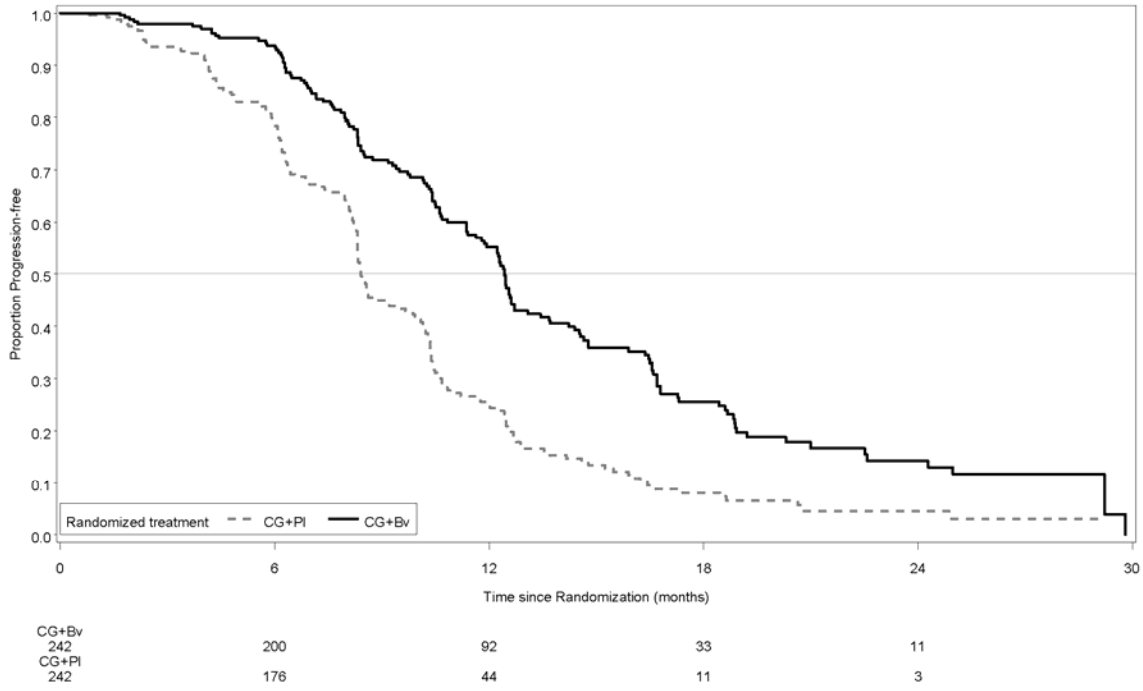
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 14 and Figure 7). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

Table 14: Efficacy Results in Study AVF4095g

Efficacy Parameter	Avastin with Gemcitabine and Carboplatin (N=242)	Placebo with Gemcitabine and Carboplatin (N=242)
Progression Free Survival		
Median PFS (months)	12.4	8.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p-value	< 0.0001	
Overall Response Rate		
% patients with overall response	78%	57%
p-value	< 0.0001	

Figure 7: Kaplan-Meier Curves for Progression Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g



Study GOG-0213

Study GOG-0213 (NCT00565851) was a randomized, controlled, open-label study of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single

agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥ 65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients.

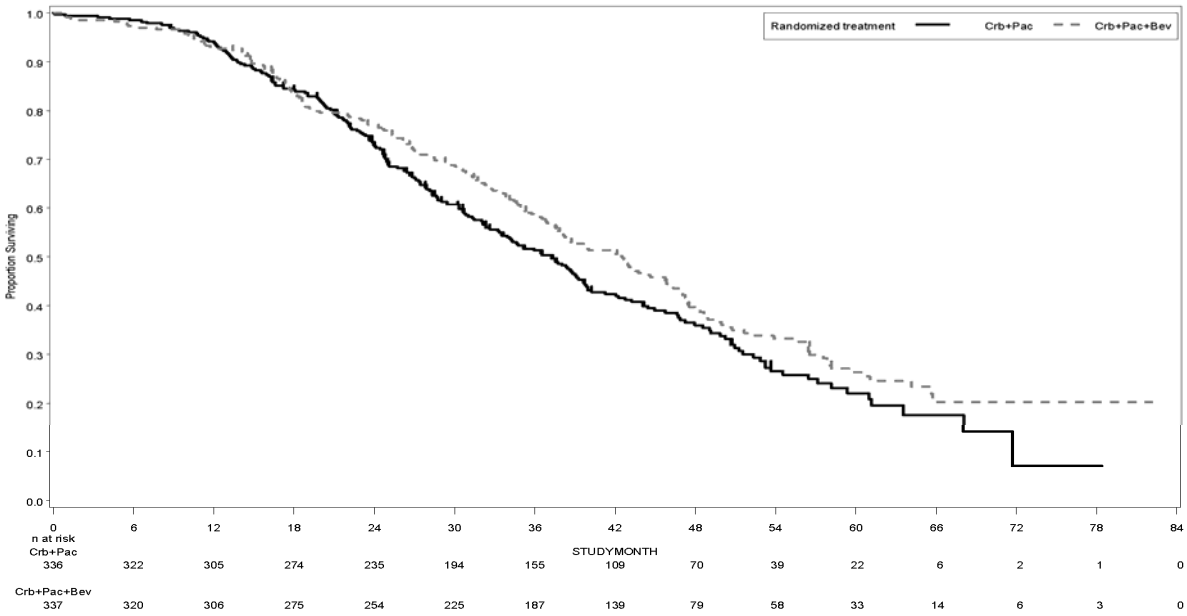
Results are presented in Table 15 and Figure 8.

Table 15: Efficacy Results in Study GOG-0213

Efficacy Parameter	**Avastin with Carboplatin and Paclitaxel (N=337)**	**Carboplatin and Paclitaxel (N=336)**
Overall Survival		
Median OS (months)	42.6	37.3
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-free Survival		
Median PFS (months)	13.8	10.4
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Overall Response Rate		
Number of patients with measurable disease at baseline	274	286
Rate, %	213 (78%)	159 (56%)

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Figure 8: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213



16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) Injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:
100 mg/4 mL (NDC 50242-060-01) and 400 mg/16 mL (NDC 50242-061-01). Each carton contains one vial.

Store refrigerated at 2–8°C (36–46°F) in the original carton until time of use to protect from light.

Do not freeze or shake the vial.

17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their health care provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolism: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion Reactions: Avastin can cause infusion reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise lactating women not to breastfeed while taking Avastin or within 6 months following their last dose of treatment *[see Use in Specific Populations (8.2)]*.

Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.

A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

OFFICER/EMPLOYEE LIST

Officer/Employee List
BLA 125085/S-319

The following officers or employees of FDA participated in the decision to approve this supplement and consented to be identified:

Barone, Amy
Demko, Suzanne
Hughes, Monica
Keegan, Patricia
Mushti, Sirisha
Papadopoulos, Elektra
Patel, Nikunj B.
Rodriguez, Lisa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 30, 2017
From	Suzanne G. Demko
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 125085/Supplement 319
Applicant	Genentech/Roche
Date of Submission	February 1, 2017
PDUFA Goal Date	February 1, 2018 (Action Date: December 1, 2017)
Proprietary Name	Avastin
Established or Proper Name	bevacizumab
Dosage Form(s)	Injection, for intravenous (IV) use
Applicant Proposed Indication(s)/Population(s)	"…indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy"
Applicant Proposed Dosing Regimen(s)	10 mg/kg intravenously every 2 weeks
Recommendation on Regulatory Action	*Approval, PMR # #2680-1Fullfilled*
Recommended Indication(s)/Population(s) (if applicable)	Avastin is…indicated for the treatment of recurrent glioblastoma in adults
Recommended Dosing Regimen(s) (if applicable)	10 mg/kg intravenously every 2 weeks

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Bevacizumab is a recombinant human monoclonal antibody that binds to human vascular endothelial growth factor (VEGF) and neutralizes its biologic activity. On May 5, 2009, FDA granted accelerated approval to bevacizumab for the treatment of adult patients with recurrent glioblastoma multiforme (GBM) under the provisions of 21 CFR 601 Subpart E Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. The current supplemental Biologics License Application (sBLA 125085/S-319) was submitted on February 1, 2017; this supplement contains the data intended to confirm the clinical benefit of bevacizumab and fulfills the postmarketing requirement (PMR) #2680-1 under 21 CFR 601.41 cited in the May 5, 2009 approval letter for sBLA 125085/S-169, as amended on August 12, 2014.

The benefit of bevacizumab for the treatment of patients with recurrent GBM is supported by data from three randomized clinical trials demonstrating a consistent and clinically meaningful improvement across studies in progression free survival (PFS), and by evidence that the use of supraphysiologic or high-dose corticosteroids (steroids) in this patient population, which can cause significant additional morbidity for patients, was either delayed or, for those taking steroids, were discontinued. Changes in health-related quality of life (HRQoL) and neurocognitive function (NCF) were also assessed; however, the analyses of these data were adversely impacted by various factors that made the data uninterpretable.

In Study EORTC 26101, a multicenter, open-label trial of 432 patients with recurrent GBM who were randomized (2:1) to receive lomustine with or without bevacizumab, the primary efficacy endpoint was overall survival (OS) with key secondary endpoints of PFS as assessed by the investigator (inv PFS), objective response rate (inv ORR) and corticosteroid use. Changes in HRQoL were also assessed as well as NCF. There was no statistically significant difference in OS demonstrated for this trial (HR 0.91, 95% CI: 0.72, 1.16; p = 0.4578); median OS was 9.1 months in the bevacizumab plus lomustine arm vs. 8.6 months in the lomustine monotherapy arm. There was a clinically meaningful, but non-significant prolongation of PFS for the bevacizumab plus lomustine arm compared with the lomustine arm (HR 0.52, 95% CI: 0.41, 0.64) characterized by median PFS times of 4.2 and 1.5 months respectively. Additionally, among patients who were receiving corticosteroids at baseline, 20% of patients (28/143) who received bevacizumab discontinued corticosteroids for ≥ 12 weeks; and more patients in the bevacizumab-containing arm decreased their daily steroid dose compared with patients in the lomustine arm (63.6% vs. 36.5%). Among patients who were not receiving corticosteroids at baseline, the number of patients who initiated steroids was similar (37.9% in the bevacizumab-containing arm and 38.7% in the lomustine arm); however, there was a delay in time to initiation of steroids, with median time to initiation of steroids in the bevacizumab arm of 3.02 months compared to the lomustine arm of 1.48 months. The results of the HRQoL and NCF analyses were considered uninterpretable because of high attrition and dropout rates. In addition, assessment of improvement in patient-reported outcomes was limited by a relatively asymptomatic population at baseline, and the lack of sensitivity of the HRQoL instruments to detect meaningful changes among the various symptoms measured.

Supporting the relevance and consistency of the bevacizumab effect on PFS were data from two large, randomized trials in which bevacizumab was added to standard of care in patients with newly diagnosed GBM, Study BO21990 (AVAglio) and Study RTOG 0825. Both trials were similar in design and patient

populations studied, and both trials were statistically powered to detect effects on PFS, independent of effects on overall survival.

AVAglio was a randomized (1:1), double-blind, two-arm, multicenter study to investigate the effectiveness of the addition of bevacizumab to temozolomide (TMZ) and radiation (RT) for the treatment of 921 patients with newly diagnosed GBM. The trial consisted of three phases: a Concurrent Phase (6-week duration), a Maintenance Phase (6 cycles of 4-week duration), and a Monotherapy Phase (3-week cycles until occurrence of progressive disease). Treatment consisted of RT plus TMZ plus bevacizumab or placebo and the bevacizumab dose was 10 mg/kg every 2 weeks in the first two phases of the trial and 15 mg/kg every 3 weeks in the final phase of the trial. After progressive disease, patients were followed every 9 weeks for safety, survival, and subsequent anti-cancer therapy. OS and PFS were co-primary endpoints; the statistical analysis plan adjusted for multiplicity by splitting the overall alpha. Corticosteroid use, HRQoL, and NCF were also assessed. There was no statistically significant difference in OS between treatment arms demonstrated in the AVAglio trial (HR 0.88, 95% CI:0.76, 1.02). The PFS analysis demonstrated a statistically significant and clinically meaningful improvement for patients treated on the bevacizumab-containing treatment arm (HR 0.64, 95% CI:0.55, 0.74) with median PFS times of 6.2 months for the placebo arm and 10.6 months for the bevacizumab arm.

Among patients on AVAglio who were receiving corticosteroids at baseline, 60% of patients who received bevacizumab discontinued corticosteroids while 49.5% of patients who received placebo discontinued corticosteroids; and more patients in the bevacizumab-containing arm decreased their daily steroid dose compared with patients in the placebo arm (88.2% vs. 80.8%). Among patients who were not receiving corticosteroids at baseline, there was a delay in time to initiation of steroids, with median time to initiation of steroids in the bevacizumab arm of 12.3 months compared to the placebo arm of 3.7 months; and 62% of patients who received bevacizumab and 73% who received placebo began treatment with corticosteroids.

RTOG 0825 was a double-blind, placebo-controlled, randomized trial (1:1) of concurrent chemoradiation and adjuvant TMZ plus bevacizumab compared with concurrent chemoradiation and adjuvant TMZ in 637 patients with newly diagnosed GBM or gliosarcoma. Randomization was stratified by MGMT methylation status (methylated, unmethylated, invalid) and molecular profile: (favorable, unfavorable, undetermined) based on nine genes. Patients were randomized to the following treatment arms:

- Arm 1: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus placebo every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28-day cycle plus placebo every 2 weeks, for a maximum of 12 cycles.
- Arm 2: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus bevacizumab every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28-day cycle plus bevacizumab every 2 weeks, for a maximum of 12 cycles

Patients with progressive disease either during or after protocol treatment could receive unblinded bevacizumab as a single agent, in combination with irinotecan, or in combination with temozolomide.

OS and PFS were composite primary endpoints in the RTOG trial, and analyses of both OS and PFS were designed to compare the bevacizumab-containing regimen to the placebo. An optional sub-study was included to evaluate HRQoL and NCF. There was no statistically significant effect on OS demonstrated in the RTOG 0825 trial (HR 1.13, 95% CI:0.93, 1.37). The PFS analysis demonstrated a statistically significant and clinically meaningful improvement for patients treated on the bevacizumab-containing treatment arm (HR 0.79, 95% CI:0.66, 0.94) with median PFS times of 7.3 months for the placebo arm and 10.7 months for the bevacizumab arm.

The safety profile of bevacizumab in patients with GBM is characterized by exposure data from approximately 1000 bevacizumab-treated patients across the three clinical studies discussed above. In each of the studies, the safety of the bevacizumab-containing regimen observed was similar to that described in the

US package insert across indicated populations. No new or unexpected adverse reactions (ARs) were identified in any of the studies.

The risk/benefit assessment of bevacizumab for treatment of patients with GBM begs the question of whether the demonstration of consistent and prolonged PFS with bevacizumab, together with decreased requirements for corticosteroids, is sufficient evidence to conclude that the direct clinical benefit of the antibody has been confirmed, thus, justifying regular approval for bevacizumab in the indicated population when there is also observed a consistent absence of an improvement in OS. In the opinion of the review team, the standards for granting regular approval have been met; and I agree with their findings and conclusions.

In my own assessment of the risks and benefit for bevacizumab in the population of patients with recurrent GBM, when the regulatory standards for approval of oncology drugs are assiduously applied, the available evidence weighs in favor of granting regular approval for the following indication: "For the treatment of recurrent glioblastoma in adults". The foregoing is my regulatory recommendation.

The factors supporting this recommendation are the totality of the evidence available to support the use of bevacizumab in patients with recurrent GBM, specifically: the serious and life threatening nature of the disease with median survival times of less than 8-9 months; lack of satisfactory available therapies; the delay, reduction, or discontinuation in the requirement for corticosteroids, which carry substantial co-morbidity in the management of patients with GBM; demonstration of consistent improvement in PFS (characterized by a 3 to 4 month increase in median PFS) across randomized, controlled clinical trials; no evidence of a decrement in survival; and the attendant risks of bevacizumab in this population of patients. The clinical benefits outweigh the risks of bevacizumab for this population of patients who have a uniformly grave prognosis, and the observed benefits to patients are both real and compelling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Universally poor prognosis after progression following first-line SoC; in Study EORTC 26101, median survival was 8-9 months. • No curative therapy • Available therapy has minimal impact on delay of disease progression and survival • Progressive disease results in profound morbidity including decline in physical functioning, cognitive decline, and alterations in personality • Progressive disease frequently results in requirement for high-dose corticosteroid use resulting in significant morbidity (new/worsening hypertension and diabetes, steroid myopathy, psychosis, cataracts)	GBM, especially in patients who have progressive disease after first-line treatment is a serious and life threatening disease. The morbidities associated with progressive GBM impact a patient's sense of "self" and lead to severe alterations in cognitive abilities, alterations in a patient's personality, as well as physical impairments. In addition, the mainstays of treatment for the disease, i.e. radiation therapy and steroids, are associated with their own significant morbidity.
Current Treatment Options	• Optune (TTF device): There was no improvement in survival demonstrated with the *Optune* TTF device in previously treated patients, rather what was demonstrated was a favorable safety profile and non-inferiority versus chemotherapy.	Many of the treatments approved for this condition were approved decades ago based on overall response rates only. Other than corticosteroids and surgical re-resection of the tumor, none of the current treatment approaches

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Carmustine wafers (Gliadel): *Carmustine wafers* were approved as an adjunct to debulking surgery at the time of progression following initial therapy, based on a 1.9-month improvement in median survival as compared to wafers with no drug. This is the only drug for progressive GBM that has demonstrated a survival advantage. • Lomustine (CCNU, Ceenu): *Lomustine* is indicated for the treatment of patients with primary and metastatic brain tumors following appropriate surgical and/or radiotherapeutic procedures. There is no evidence that lomustine improves progression-free or overall survival • Carmustine (BiCNU): *Carmustine (BiCNU)* is indicated as palliative therapy as a single agent or in established combination therapy for glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors. There is no evidence that carmustine improves progression-free or overall survival • Radiation therapy: Although not FDA-approved, *radiation therapy* (RT) is the single most effective treatment for improving survival in patients with GBM in the first-line setting. Re-irradiation has been administered as a palliative option for patients with recurrent GBM; however, there is no evidence that re-irradiation improves PFS or OS.	for recurrent GBM have demonstrated a survival advantage nor do they have an impact on neurological symptoms and patient functioning. The treatment landscape for patients with progressive GBM is unsatisfactory, and there is an unmet medical need patients with this condition.
Benefit	• Totality of the evidence considered • Consistent improvement in PFS across randomized trials (median PFS increased by 3-4 months) likely to result in delay in time to new/worsening disease-related symptoms • No decrement in OS across studies for a serious and life threatening disease • Corticosteroid-sparing effect with increased rate of discontinuation of steroids for ≥ 12 weeks or delay in time to initiation of steroids, avoiding morbidity of high-dose corticosteroids.	The totality of the evidence considered during this review meets the statutory evidentiary standard for regular approval. Although the primary endpoint of OS was not met in one of the trials considered in this application, (EORTC 26101), the observed PFS improvement of 2.7 months in this trial, while not statistically significant because of the failed OS primary endpoint, is clinically meaningful to patients. In addition, the improvement in PFS was consistent across the studies submitted to support this application. In both the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Well known toxicity profile considered acceptable for the indicated population. These include common adverse reactions of hypertension, epistaxis, fatigue, headache, proteinuria, and decreased weight and serious adverse reactions of hemorrhage, perforation, wound healing complications, and arterial thromboembolic events. • No new adverse reactions identified in patients with GBM in safety database of over 1000 patients • Prescribers familiar with toxicity and able to manage by dose modification and patient selection	The observed safety profile for bevacizumab for the population of patients with progressive GBM is acceptable in the context of this unrelenting serious and life threatening disease. Significant and serious adverse reactions are well covered in the bevacizumab label, which was updated during the conduct of this review. There were no new significant safety concerns identified during the review and additional risk management measures, including a Risk Management and Mitigation Strategy, are not warranted.

2. Background

For complete background information on bevacizumab, please see the primary clinical and statistical review of Amy Barone, M.D., Joohee Sul, M.D., and Sirisha Mushti, Ph.D. from which the below information was excerpted and adapted.

Product information
Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). The antibody is supplied in 100 mg and 400 mg preservative free, single use vials intended for intravenous administration. FDA granted accelerated approval to bevacizumab on May 5, 2009 as a single agent for the treatment of patients with GBM who had progression of disease after prior therapy. Bevacizumab is also FDA-approved for the following indications:

- Metastatic colorectal cancer, with 5 fluorouracil–based chemotherapy for 1st or 2nd line treatment
- Metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for 2nd line treatment in patients who have progressed on a first-line bevacizumab-containing regimen
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for 1st line treatment of unresectable, locally advanced, recurrent or metastatic disease
- Metastatic renal cell carcinoma with interferon alfa
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is
  - platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan,
  - platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent

Therapeutic context
Glioblastoma multiforme (GBM) is the most aggressive of the primary brain tumors. The current standard of care for newly diagnosed GBM was established by a large, randomized clinical trial demonstrating improved progression-free survival (PFS) and overall survival (OS) for patients receiving concurrent radiation therapy (RT) and temozolomide (TMZ) when compared with patients receiving RT-alone. Even with aggressive first-line therapy consisting of maximal safe surgical resection, RT, and chemotherapy, the median OS remains 12-14 months for patients who have this disease.

Response rates for patients with disease recurrence are <10%, with median PFS of about 9 weeks. Treatments for these patients include repeat surgical resection, re-irradiation, systemic therapies, including nitrosoureas or re-challenge with TMZ, and investigational agents.

Corticosteroids are a mainstay of treatment for patients with GBM because of their action in reducing capillary permeability leading to a reduction in peritumoral cerebral edema. There are few prospective randomized trials characterizing the clinical benefit and optimal dose of steroids in this setting; however, their ability to provide a measure of symptomatic relief for patients with central nervous system tumors is well described. Steroid treatment has the potential for severe toxicity, especially at supraphysiologic doses. Adverse effects include vision changes, myopathy, hyperglycemia, infection, gastrointestinal bleeding, edema, weight gain, behavioral changes, osteoporosis, wound healing complications, and psychosis; such adverse reactions are routinely observed in patients with GBM receiving corticosteroids at the doses generally administered for management of cerebral edema.

Since approval, bevacizumab has been utilized for the treatment of patients with recurrent GBM; its mechanism of action is thought to be reduction in tumor-associated cerebral edema rather than direct effects on reduction of tumor. In the community of treating neuro-oncologists, bevacizumab has been largely reserved for treatment of patients who exhibit clinical symptoms of significant edema, that is, as a steroid sparing agent. FDA is also aware of recent clinical trials that have substituted bevacizumab for steroids to manage cerebral edema to avoid the deleterious effects of steroids.

Regulatory background and history
In 2009, bevacizumab received accelerated approval in the United States for the treatment of patients with recurrent GBM based on durable ORR. Two studies demonstrated ORRs of 25.9% and 19.6% and median duration of response of 4.2 months and 3.9 months, respectively. Determining true radiographic response with bevacizumab has been challenging as inhibition of angiogenesis results in decease in contrast enhancement, resulting in a phenomenon dubbed “pseudo-response”. An Oncologic Drugs Advisory Committee (ODAC) meeting was held on March 31, 2009; FDA sought advice from the ODAC as it was unclear whether the radiographic improvement accompanied by decreased requirement for corticosteroids reported by the Applicant was the result of an anti-tumor effect of bevacizumab or whether it represented improvement in tumor associated brain edema. While the ODAC members were unsure whether the changes on the radiographic images were due to changes in vascular permeability and/or reduction in tumor, they stated that the changes resulted in a positive benefit in respect to symptoms based on the decreased steroid requirement and anecdotal reports. Additionally, members felt that future studies should assess effects on quality of life, but might not demonstrate improvement in overall survival. After discussion, the ODAC unanimously agreed that the response rate was of sufficient magnitude (i.e., clinically meaningful) to serve as a surrogate reasonably likely to predict clinical benefit for accelerated approval in recurrent GBM.

On May 5, 2009, FDA granted accelerated approval to bevacizumab as a single agent for patients with GBM and progressive disease following prior therapy. This approval was contingent upon completion of a study to verify the clinical benefit of bevacizumab. The Applicant was required to submit the final study report, including summary analyses and datasets and revised labeling, on the results of Study AVF4396g/BO20990 entitled “A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus

Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma AVAglio)," which was accepted under a Request for Special Protocol Assessment on December 29, 2008. The required reports and data from the AVAglio trial were submitted as of this supplement.

3. Product Quality

No new product quality data were submitted for review in this application. No facilities inspections were performed for this application**.**

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted for review in this application.

5. Clinical Pharmacology

No new nonclinical data were submitted for review in this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The information below was excerpted and adapted from the primary clinical and statistical review of Amy Barone, M.D., Joohee Sul, M.D., and Sirisha Mushti, Ph.D. For a complete discussion of the trials and data referenced below, please refer to the primary review.

I am in full agreement with the content and conclusions contained in the primary clinical and statistical review and the recommendation to grant regular approval for bevacizumab for the following indication:

" Avastin is a vascular endothelial growth factor directed antibody indicated for the treatment of recurrent glioblastoma in adults."

Study EORTC 26101
The primary clinical trial results submitted supporting this sBLA are from Study EORTC 26101, an open-label, randomized (2:1), multicenter trial of bevacizumab plus lomustine versus lomustine alone in 437 patients. Randomization was stratified by investigational site, performance status (0,> 0), steroid use (yes, no), and largest tumor diameter (≤ 40 mm, > 40 mm). The primary endpoint of the study was OS; the primary analysis was a stratified log-rank test performed on the intent-to-treat (ITT; all randomized) population. Key secondary endpoints were investigator-assessed PFS and ORR as determined by the modified RANO criteria.

The study did not demonstrate an improvement in OS; however, there was a numerically superior and clinically meaningful improvement in PFS for patients randomized to the bevacizumab plus lomustine arm compared with the lomustine monotherapy arm. Additional data confirming the clinical benefit of bevacizumab in Study EORTC 26101 comes from data collected on the use of corticosteroids. Among patients who were receiving corticosteroids at baseline, more patients who received bevacizumab discontinued corticosteroids for ≥ 12 weeks, 20% of patients (28/143); and more patients in the bevacizumab-containing arm decreased their daily steroid dose compared with patients in the lomustine arm (63.6% vs. 36.5%). Among patients who were not receiving corticosteroids at baseline, the number of patients who initiated steroids was similar (37.9% in the bevacizumab-containing arm and 38.7% in the lomustine arm); however, there was a delay in time to initiation of steroids, with median time to initiation of steroids in the bevacizumab arm of 3.02 months compared to the lomustine arm (1.48 months). The results of the HRQoL and NCF analyses were considered uninterpretable because of high attrition and dropout rates. In addition, there was a lack of sensitivity of the HRQoL instruments to detect meaningful changes among the various symptoms measured.

Additional data supporting the relevance of an improvement in PFS in the GBM population comes from two other large, randomized trials in which bevacizumab was added to standard of care in patients with newly diagnosed GBM, Study BO21990 (AVAglio) and Study RTOG 0825. Both trials were similar in design and patient populations studied, and both trials were statistically powered for their analyses of PFS, independent of the effects on OS.

Study BO21990 (AVAglio)
AVAglio was a randomized (1:1), double-blind, two-arm, multicenter study to investigate the efficacy of the addition of bevacizumab to temozolomide (TMZ) and radiation (RT) for the treatment of 921 patients with newly diagnosed GBM. The trial consisted of three phases: a Concurrent Phase (6-week duration), a Maintenance Phase (6 cycles of 4-week duration), and a Monotherapy Phase (3-week cycles until occurrence of progressive disease). Treatment consisted of RT plus TMZ plus bevacizumab or placebo and the bevacizumab dose was 10 mg/kg every 2 weeks in the first two phases of the trial and 15 mg/kg every 3 weeks in the final phase of the trial. After progressive disease, patients were followed every 9 weeks for safety, survival, and subsequent anti-cancer therapy. OS and PFS were co-primary endpoints and the statistical plan adjusted for multiplicity and the overall alpha was split. Corticosteroid use, HRQoL, and neurocognitive function were also assessed.

There was no statistically significant difference in OS demonstrated in the AVAglio trial (HR 0.88, 95% CI:0.76, 1.02). The PFS analysis demonstrated a statistically significant and clinically meaningful improvement for patients randomized to the bevacizumab-containing treatment arm (HR 0.64, 95% CI:0.55, 0.74) with median PFS times of 6.2 months for the placebo arm and 10.6 months for the bevacizumab arm.

Among patients on AVAglio who were receiving corticosteroids at baseline, 60% of patients who received bevacizumab discontinued corticosteroids while 49.5% of patients who received placebo discontinued corticosteroids; and more patients in the bevacizumab-containing arm decreased their daily steroid dose compared with patients in the placebo arm (88.2% vs.

80.8%). Among patients who were not receiving corticosteroids at baseline, 62% who received bevacizumab and 73% who received placebo began treatment with corticosteroids; and there was a delay in time to initiation of steroids, with median time to initiation of steroids in the bevacizumab arm of 12.3 months compared to the placebo arm of 3.7 months.

Study RTOG 0825
RTOG 0825 was a double-blind, placebo-controlled, randomized trial (1:1) of concurrent chemoradiation and adjuvant TMZ plus bevacizumab compared with concurrent chemoradiation and adjuvant TMZ in 637 patients with newly diagnosed GBM or gliosarcoma. Randomization was stratified by MGMT methylation status (methylated, unmethylated, invalid) and molecular profile: (favorable, unfavorable, undetermined) based on nine genes. Patients were randomized to the following treatment arms:

- Arm 1: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus placebo every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28-day cycle plus placebo every 2 weeks, for a maximum of 12 cycles.
- Arm 2: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus bevacizumab every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28-day cycle plus bevacizumab every 2 weeks, for a maximum of 12 cycles

Patients with progressive disease either during or after protocol treatment could receive unblinded bevacizumab as a single agent, in combination with irinotecan, or in combination with temozolomide.

OS and PFS were composite primary endpoints in the RTOG trial, and analyses of both OS and PFS were designed to compare the bevacizumab-containing regimen to the placebo. An optional sub-study to was included to evaluate HRQoL and neurocognitive functioning.

There was no statistically significant difference in OS demonstrated in the RTOG 0825 trial (HR 1.13, 95% CI:0.93, 1.37). The PFS analysis demonstrated a statistically significant and clinically meaningful improvement for patients randomized to the bevacizumab-containing treatment arm (HR 0.79, 95% CI:0.66, 0.94) with median PFS times of 7.3 months for the placebo arm and 10.7 months for the bevacizumab arm.

Both studies AVAglio and RTOG 082 were conducted in patients with newly diagnosed GBM. The consistency of trial designs was mirrored by the consistency of the primary outcomes, with both trials showing a 3-to-4-month prolongation of progression-free survival with bevacizumab, but no statistically significant effect on overall survival.

Conclusions on Substantial Evidence of Effectiveness

The Applicant has provided the substantial evidence of effectiveness of treatment effects on PFS that are of a clinically meaningful magnitude, supported by evidence of a corticosteroid-sparing effect (discontinuation of corticosteroids or delay in time to initiation of corticosteroids). These data support approval and verify the clinical benefit of bevacizumab in the indicated population.

8. Safety

The information below was excerpted and adapted from the primary clinical and statistical review of Amy Barone, M.D., Joohee Sul, M.D., and Sirisha Mushti, Ph.D.

I am in full agreement with the content and conclusions on the safety of bevacizumab in patients with GBM contained in the primary clinical and statistical review.

The safety profile of bevacizumab for the treatment of patients with GBM is based on exposure in approximately 1000 patients across three clinical studies. The studies evaluated to assess the safety of bevacizumab were EORTC 26101, AVAglio, and RTOG 0825. In each of the studies, the safety of the bevacizumab-containing regimen observed was similar to the known safety profile of the drug. No new or unexpected adverse reactions (ARs) were observed in any of the three studies. Also noteworthy is the fact that although none of the studies demonstrated an improvement in OS, there was no decrement observed for OS any study.

The overall incidences of Grade ≥ 3 AEs, deaths, serious AEs (SAEs), and AEs leading to discontinuation of study treatment were more frequent in the bevacizumab-containing arms compared with the comparator arms. Most of the increases in AE incidence in the bevacizumab-containing arm were attributable to known adverse reactions of bevacizumab as described in product labeling. In the EORTC trial, adverse reactions of hypertension, epistaxis, fatigue, headache, and decreased weight occurred with a ≥ 10% higher incidence in the bevacizumab + lomustine arm compared with the lomustine monotherapy arm. In the AVAglio trial, adverse reactions that occurred with at least a 10% higher incidence in the bevacizumab + radiation + TMZ arm compared with the placebo + radiation + TMZ arm were hypertension, epistaxis, and proteinuria. The incidence of patients with AEs of special interest (AESIs), as assessed in studies EORTC 26101 and AVAglio, was higher in the bevacizumab-containing arms than in the comparator arms; this was not an unexpected finding as the AEs considered as AESIs were those known to be associated with bevacizumab treatment. The incidence of patients with AESIs in the bevacizumab-containing arms was generally similar to previous clinical experience as described in product labeling, except for the difference in the incidence of arterial thromboembolic events observed in AVAglio (5.9% in the bevacizumab arm, 1.6% in the placebo arm). In EORTC 26101, the incidence of arterial thromboembolic events in the bevacizumab + lomustine arm was comparable with that in the lomustine arm, although it was higher than expected (11.5% of patients compared with 10.9% in the Lom arm) and higher than the incidence in the AVAglio trial.

9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this sBLA because the application did not raise significant public health questions that would benefit from an advisory committee discussion. In addition, the safety profile for bevacizumab is acceptable for the indicated patient population.

10. Pediatrics

The requirements of the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) were not triggered by this application as it does not contain new active ingredients and did not seek new indications, new dosage forms, new dosing regimens, or new routes of administration. Additionally, a previous study was conducted in pediatric patients with GBM and this study is described in product labeling. The labeling currently states that Avastin is not approved for use in patients under the age of 18 years, antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan, and that there is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin.

11. Other Relevant Regulatory Issues

For a complete discussion of other regulatory issues of interest, please see the joint primary clinical and statistical review of *Amy Barone, M.D., Joohee Sul, M.D., and Sirisha Mushti, Ph.D.*

12. Labeling

Prescribing Information
Final labeling negotiations are ongoing. Please see the final published label.

In general, labeling was updated to conform to current FDA standards and applicable laws pertaining to prescribing information. Formatting and other editorial changes as appropriate to improve the accuracy and readability of the label were also made. Following is a high-level review of major changes made to the label:

- INDICATIONS AND USAGE:
  - The following language was removed from the label: "*Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.*"
  - The current indication is: " Avastin is a vascular endothelial growth factor directed antibody indicated for the treatment of recurrent glioblastoma in adults".

- DOSAGE AND ADMINISTRATION:
  - No change

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - The Warnings and Precautions section of the label was revised to add the new warning of Congestive Heart Failure (CHF) as section 5.12

- CLINICAL STUDIES section:

  - Multiple subsections were revised for clarity and to update with known new information. Section 14.4, Recurrent Glioblastoma was revised to include the information submitted in the current sBLA.

- PATIENT COUNSELING INFORMATION section:
  - CHF added and section revised and updated

13. Postmarketing Recommendations

There are no postmarketing requirements and no postmarketing commitments identified for this application. There is no requirement for a Risk Management and Mitigation Strategy, as product labeling includes all necessary precautions for the use of this drug.

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/s/

SUZANNE G DEMKO
12/01/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	BLA 125085/S-319
Priority or Standard	Standard
Submit Date(s)	February 1, 2017
Received Date(s)	February 1, 2017
PDUFA Goal Date	December 1, 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Amy Barone, MD Joohee Sul, MD Sirisha Mushti, PhD Lisa Rodriguez, Statistical Team Lead Suzanne Demko, PA-C Team Lead
Review Completion Date	November 30, 2017
Established Name	Bevacizumab
(Proposed) Trade Name	Avastin
Therapeutic Class	Monoclonal antibody
Applicant	Genentech/Roche
Formulation(s)	Intravenous (IV)
Dosing Regimen	10 mg/kg IV every 2 weeks
Indication(s)	Treatment of adult patients with recurrent glioblastoma
Intended Population(s)	≥ 18 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the review team recommends approval of this supplemental biologics license application (sBLA) for bevacizumab (Avastin) to modify the current glioblastoma (GBM) approved indication by:

- Revising the current indication from "Avastin is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent. The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. [See Clinical Studies (14.4).]:

  to

- "Avastin is indicated for the treatment of recurrent glioblastoma in adults" and deleting (in strikethrough) the following statement: "~~Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease related symptoms or survival with Avastin.~~"

Data from the European Organization for Research and Treatment of Cancer (EORTC) Study 26101 (Study EORTC 26101) fulfills the post-marketing requirement (2680-1) in the May 5, 2009 approval letter for AVASTIN as well as the revised post-marketing requirement in the August 12, 2014 letter. Furthermore, the data provided verify the clinical benefit of Avastin in the indicated population.

The verification of clinical benefit is based on a favorable risk/benefit assessment from Study EORTC 26101, a randomized (2;1), active-controlled trial in 432 patients with GBM that has progressed after receipt of a standard first-line regimen. Patients were randomized to receive bevacizumab plus lomustine (n=283) or lomustine (n=149). Although the trial failed to demonstrate a treatment effect on overall survival (OS), progression-free survival (PFS) was prolonged in patients receiving bevacizumab plus lomustine compared with lomustine alone (HR 0.52, 95% CI: 0.41, 0.64) and there was a decrease in requirement for corticosteroids in the bevacizumab arm. The effect on PFS is supported by results of two additional randomized trials, providing confidence in the treatment effect on PFS. The safety assessment of bevacizumab in this patient population did not reveal new safety concerns; the toxicity profile of Avastin is considered acceptable in light of the serious and life-threatening nature of recurrent GBM.

1.2 Risk Benefit Assessment

The effectiveness of bevacizumab for the proposed indication is primarily supported by data from Study EORTC 26101, a multicenter, open-label trial of 432 patients with recurrent GBM who were randomized (2:1) to receive lomustine with or without bevacizumab. The primary efficacy endpoint was overall survival (OS) with key secondary endpoints of progression-free survival (PFS) as assessed by the investigator (inv PFS), objective response rate (inv ORR) and corticosteroid use. Study EORTC 26101 failed to demonstrate an OS benefit (HR 0.91, 95% CI: 0.72, 1.16; p = 0.4578); median OS was similar between arms: 9.1 months in the bevacizumab plus lomustine arm vs. 8.6 months in the lomustine arm. However, there was an improvement in inv PFS for the bevacizumab plus lomustine arm compared with the lomustine alone arm (HR 0.52, 95% CI: 0.41, 0.64); the median PFS times were 4.2 months in the bevacizumab-containing arm and 1.5 months in the lomustine arm.
Information on corticosteroid dosing was captured at baseline, every 6 weeks for 6 months, then every 12 weeks. Half of patients in both arms were receiving corticosteroids at baseline, with similar mean daily doses. More patients in the bevacizumab-containing arm decreased their corticosteroid use compared with the lomustine arm (64% vs 36%) with 20% of patients (28/143) who received bevacizumab discontinuing corticosteroids for ≥ 12 weeks. Changes in health-related quality of life and (HRQoL) was assessed using the EORTC QLQ C-30 and the brain cancer specific module, EORTC QLQ BN20. Neurocognitive function (NCF) was assessed using the Mini-Mental State Examination (MMSE) and three neuropsychological tests were included in a sub-study of patients from countries that had validated translations of the tests. The results of the HRQoL and NCF analyses were considered uninterpretable due to multiple factors including high attrition and dropout rates, high floor effects at baseline (indicating a patient population without significant clinical symptoms at baseline) and lack of meaningful change among various domains/symptoms of the HRQoL instruments.
In Study RTOG 0825, 637 patients were randomized to receive bevacizumab with SoC (n=320) or placebo with SoC (n=317). Study AVAglio, with a similar design and treatment plan, randomized 458 patients to bevacizumab with SoC and 463 patients with placebo with SoC. Neither trial demonstrated an OS benefit; however, PFS was prolonged in both studies as summarized in the table below:

	AVAglio	**RTOG 0825**
Randomized (ITT)	921 patients	637 patients
• **SoC + bevacizumab** • **SoC + placebo**	458 463	320 317
Primary endpoints		
• **OS (HR)**	0.88 (95 % CI:0.76,1.02) p 0.0987	1.13 (95% CI:0.93,1.37) p 0.11
• **KM median (months)**	16.7 (SoC + placebo) 16.8 (SoC + bevacizumab)	16.1 (SoC + placebo) 15.7 (SoC + bevacizumab)
• **PFS (HR)**	0.64 (95% CI:0.55,0.74) p < 0.0001	0.79 (95% CI: 0.66,0.94) p 0.004

	AVAglio	RTOG 0825
• **KM median (months)**	6.2 (SoC + placebo) 10.6 (SoC + bevacizumab)	7.3 (SoC + placebo) 10.7 (SoC + bevacizumab)

ITT: intent to treat; SoC: standard of care; HR: hazard ratio; CI: confidence interval; KM: Kaplan-Meier method; OS: overall survival; PFS: progression-free survival.

Taken together, Studies EORTC 26101, RTOG 0825 and AVAglio demonstrate a consistent improvement in PFS in patients with recurrent and newly-diagnosed GBM receiving bevacizumab compared with SoC therapies.

The primary uncertainty of the risk/benefit assessment of bevacizumab for treatment of recurrent GBM is whether the demonstration of prolonged PFS with bevacizumab (across multiple trials), together with decreased requirements for corticosteroids, is evidence of direct clinical benefit, in the absence of any effect on OS (across multiple trials). In analyzing the risk/benefit, the reviewers applied the regulatory standards for approval of oncology drugs, taking into consideration the totality of the evidence to support the use of bevacizumab in patients with recurrent GBM, in the context of key relevant factors: the serious nature of the disease, lack of satisfactory available therapies for recurrent GBM, the requirement for corticosteroids in the management of GBM which results in substantial co-morbid toxicity, the significance of an improvement in PFS in this population, and the attendant risks of bevacizumab in this population.

Disease background and available therapies
Patients with GBM have a universally poor prognosis. Once the disease progresses after SoC first-line treatment, the course is generally unrelenting and currently available therapies have minimal impact on delaying disease progression or prolonging survival. Moreover, progression of disease results in profound morbidity of the “self”; impairment in physical functioning, decline in cognitive abilities and alteration of personality are hallmarks of the GBM that set this cancer apart from other solid tumors.

Tumor treating fields (TTF) applied via a portable device (i.e., Optune) was approved for treatment of recurrent GBM; the single randomized trial supporting approval did not demonstrate an improvement in OS compared with physician’s choice chemotherapy. The approval was based on a favorable safety profile and claims of non-inferiority on OS and less morbidity that with chemotherapy.

Other FDA-approved available therapies for treatment of recurrent GBM are as follows:

- Carmustine wafers (Gliadel) is indicated for the treatment for the treatment of patients with recurrent glioblastoma multiforme, as an adjunct to surgery, based on a 1.9-month improvement in median survival as compared to wafers with no drug.
- Lomustine (CCNU, Ceenu) is indicated for the treatment of patients with primary and metastatic brain tumors following appropriate surgical and/or radiotherapeutic procedures.

- Carmustine (BiCNU) is indicated as palliative therapy as a single agent or in established combination therapy for glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.

With the exception of Gliadel, these cytotoxic drugs were approved decades ago based on overall response rates (ORR). None of these treatment modalities have demonstrated evidence of significant improvement on PFS or OS in patients with recurrent GBM; yet given the dearth of options, they are commonly prescribed.

Although not FDA-approved, radiation therapy (RT) remains the single most effective treatment for improving survival in patients with high grade gliomas (HGG), and is a vital component of first-line therapy for GBM. Re-irradiation has been administered as a palliative option for patients with recurrent GBM; however, there have been no randomized studies demonstrating a benefit or re-irradiation on PFS or OS. Other than corticosteroids and surgical re-resection of tumor, both which primarily improve cerebral edema and do not treat the underlying disease, none of the current treatment approaches for recurrent GBM setting appear to have an impact on neurological symptoms and patient functioning.

Corticosteroid use in patients with GBM
Corticosteroids are an integral component of the treatment of HGG. The effects of corticosteroids on neurological symptoms in patients with brain tumors was first noted in the 1950s, leading to their longstanding use for management of central nervous system (CNS) tumors. Although early studies investigated their potential for direct anti-tumor activity in HGG, their principal action is ascribed to reduction of capillary permeability, leading to reduction in peritumoral cerebral edema. Despite their widespread application, clinical use of corticosteroids for brain edema is primarily based on empirical information as there are few prospective randomized trials characterizing the clinical benefit (or optimal dose). The ability of corticosteroids to provide symptomatic improvement for patients with CNS tumors has been well documented and described; however, these results often come at the expense of considerable toxicity. Adverse effects of supraphysiologic doses of exogenous corticosteroids include vision changes, myopathy, hyperglycemia, infection, gastrointestinal bleeding, edema, weight gain, behavioral changes, osteoporosis, wound healing complications, and psychosis; such adverse reactions are routinely observed in patients with GBM receiving corticosteroids at the doses generally administered for management of cerebral edema. Moreover, recent data suggests that corticosteroids may compromise survival in GBM, possibly interfering with the effectiveness of RT and chemotherapy.[1,2]

Bevacizumab use in patients with GBM
Since its approval on May 5, 2009, bevacizumab had been used regularly to manage cerebral edema, whether associated with tumor, radiation necrosis, or inflammatory changes in patients with recurrent GBM. With the absence of data demonstrating improvement in OS, neuro-oncologists have generally reserved bevacizumab for those

circumstances that would warrant corticosteroids (i.e., patients with significant edema associated with clinical symptoms). More recently, numerous clinical trials have incorporated bevacizumab as a "steroid-sparing" agent to manage cerebral edema potentially related to the investigational therapy (e.g. immunotherapies, RT) without the attendant ill effects of corticosteroids.

Risk/benefit assessment
Although randomized trials of bevacizumab have failed to demonstrate improvement in OS, the reviewers consider the consistent demonstration of prolonged PFS and the decrease in corticosteroid dose to represent a clinical benefit for patients. Given the negative side effects of corticosteroids, decreased use of corticosteroids is clinically important. Reliance on PFS as an endpoint may be criticized as specious, as PFS may be simply a measurable outcome that does not adequately capture a clinically meaningful effect (i.e. the McNamara fallacy). The consistent demonstration of prolonged PFS across multiple randomized clinical trials of bevacizumab in patients with GBM supports that this is not a spurious (false negative) finding. Whether the PFS observed with bevacizumab is truly delay in *disease* progression versus an artifact related to effects on peritumoral edema is an ongoing debate. However, given the negative impact of peritumoral edema and the side effects of corticosteroids, improved control of edema (such that the corticosteroid dose can be reduced or initiation delayed) related to bevacizumab constitutes a clinical benefit for patients.

A high degree of toxicity would be acceptable for a treatment in this disease, considering the dismal prognosis. No new safety signals were identified in the review of the data submitted in the sBLA, and the toxicity profile of bevacizumab is acceptable for the treatment of GBM. Based on a review of the totality of the data, the reviewers conclude that the consistent demonstration of prolonged PFS, associated with decrease in corticosteroid use, outweighs the potential risks of bevacizumab for patients with recurrent GBM. Given the uncertainty of the true anti-tumor effect of bevacizumab on GBM, this reviewer recommends modifying the approved indication to describe the specific associated clinical benefit.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Glioblastomas (GBM) are the most aggressive of the primary brain tumors and exhibit steadfast resistance to treatment. The current standard of care (SoC) for newly diagnosed GBM was established by a large randomized trial that demonstrated improved progression-free survival (PFS) and overall survival (OS) for patients receiving concurrent radiation therapy (RT) and temozolomide (TMZ) when compared with the RT-alone group.[3] Despite aggressive first-line therapy with maximal safe surgical resection, RT and chemotherapy, median OS is 12-14 months and disease progression is invariable.

Historic response rates for salvage therapies are <10%, with median PFS of ~9 weeks.[4] Treatment strategies for patients with recurrent disease include repeat surgical resection, re-irradiation, clinical trials and systemic therapies including nitrosoureas or re-challenge with TMZ. In two recent randomized studies where lomustine was the control arm treatment, response rates ranged from 4-9% with PFS rate at 6 months (PFS-6) of 19 -25%.[3,4]

In 2009, bevacizumab received accelerated approval in the United States (US) for the treatment of patients with recurrent GBM based on durable ORR. Two studies demonstrated ORRs of 25.9% and 19.6% and median duration of response of 4.2 months and 3.9 months, respectively.[5,6] Determining true radiographic response with bevacizumab has been challenging as inhibition of angiogenesis results in decease in contrast enhancement, resulting in a phenomenon dubbed “pseudo-response”. An Oncology Drugs Advisory Committee (ODAC) meeting was held on March 31, 2009 and FDA sought advice from the ODAC as it was unclear whether the radiographic improvement accompanied by decreased requirement for corticosteroids reported by the Applicant was the result of an anti-tumor effect of bevacizumab or whether it represented improvement in tumor associated brain edema. After public debate, the ODAC unanimously recommended accelerated approval of bevacizumab for the treatment of GBM.

On May 5, 2009, FDA granted accelerated approval to bevacizumab as a single agent for patients with GBM and progressive disease following prior therapy. This approval was contingent upon completion of a study to verify the clinical benefit of bevacizumab. The Applicant was to submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling, on the results of Study AVF4396g/BO20990 entitled “A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma,” which was accepted under a Request for Special Protocol Assessment on December 29, 2008.

Recurrent GBM is the only population for which bevacizumab has been approved for use as a single agent; every other indication has received approval based on combination with other antineoplastic agents.

2.1 Product Information

Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab is supplied in 100 mg and 400 mg preservative free, single use vials.

2.2 Tables of Currently Available Treatments for Proposed Indications

The table below summarizes the available therapies for patients with recurrent GBM. Other treatment approaches include re-irradiation and re-resection of tumor, which are generally considered palliative.

Table 1 Available therapies and Drugs Identified in NCCN Guidelines for recurrent GBM

Treatment	Mechanism of Action	Population	Approval?	Endpoint	Year
Lomustine (CCNU)	Alkylating chemotherapy (oral)	Primary and metastatic brain tumors	Yes	ORR	1976
Carmustine (BCNU)	Alkylating chemotherapy (intravenous)	Primary and metastatic brain tumors	Yes	ORR	1977
Gliadel wafers (carmustine)	Alkylating chemotherapy (local surgical delivery)	Recurrent GBM	Yes	OS	1996
		1st line high grade glioma	Yes	OS	2003
Temozolomide (Temodar)	Alkylating chemotherapy (oral)	Refractory anaplastic astrocytoma	AA	Durable ORR	1999
		1st line GBM	Yes	OS	2005
Bevacizumab (Avastin)	Anti-angiogenesis agent	Recurrent GBM	AA	Durable ORR	2008
NovoTTF (Optune)	Alternating electrical fields, anti-mitotic (device)	Recurrent GBM	Yes	Comparable OS vs. SoC	2011
		Newly diagnosed GBM	Yes	OS	2015
Carboplatin	Platinum chemotherapy	Recurrent high grade glioma	Off-label	N/A	N/A
Irinotecan	Topoisomerase inhibitor	Recurrent high grade glioma	Off-label	N/A	N/A
Etoposide	Topoisomerase inhibitor	Recurrent high grade glioma	Off-label	N/A	N/A

AA: Accelerated Approval; ORR: Objective response rate; OS: Overall Survival; SoC: Standard of Care; N/A: Not Applicable

2.3 Availability of Proposed Active Ingredient in the United States

Bevacizumab is FDA approved for the following indications:

- Metastatic colorectal cancer, with 5 fluorouracil–based chemotherapy for 1st or 2nd line treatment
- Metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for 2nd line treatment in patients who have progressed on a first-line bevacizumab-containing regimen
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for 1st line treatment of unresectable, locally advanced, recurrent or metastatic disease
- Metastatic renal cell carcinoma with interferon alfa
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is
    - platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan,
    - platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent

2.4 Important Safety Issues With Consideration to Related Drugs

The following warnings and precautions are described in Section 5 of the bevacizumab prescribing information (label) for healthcare providers to consider:

- Discontinue Avastin for the following:
    - Perforation or fistula
    - Severe arterial thromboembolic events
    - Life-threatening venous thromboembolic events
    - Hypertensive crisis or hypertensive encephalopathy
    - Posterior Reversible Encephalopathy Syndrome (PRES)
    - Nephrotic syndrome
- Monitor blood pressure and treat hypertension (HTN). Temporarily suspend Avastin if not medically controlled.
- Monitor urine protein. Temporarily suspend Avastin for moderate proteinuria
- Stop Avastin for severe infusion reactions
- Potential embryo-fetal toxicity
- Potential ovarian failure

2.5 Summary of Presubmission Regulatory Activity Related to Submission

May 26, 2006: Bevacizumab was granted Orphan Drug Designation for the treatment of malignant glioma.

May 5, 2009: Bevacizumab was approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) for treatment of recurrent GBM based on demonstration of durable objective response rate (ORR) in two trials; AVF3708g and NCI 06-C-0064E. The approval letter contained a post-marketing requirement (PMR) under 21 CFR 601 Subpart E to conduct studies to verify and describe the clinical benefit of bevacizumab for the treatment of GBM as follows:

> *To submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling based on the results of study AVF4396g/BO21990 entitled "A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma," which was accepted under a Request for Special Protocol Assessment on December 29, 2008.*

March 26, 2014: A Type B meeting was held during which FDA provided feedback regarding the suitability of an ongoing randomized, multicenter trial in patients with recurrent GBM (EORTC 26101) to fulfill the PMR for bevacizumab. At that time, FDA stated that the decision to grant conversion from accelerated to full approval will be based on the totality of the evidence including the results of Studies EORTC 26101, AVAglio (BO21990), and Radiation Therapy Oncology Group (RTOG) 0825.

April 5, 2016: A Type B meeting was held during which the Applicant stated that the totality of data supports a favorable benefit–risk profile of bevacizumab as a treatment for patients with GBM, given the consistent effects on PFS across multiple randomized studies. The Applicant also stated that PFS was associated with maintenance of health-related quality of life (HRQoL), neurocognitive function (NCF), and reduced steroid use in studies AVAglio and EORTC 26101. FDA stated that the effect on PFS supported by evidence of a decrease in corticosteroid use and delay in time to initiation of corticosteroids reported for Study EORTC 26101 may be sufficient to verify the clinical benefit of bevacizumab for the second line treatment of GBM. FDA requested that the sBLA contain a thorough and comprehensive assessment of corticosteroid use in studies EORTC 26101 and AVAglio in the sBLA, based on all available data. FDA stated that determination that the results and the benefit-risk assessment of bevacizumab for the treatment of patients with GBM (including the wording of the indication) will be addressed during review of the sBLA.

2.6 Other Relevant Background Information

On November 19, 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended refusing a change to the marketing authorization for bevacizumab to add treatment of GBM after relapse. On May 22, 2014, the CHMP recommended refusing a change to the marketing

authorization for bevacizumab to add treatment of GBM. The Applicant requested a re-examination, and after re-examining the initial opinion, the CHMP confirmed the refusal of the marketing authorization on September 22, 2014. Bevacizumab is not approved for the treatment of GBM by the EMA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sBLA submission contained all of the required components of the electronic common technical document (eCTD) including a debarment certificate, sufficient datasets, and relevant case report forms (CRFs). The submission was generally well organized.

The CRFs were audited by the clinical reviewers to verify that the data transmitted in the datasets were an accurate representation of the patient information documented.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all the studies included in this submission were conducted in accordance with the principles of the "Declaration of Helsinki" and with Good Clinical Practice guidelines. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all the studies and written informed consent was obtained from each patient participating in the studies.

No audits were conducted for Study EORTC 26101 by the Roche Clinical Quality Assurance group or its designees. No audits were conducted for this study by EORTC. In study AVAglio, the Roche Clinical Quality Assurance group or designee conducted audits at three investigator sites as well as four audits at external service providers. Further audits were performed by alliance partner (b) (4) and co-development partner Chugai. No critical audit findings were observed. For Study RTOG 0825, Roche was not the sponsor and therefore no audits were performed by Roche or its designees. NCI was the sponsor and conducted audits according to the NCI guidelines. Audit findings were not disclosed to Roche.

3.3 Financial Disclosures

This submission contained the required financial disclosure information for the clinical investigators who participated in Trials EORTC 26101 and AVAglio. In accordance with 21 CFR 54, the Applicant submitted the following financial information:

FDA form 3455, 3545, and a list of clinical investigators/subinvestigators certified to have no financial interests or arrangements that could affect the outcome of the trial.

Summary of Findings

EORTC 26101
A total of 24 out 25 principal investigators responded. A signed financial disclosure was not obtained for one principal investigator. The Applicant states that the EORTC acted with due diligence to obtain this information.

Of those clinical investigators who participated and enrolled on Study EORTC 26101, two principal investigators reported financial disclosure interests. These disclosures are summarized in the following table.

Table 2 Financial Disclosures for EORTC 26101

Clinical Site Number	Investigator Name	Patient Enrollment	Disclosure
(b) (6)	(b) (6)	(b) (6)	Receipt of research grant to institution totaling $25,000 or more from Roche
(b) (6)	(b) (6)	(b) (6)	Compensation from Roche relating to participation at ASCO and EANO Congresses in 2014

Methods used to minimize bias:

- Multiple investigators participated in the conduct of the trial. The study enrolled 437 patients from 25 institutions in Europe.
- The study included independent data monitoring by the EORTC Independent Data Monitoring Committee.
- Both cases of investigator positive disclosures were reviewed by Roche and assessed whether their financial interest in Roche was significant per the Agency's guidance for industry – Financial Disclosure by Clinical Investigators. To ensure potential bias has not affected the study integrity, the number of patients enrolled by these positive disclosed investigators was also evaluated.

AVAglio
Of those clinical investigators who participated and enrolled on Study AVAglio, one principal investigator reported financial disclosure interest.

Table 3 Financial Disclosures for AVAglio

Clinical Site Number	Investigator Name	Patient Enrollment	Disclosure
(b) (6)	(b) (6)	(b) (6)	Consultant for Roche, support for ongoing research

Methods used to minimize bias:

- Multiple investigators participated in the conduct of the trial. The study enrolled 921 patients from 120 institutions in the US, Canada, Australia, New Zealand, Europe and Asia.
- The study included independent data monitoring by a Data and Safety Monitoring Committee, or Data Monitoring Committee and Data and Safety Monitoring Board.
- On-site auditing procedures were compliant with Roche's auditing guidelines.
- All investigator positive disclosures were reviewed by Roche/Genentech, Inc. and assessed whether their financial interest in Roche, Genentech and/or Chugai was significant per the Agency's guidance for industry – Financial Disclosure by Clinical Investigators. To ensure potential bias has not affected study integrity, the number of patients enrolled by the positive disclosed investigator was also evaluated.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the FDA Chemistry Manufacturing and Controls (CMC) review from the original BLA submission. There were no safety or efficacy issues identified in this submission related to CMC.

4.2 Clinical Microbiology

Please refer to the FDA CMC BLA review from the original submission for details. There were no safety or efficacy issues identified in this submission related to Clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the FDA Pharmacology/Toxicology review from the original BLA for details. There were no safety or efficacy issues identified in this submission related to Preclinical Pharmacology/Toxicology.

4.4 Clinical Pharmacology

Please refer to the FDA Clinical Pharmacology review and to the original BLA for details. There were no safety or efficacy issues identified in this submission related to Preclinical Pharmacology/Toxicology.

4.4.1 Mechanism of Action

As described in the currently approved label, bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis.

4.4.2 Pharmacodynamics

No new pharmacodynamic studies were included in this submission.

4.4.3 Pharmacokinetics

The pharmacokinetic interaction between bevacizumab and temozolomide (TMZ) was evaluated in a limited number of patients with newly diagnosed GBM in Study AVAglio during the maintenance phase of the treatment regimen. The influence of bevacizumab on TMZ pharmacokinetics was not established due to the study being underpowered, owing to the limited number of patients enrolled in the drug-drug interaction sub-study.

5 Sources of Clinical Data

The analysis of clinical safety and efficacy was primarily based on data from Study EORTC 26101 which evaluated the addition of bevacizumab to lomustine in patients with recurrent GBM. Supportive data from Study AVAglio and Study RTOG 0825 which evaluated the addition of bevacizumab to RT and chemotherapy in patients with newly diagnosed GBM or gliosarcoma, are also included.

5.1 Tables of Studies/Clinical Trials

Table 4 Summary of Clinical Studies Contributing to the Efficacy Evaluation

Study	Study design	Patient population	Study treatments	Endpoints
EORTC 26101	Randomized (2:1) Open-label Multicenter Comparing bevacizumab plus lomustine to lomustine	1st recurrence GBM after prior chemoradiation	• Bevacizumab 10 mg/kg q 2 wks plus lomustine 90 mg/m² q 6 wks [a]; • Lomustine 110 mg/m² q 6 wks	Primary: OS Secondary: inv PFS, ORR, HRQoL, neurological deterioration-free survival, NCF, steroid use.
AVAglio	Randomized (1:1) Double-blind Placebo-controlled Multicenter Comparing SoC with or without bevacizumab	Newly diagnosed, supratentorial GBM	Administered in conjunction with first-line SoC (including temozolomide chemotherapy) • Placebo • Bevacizumab 10 mg/kg q 2 wks	Co-primary: OS, inv PFS Secondary: OS 1 and 2 year, PFS (IRRC), HRQoL, safety
RTOG 0825	Randomized (1:1) Double-blind Placebo-controlled Multicenter Comparing SoC with or without bevacizumab	Newly diagnosed, GBM or gliosarcoma	Administered in conjunction with first-line SoC (including temozolomide chemotherapy) • Placebo • Bevacizumab 10 mg/kg q 2 wks	Co-primary: OS, PFS Secondary: HRQoL, NCF, safety

GBM: glioblastoma; SoC: radiation therapy with concomitant temozolomide, followed by temozolomide; RT/T = bevacizumab plus radiotherapy; wks: weeks; OS: overall survival; PFS: progression-free survival; inv: investigator assessed; IRC: independent review committee; HRQoL: health related quality of life; NCF: neurocognitive function; IRRC: independent radiological review committee.
[a] in the absence of >grade 1 hematologic toxicity during cycle 1, the dose of lomustine could be escalated to 110 mg/m² in subsequent cycles.

5.2 Review Strategy

The focus of the clinical review was on the efficacy and safety data from study EORTC 26101. Supportive data from AVAglio and RTOG 0825 were also reviewed. The electronic submission, with the CSRs (where available), and other relevant portions of all three studies were reviewed and analyzed. The key review materials and activities are outlined below:

- Review of the current literature on the epidemiology and treatment of GBM
- Review of Study EORTC 26101, including the CSR, protocol, and protocol amendments
- Review and assessment of the Applicant's analysis of bevacizumab safety and efficacy in the CSR
- Review of the datasets submitted
- Review of patient narratives of SAE and deaths
- Review of minutes of key meetings conducted during the development of bevacizumab for the proposed indication
- Relevant submissions in response to the medical officers' information requests
- The Applicant's presentation to FDA on February 28, 2017
- Formulation of the risk/benefit analysis and recommendations

The majority of efficacy and safety analyses were reproduced or audited using the JMP/SAS datasets submitted electronically with the sBLA for Studies AVAglio and EORTC 26101. Limited datasets were submitted for Study RTOG 0825.

5.3 Discussion of Individual Studies/Clinical Trials

Study Title

EORTC 26101: "Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of a glioblastoma"

Study Design and Treatment Plan

Study EORTC 26101 was a randomized, open-label, multicenter study to investigate the efficacy and safety of bevacizumab plus lomustine compared to lomustine alone in patients with recurrent GBM. Study EORTC 26101 was initially designed as a 4-arm, randomized, noncomparative study intended to investigate the optimal incorporation and sequencing of bevacizumab and lomustine in this setting. Patients were randomized in a 2:2:2:1 ratio to the following arms:

- Arm 1: bevacizumab 10 mg/kg every 2 weeks + lomustine 90 mg/m^2 every 6 weeks
- Arm 2: lomustine 110 mg/m^2 every 6 weeks until PD, then bevacizumab 10 mg/kg every 2 weeks
- Arm 3: bevacizumab 10 mg/kg every 2 weeks until PD then continue bevacizumab and add lomustine 90 mg/m^2 every 6 weeks
- Arm 4: lomustine 110 mg/m^2 every 6 weeks

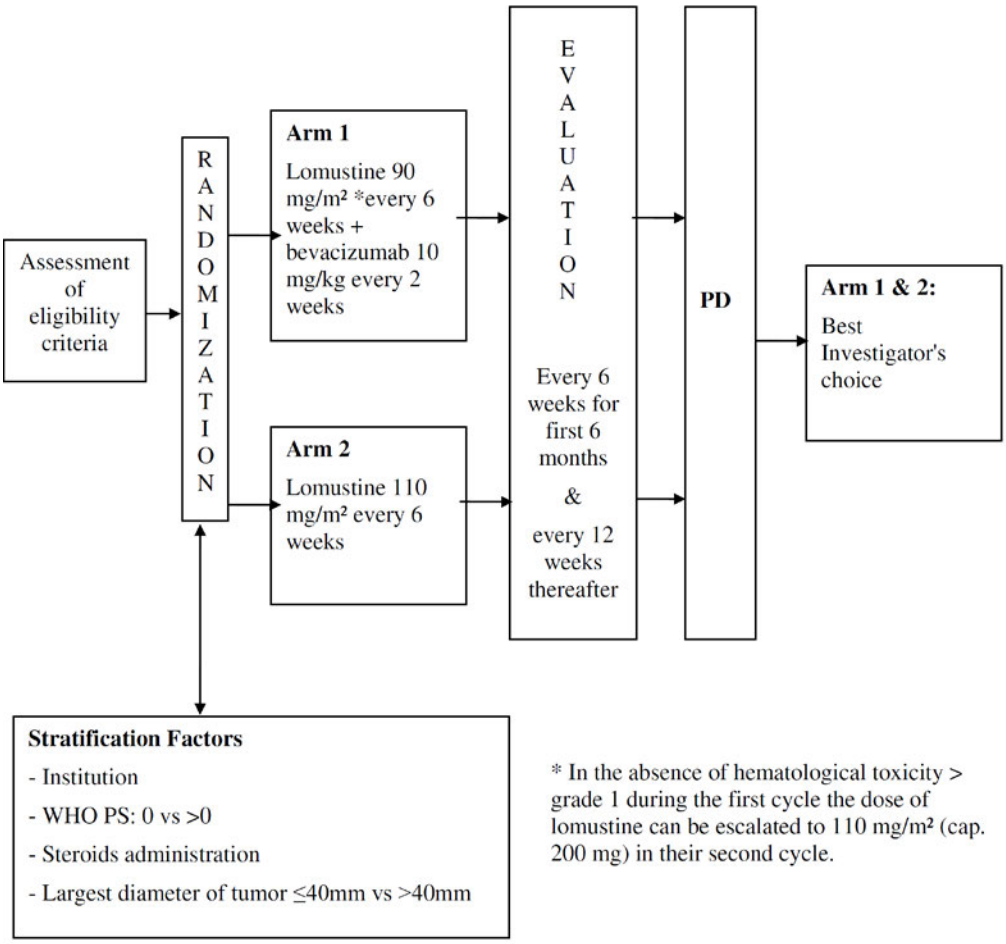
The primary endpoint was OS at 12 months with a target accrual of 249 patients. The study was amended to drop Arms 2 and 3, based on results from a Dutch study in recurrent GBM[9] describing a survival benefit with bevacizumab with lomustine compared with either drug alone. The amendment was implemented prior to any analysis of the original 4-arm part of the study.

Following the amendment, patients continued to be randomized in a 2:1 ratio to receive either bevacizumab with lomustine or lomustine alone (Arms 1 and 4). One cycle was defined as 6 weeks for all arms. Randomization was stratified by institution, WHO PS (0 or > 0), steroid administration (yes or no), and largest tumor diameter (≤ 40 mm or > 40 mm). Patients were treated until disease progression, withdrawal of consent, intolerable toxicity, treatment was not thought to be in their best interest, the start of any other anti-cancer agent, or pregnancy. At disease progression, treatment was per the investigator's discretion. Response to treatment was assessed by MRI every 6 weeks for the first 6 months and every 12 weeks thereafter, using the modified Response Assessment in Neuro-Oncology (RANO) criteria (including radiological tumor response assessments, clinical examination, and corticosteroid use).

Reviewer comment: The RANO criteria were modified to include quantitative assessment of T2 or FLAIR changes consistent with PD. A 25% increase in the sum of the products of perpendicular diameters of areas with abnormalities on FLAIR/T2 images compared to the nadir time point (point with the smallest FLAIR/T2 abnormalities) was considered progression.

The study design is depicted below.

Figure 1: Study schema for EORTC 26101



Source: Protocol Version 2.0, July 4, 2013

Key Eligibility Criteria (modified from the protocol, Version 2.0)

- Histologically confirmed de novo GBM (primary) with unequivocal first progression after RT concurrent/adjuvant chemotherapy, at least 3 months from concomitant chemoradiation.
- ≥18 years of age
- No more than one line of chemotherapy
- No prior treatment with bevacizumab or other VEGF or VEGFR inhibitors
- No prior treatment with nitrosoureas

- Recurrent disease must be at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on MRI scan done within 2 weeks prior to randomization
- Patient may have been operated for recurrence. If operated:
    - Measurable disease after surgery is not required but surgery must confirm recurrent disease
    - A post-surgery MRI should be available within 48 hours following surgery
    - Surgery completed at least 2 weeks before randomization and patients should have fully recovered
- Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan
- Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization
- No radiotherapy within 3 months prior to diagnosis of progression
- No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven
- Absence of any cardiovascular disorder, any thrombotic or hemorrhagic event, and known hypersensitivity to study drugs
- Normal hematological, liver and renal function
- WHO PS 0-2

Objectives/Endpoints

Primary Objective/Endpoint
The primary objective of this study was to investigate whether the addition of bevacizumab to lomustine improved OS in patients with recurrent GBM compared with lomustine alone.

Secondary Endpoints
- PFS assessed by the investigator using the modified RANO criteria
- Response rates (i.e., complete response and partial response) and median duration of response by modified RANO criteria
- HRQoL
- Clinical/neurological deterioration-free survival (NDFS)
- Steroid use
- Cognitive function assessed by:
    - Hopkins verbal learning test (HVLT)
    - Trail making test (TMT) Part A and Part B
    - Controlled oral word association (COWA)
- OS at 9, 12, and 24 months
- PFS at 6 and 12 months

- Clinical/Neurological disease free survival (NDFS) at 6 and 12 months
- Safety profile

Reviewer comment: Clinical/Neurological deterioration was defined as a decrease in WHO PS as follows:

- patients with baseline WHO PS of < 2: deterioration to WHO PS 2 worse for which no other explanation was present, maintained for at ≥ 3 weeks
- patients with baseline WHO PS of 2: deterioration to WHO PS 3 or worse for which no other explanation was present, maintained for ≥ 3 weeks

Dose Modifications/Dose Discontinuations:
The protocol included acceptable dose modification and dose discontinuation guidelines for both bevacizumab and lomustine. In the bevacizumab plus lomustine arm, dose reductions or delays were to be made for the likely causative agent. If one of the study drugs was stopped in for any reason other than PD, the patient was permitted to continue on the other agent. Patients who required a delay in administration of one of the study drugs for more than 4 weeks were not permitted to re-start that study drug.

Procedures and Study Schedule:
Performance status (WHO PS) was assessed at baseline, every 6 weeks for the first 6 months and every 12 weeks thereafter until documented progression. The WHO PS was also used to determine clinical neurological deterioration. The EORTC QLQ-C30 and the supplemental 20-item brain-specific quality of life questionnaire (BN20) were used to assess disease and treatment impacts on HRQoL, symptoms, and functioning. These assessments were performed at baseline and then every 12 weeks until disease progression. Neurocognitive function (NCF) was assessed by trained psychologists during clinical visits using the HVLT, TMT Part A and Part B, and COWA at baseline and then every 12 weeks until disease progression. Safety was assessed separately for each cycle of therapy and then every 12 weeks after the end of study treatment until disease progression.

Descriptive summaries of the extent of corticosteroid use over time were provided by treatment arm. The lowest percentage was calculated as the minimum of the percentage change (i.e., maximum percentage decrease) from baseline in corticosteroid dose recorded across timepoints.

The schedule of study procedures for the protocol are provided in Table 5.

Table 5 Schedule of assessments EORTC 26101

	Screen [14 days]	Protocol Treatment phase (j) until one of the withdrawal criteria is met			Follow-up: from end of study treatment until PD	Follow-up: From PD until death
		Every 2 weeks	Every 6 weeks	Every 12 weeks	Every 12 weeks	Every 12 weeks
Signed informed consent	X					
Medical history	X					
Prior cancer therapy	X					
Concomitant medication collection	X			X	X (i)	
Steroid dosage	X		X	X	X	
Complete physical examination with height(baseline) /neurological examination	X		X			
Weight	X		X			
Vital signs (a)	X	X	X		X (i)	
WHO-PS	X		X		X	
Adverse events evaluation (b)	X	X	X		X (if not resolved or newly emerging)	X (if not resolved or newly emerging)
ECG	X		X (i)			
Quality of life assessment (c)	X			X	X	
Neurocognitive assessment (d)	X			X	X	
Hematology (e)	X	X	X			
Biochemistry (e)	X		X			
INR and aPTT	X		X			
Serum/urine pregnancy test	X (f)					
Urine dipstick	X	X	X			
Gd-MRI	X (g)		X(g)	X(g)	X(g)	X(g)
Survival follow-up						X
Biological samples availability for central review and translational research	X(h)	X(h)	X(h)	X(h)		

(a) Including blood pressure to collect possible hypertension

(b) Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure

(c) EORTC QLQ-C30 and EORTC-BN20 to be completed by both patients and caregivers/relatives (cf. Chapter 10).

(d) Neurocognitive assessment, including Hopkins Verbal Learning Test-revised (HLVT-R), trail making test Part A, trail making test Part B and controlled oral word association (COWA; cf. Appendix F)

(e) Including complete blood counts (hemoglobin, hematocrit, white blood cells and differentiate -neutrophils and lymphocytes-, platelets) and serum chemistry (sodium, potassium, calcium, phosphates, chloride, creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatases, total protein, albumin)

(f) Serum pregnancy test for premenopausal female patients within 72 hours prior to treatment

(g) Every 6 weeks for the first 6 months (all patients without progression will be followed every 6 weeks for the first 6 months) and then every 12 weeks thereafter

(h) Refer to translational research chapter

(i) If clinically relevant

(j) As long as patient will receive protocol treatment

Source: Protocol Version 2.0, July 4, 2013

Tumor assessment and determination of response

Response was assessed for target lesion(s) that were selected before start of study drugs. Tumor size is defined as the product of the two largest perpendicular diameters. Quantitative measurement of T2/FLAIR changes were also included (see Study Design and Treatment Plan, above). Target lesions must initially be measured in their two perpendicular dimensions, and these measurements were to be repeated at each evaluation of the disease by the same method. Objective response was not assessed in patients having undergone second surgery with complete removal of contrast enhancing lesions prior to study entry.

Summary of Statistical Plan

Analysis Methods for OS, PFS and NDFS

OS is defined as the time from the date of randomization to death due to any cause. Patients still alive or lost to follow-up at the time of the final analysis will be censored at the last date they were known to be alive.

PFS is defined as the time between randomization and first documentation of disease progression or death due to any cause, whichever occurs first. Patients without a PFS event by the clinical cut-off date will be censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.

NDFS is defined as the time between randomization and first documentation of clinical/neurological deterioration or death, whichever occurs first. Clinical/Neurological deterioration is defined as a decrease in WHO performance status as follows:

- For patients with WHO performance status 0 or 1 at baseline: deterioration to WHO performance status 2 or worse, and which is maintained for at least 3 weeks
- For patients with WHO performance status 2 at baseline: deterioration to WHO performance status 3 or worse, and which is maintained for at least 3 weeks

Death will only be considered as an event in the absence of prior clinical/neurological deterioration if it occurred within 12 weeks of the last WHO performance status assessment. Patients without evidence of neurological deterioration will be censored at the last WHO assessment date or at baseline if patient has no post-baseline WHO assessments.

The analysis of OS, PFS and NDFS were conducted using a one-sided (0.025 significance level) log-rank test stratified by WHO PS (0 vs. > 0), steroid administration (yes or no), and largest tumor diameter (≤ 40 mm vs. > 40 mm) and a variable indicating if the patient was recruited in the Phase II or Phase III portion of the study. The medians were estimated using the Kaplan-Meier method and the corresponding 95% confidence intervals were reported. The treatment effect was measured using hazard ratio and the corresponding 95% CI, calculated using the stratified cox-proportional hazards model, with treatment arm as a single covariate.

Sensitivity analyses methods for OS
To account for the potential effect of crossover to subsequent bevacizumab treatment on the OS of patients randomized to the control arm, analysis using the rank-preserving structural failure time (RPSFT) model was performed based on the following assumptions regarding the time on/off bevacizumab in the two treatment arms: 1) patients in the Bev + Lom arm who did not receive bevacizumab after progression are assumed to be on bevacizumab until date of last study treatment; 2) patients in bevacizumab + Lom arm who received bevacizumab after progression are assumed to be on bevacizumab until date of death; 3) patients in the Lom arm who received bevacizumab after progression are assumed to be on bevacizumab from the date of first bevacizumab dose until date of death.

Analysis Methods for ORR
Objective response rate (ORR) is defined as the proportion of patients with a complete or partial best overall response based on the modified RANO criteria as assessed by the investigator. The analysis will be based on patients with measurable disease, defined as a clearly enhancing tumor with two perpendicular diameters ≥1 cm, at baseline.

Analysis of ORR was performed using a Cochran-Mantel Haenszel (CMH) test stratified by institution, WHO PS (0 vs. > 0), steroid administration (yes or no), and largest tumor diameter (≤ 40 mm vs. > 40 mm) and a variable indicating if the patient was recruited in the Phase II or Phase III portion of the study. The point estimates of ORR and its corresponding 95% CI using Pearson-Clopper method were calculated.

Multiplicity Adjustment
In order to ensure that the type I error is adequately controlled when analyzing multiple endpoints the following hierarchy was implemented in the analysis of the endpoints:

- OS
- PFS assessed by the investigator based on the modified RANO criteria
- Objective response rate based on the modified RANO criteria
- HRQoL (global health status, cognitive functioning and pain scales)
- Clinical/neurological deterioration free survival

Sample size calculations

Assuming that the true OS hazard ratio (HR) was 0.72 corresponding to median OS of 6.8 in the lomustine monotherapy arm and 9.5 months in the bevacizumab plus lomustine arms, a total of 327 events were needed to show a statistically significant difference in overall survival between the treatment and control arm based on stratified log-rank test with 80% power at a 1-sided alpha level of 0.025. Approximately 433 patients were to be randomized to observe 327 deaths. A non-linear recruitment period

of 37 months (accrual rate of 5.12 patients/month during the first 17 months, 9.1 patients\month during the next 6 months and 20 patients/month for the last 14 months) was assumed, with a minimum follow-up of 8 months for the last patient enrolled, to observe 327 deaths.

Interim analysis
No formal interim analysis was planned.

Subgroup Analyses
OS results were further investigated in the subgroups described below. A forest plot of the estimated HRs and their 95% CIs were presented to identify the difference (exploratory analysis) between the two treatment arms in the subgroups.

- Age (< 65, ≥ 65 years)
- Age (<50, 50-59, 60-69 and >70)
- Gender (Male, Female)
- WHO PS (0, 1, 2)
- MGMT gene promoter status (methylated, un-methylated, missing)
- Surgery for the first recurrence/progression (yes, no)
- Corticosteroid use at baseline (yes, no)
- Largest lesion diameter at baseline (≤40mm, >40mm)

Studies in patients with newly diagnosed GBM
Two contemporaneous, randomized, placebo-controlled trials evaluated the clinical benefit of adding bevacizumab to the standard first-line treatment for newly diagnosed GBM (AVAglio and RTOG 0825). The two trials were similar in design, patient characteristics, and the objectives; therefore, these studies will be discussed together. The results from these studies were considered as supportive data for the primary study (EORTC 26101). Important differences in study design, patient populations, endpoints, and statistical analyses plans are highlighted in Table 6 below, followed by discussion of the individual studies.

Table 6 Key differences between AVAglio and RTOG 0825 study design

Study	Sample size	Stratification factors	Treatment regimen	Endpoints	Instruments to measure HRQoL
AVAglio	Randomized (1:1) to SoC with: Placebo (n=463) OR Bevacizumab (n=458)	RPA Class Region	Concurrent phase: 6 weeks RT plus TMZ 75 mg/m^2/daily with: • Placebo or bevacizumab 10 mg/kg q 2 wks Maintenance phase (6 cycles): TMZ 150-200 mg/m^2 days 1-5/28 with: • Placebo or bevacizumab 10 mg/kg q 2 wks Monotherapy phase (until PD): • Placebo or bevacizumab 15 mg/kg q 3 wks	Co-primary: OS and inv PFS Key Secondary: PFS by IRF OS 1 and 2 years Safety HRQoL	EORTC-QL30/BN20
RTOG 0825	Randomized (1:1) to SoC with: Placebo (n=309) OR Bevacizumab (n=312)	MGMT status Molecular profile	Concurrent phase: 6 weeks RT plus TMZ 75 mg/m^2 qd for 21 days, then RT plus TMZ 75 mg/m^2 qd for 21 days with: • Placebo or bevacizumab 10 mg/kg q2 wks Adjuvant phase: (maximum 12 cycles) TMZ 150-200 mg/m^2 days 1-5/28 with: • Placebo or bevacizumab10 mg/kg q2 wks	Composite primary: OS and PFS Key Secondary: Determine if mesenchymal/angiogenic phenotype is associated with benefit with bevacizumab	EORTC-QL30/BN20 MDASI-BT

RT: radiation therapy; TMZ: temozolomide; wks: weeks; PD: progressive disease; MGMT: O6-methylguanine–DNA methyltransferase; PFS: progression-free survival; OS: overall-survival; IRF: independent review facility; HRQoL: Health-related quality of life; MDASI-BT: M.D. Anderson Symptom Inventory Brain

Reviewer comment:
- The RPA class included age, WHO PS, mini-mental status exam (MMSE), surgery or biopsy.
- An unrestricted educational grant was provided by Genentech in support of Study RTOG 0825. Genentech did not collect or provide analyses of the findings.

Study Title

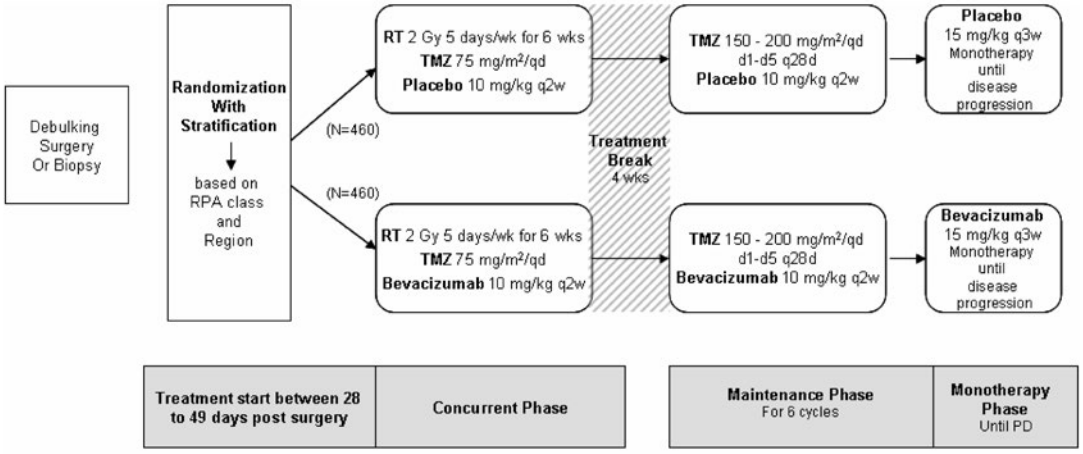
BO21990: "A randomized, double-blind, placebo-controlled, multicenter Phase III trial of bevacizumab (bevacizumab), temozolomide (TMZ) and radiotherapy (RT), followed by bevacizumab and TMZ versus placebo (Pl), TMZ and RT followed by Pl and TMZ in patients with newly diagnosed glioblastoma (AVAglio)"

Study Design and Treatment Plan

Study BO21990 (also known as study AVAglio) was a randomized (1:1), double-blind, two-arm, multicenter study to investigate the efficacy of the addition of bevacizumab to TMZ and RT for the treatment of patients with newly diagnosed GBM. The trial consisted of three phases:

- Concurrent Phase (6-week duration)
- Maintenance Phase (6 cycles of 4-week duration)
- Monotherapy Phase (3-week cycles until occurrence of PD. An overview of the study design is presented in Figure 2. After PD, patients were followed for safety, survival, and subsequent anti-cancer therapy use every 9 weeks.

Figure 2: Study schema AVAglio



RT: radiation, TMZ: temozolomide

Source: Protocol, Version C, August 29, 2012

An independent review of patients' magnetic resonance imaging (MRI) studies was carried out at an Independent Review Facility (IRF). Descriptive summaries of the extent of corticosteroid use over time were collected by treatment arm as an exploratory objective.

Tumor assessment and determination of response

The evaluation of disease status was performed per adapted Macdonald response criteria, and included radiological tumor response assessments, neurological examination, and corticosteroid use. Qualitative assessment of non-index lesions, non-enhancing lesions on FLAIR/T2-weighted sequences, and non-measurable lesions were also included. Patients who had clear neurological worsening with unchanged or increased corticosteroid dose compared to the previous disease assessment were considered to have PD. All patients' MRI scans performed for the study disease assessments were sent for blinded centralized review to an independent review facility (IRF).

Summary of Statistical Plan

The study had co-primary endpoints: OS and PFS. In order to adjust for multiplicity, the overall alpha of 5% was split with 4% assigned for OS and 1% for PFS. The hazard rates for OS and PFS in the placebo plus RT and TMZ arm were to be compared with those in the bevacizumab plus RT and TMZ arm. For PFS, the assumed median PFS duration was 9.1 months in the bevacizumab-containing arm and 7 months in the placebo arm (corresponding to a hazard ratio of 0.769, or a reduction in the immediate risk of progression or death by 23%); therefore, it was determined that 677 events are required to achieve 80% power of the log rank test at a 2-sided 1% alpha level. The final analysis of PFS was planned after 677 patients had a PFS event (first of PD or death). Assuming a median duration of survival of 18.3 months for the bevacizumab-containing arm and 14.6 months for the placebo containing arm, (corresponding to a hazard ratio of 0.80, or a reduction in the immediate risk of death by 20%), 683 events are required to achieve 80% power of the log rank test at a 2-sided overall 4% alpha level. Two interim analyses for OS were planned; the first when at least 50% of events for the final OS analysis had been observed, the second at the time of the final PFS analysis when at least 72% of events for the final OS had been observed. The final analysis of OS was planned to be performed when approximately 683 deaths had occurred.

Corticosteroid Use

Corticosteroid use was to be analyzed in two subsets of patients according to their baseline corticosteroid dose: this was defined as the average dexamethasone equivalent dose administered for GBM within 5 days before the first trial treatment. Patients were categorized as "on" corticosteroids if the dose was ≥ 2 mg. If a dose was not reported, this was captured as a 0 mg dose.

Health-Related Quality of Life and Neurocognitive function

Changes in HRQoL were to be assessed using the EORTC QLQ C-30 and the brain cancer specific module, EORTC QLQ BN20. Five subscales were pre-selected for the primary analyses of HRQoL (considered most relevant to the GBM population based on clinical experience):

- QLQ-C30 global health status/quality of life (QoL)
- QLQ-C30 physical functioning

- QLQ-C30 social functioning
- BN20 motor dysfunction
- BN20 communication deficit

Neurocognitive function was to be assessed using the with the MMSE. Three neuropsychological tests were also included in a sub-study of patients from countries that had validated translations of the tests: the HVLT-R, TMT (Part A and Part B), and the COWA.

These COA instruments were administered at baseline, every 12 weeks until disease progression, death, loss of follow-up or patient's withdrawal of consent. Trained and certified healthcare professionals at each site administered the cognitive function tests.

Neurological Assessments
Evaluation of neurological function was based on the investigator's overall assessment of the patient's neurological state compared to that at the time of the last disease assessment and was recorded as improved, unchanged, or worsened.

Safety analysis
Adverse Events (AEs) were collected throughout the study and up to 90 days after the last dose of study drug. Adverse events of special interest (AESI) were collected up to 6 months after the last dose of study drug, and serious adverse events (SAEs) considered related to trial treatment by the investigator were to be reported indefinitely. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.

Adverse Events of Special Interest (AESIs) were pre-defined in the protocol and in addition, seizures were monitored as an AE of special interest for GBM.

Study Title

RTOG 0825: "A Phase III, double-blind, placebo-controlled trial of conventional concurrent chemoradiation and adjuvant temozolomide plus bevacizumab versus conventional concurrent chemoradiation and adjuvant temozolomide in patients with newly diagnosed glioblastoma"

Study Design and Treatment Plan
Study RTOG 0825 was a double-blind, placebo-controlled, randomized trial (1:1) of concurrent chemoradiation and adjuvant TMZ plus bevacizumab compared with concurrent chemoradiation and adjuvant TMZ in patients with newly diagnosed GBM or gliosarcoma.

The randomization was stratified on the basis of the following:

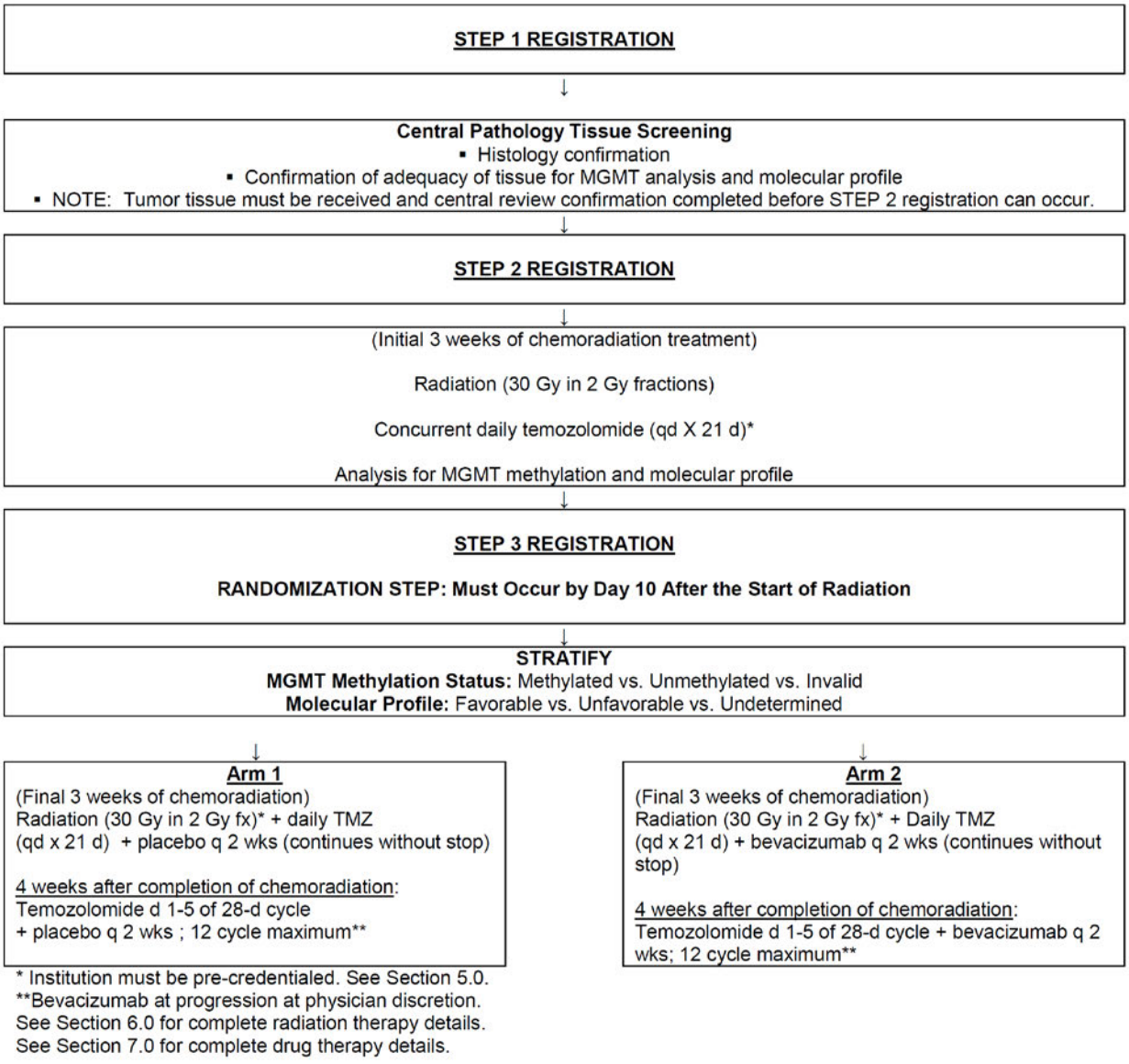
- MGMT methylation status (methylated, unmethylated, invalid)
- Molecular profile: (favorable, unfavorable, undetermined) based on nine genes

Randomization was to the following arms:

- Arm 1: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus placebo every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28 day cycle plus placebo every 2 weeks, for a maximum of 12 cycles.
- Arm 2: Final 3 weeks of chemoradiation: RT and concurrent daily TMZ plus bevacizumab every 2 weeks. Four weeks after completion of chemoradiation: TMZ on days 1-5/28 day cycle plus bevacizumab every 2 weeks, for a maximum of 12 cycles.

The study design is summarized in Figure 3.

Figure 3: Study schema for Study RTOG 0825



* Institution must be pre-credentialed. See Section 5.0.
**Bevacizumab at progression at physician discretion.
See Section 6.0 for complete radiation therapy details.
See Section 7.0 for complete drug therapy details.

Patient Population: (See Section 3.0 for Eligibility)

- Histopathologically confirmed glioblastoma (WHO Grade IV) **confirmed by central pathology tissue screening prior to step 2 registration**
- Tumor tissue that is **determined by central pathology tissue screening prior to step 2 registration** to be of sufficient size for analysis of MGMT status and determination of molecular profile
- The tumor must have a supratentorial component

Required Sample Size: 942 patients

Source: Protocol, Amendment 7, June 30, 2014

Patients with progressive disease either during or after protocol treatment could, if eligible, receive unblinded bevacizumab as follows:

- as a single agent
- in combination with irinotecan
- in combination with temozolomide

Tumor assessment and determination of response

The evaluation of disease status was performed by serial measurements of the product of the two largest cross-sectional diameters. Response was to be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). Patients with partial (PR) or minor response (MR) should be receiving stable or decreasing doses of steroids. In order to address the phenomenon of "pseudo-progression", in the absence of neurological worsening or a new area of disease distant to the primary, the initial post-RT scan was not to be used to declare progression.

Net clinical benefits (NCB) sub-study

An optional sub-study to evaluate HRQoL and NCF was included. The M.D. Anderson symptom inventory brain tumor module (MDASI-BT) and EORTC QLQ-30/BN 20, were to be used to evaluate HRQoL. Neurocognitive function was assessed using the HVLT-R, TMT Part A and B, and the COWA test.

Summary of Statistical Plan

The study had a composite primary endpoint of OS and PFS. Treatment related toxicity was a secondary endpoint. The composite primary endpoint was to test OS for the hypothesized hazard ratio of 0.75 and PFS for the hypothesized hazard ratio of 0.70. The hazard ratios compare the bevacizumab-containing regimen to the placebo arm. The statistical power was set as 0.8 and the significance levels for OS and PFS were 0.023 and 0.002 (both one-sided), respectively, to maintain an overall significance level of 0.05 at the time of final OS analysis. The null hypothesis for overall survival was that both arms will have a median OS of 14 months and the alternative hypothesis was that patients receiving the bevacizumab-containing regimen will have a median OS of at least 18.7 months, corresponding to a 25% relative hazard reduction. Using a one-sided test with alpha of 0.023 and four planned analyses (three interim analyses when 25%, 50% and 75% cumulative information for OS is available and one final analysis when complete information for OS is available), a total of 390 deaths would be required to detect the hypothesized survival difference with 80% power. Assuming median PFS of 6.7 and 9.6 months for the control and experimental arms, respectively, in order to maintain the overall type I error of 0.025 (one-sided) the PFS difference was to be tested at the one-sided significance level of 0.002. The trial would be declared positive if either the OS or PFS comparison is statistically significant favoring the bevacizumab-containing arm at 0.023 and 0.002, respectively.

6 Review of Efficacy

Efficacy Summary

Recurrent GBM:
Study EORTC 26101 was an open-label, randomized (2:1), multicenter trial of bevacizumab plus lomustine versus lomustine alone in 437 patients. Randomization was stratified by investigational site, performance status (0,> 0), steroid use (yes, no), and largest tumor diameter (≤ 40 mm, > 40mm). The primary endpoint of the study was OS and the primary analysis was a stratified log-rank test performed on the ITT population. Key secondary endpoints were investigator-assessed PFS and ORR as determined by the modified RANO criteria. The study did not demonstrate an improvement in OS; however, there was a statistically significant improvement in PFS for patients randomized to the bevacizumab plus lomustine arm compared with the lomustine alone arm.

In Study EORTC 26101, among patients who were receiving corticosteroids at baseline, more patients in the bevacizumab-containing arm were likely to decrease their dose compared with patients in the lomustine alone arm (63.6% vs. 36.5%). Among patients who were not receiving corticosteroids, 37.9% in the bevacizumab-containing arm and 38.7% in the lomustine arm initiated steroids. The median time to initiation was longer in the bevacizumab arm (3.02 months) than in the lomustine arm (1.48 months).

Newly diagnosed GBM:
Both Study AVF4396g and Study RTOG 082 were conducted in patients with newly diagnosed. Key differences in study design, treatment plan, and disease assessment are described above. The consistency of trial design was mirrored by the consistency of the primary outcomes, with both trials showing a 3-to-4-month prolongation of progression-free survival with bevacizumab but no significant effect on overall survival.

Although none of the randomized studies conducted in patients with GBM demonstrated an improvement in OS with the addition of bevacizumab to standard of care treatments, PFS was consistently improved for patients receiving bevacizumab. This finding is consistent with the objective responses that are seen with bevacizumab in the GBM population. Evaluation of endpoints such as patient functioning or corticosteroid use may be used to support the demonstrated improvement in PFS; however, there were inconsistent findings of clinical outcomes among the three studies.

6.1 Indication

The Applicant proposes the following indication for the bevacizumab label:
“Avastin® (bevacizumab) is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy”.

6.1.1 Methods

Study EORTC 26101 evaluated the addition of bevacizumab to lomustine in patient with recurrent glioblastoma (rGBM). The primary endpoint was OS with key secondary endpoints of investigator-assessed PFS and corticosteroid usage. To further support the benefit-risk assessment of bevacizumab in patients with GBM, additional exploratory analyses of concomitant corticosteroid therapy were performed in randomized study of standard chemoradiation with or without bevacizumab in patients with newly diagnosed GBM (AVAglio). The co-primary endpoints of AVAglio were OS and PFS.

6.1.2 Patient Disposition and Demographics

EORTC 26101

Patient Population

This study was conducted at 38 centers in eight Western European countries. The first patient was randomized on November 21, 2011 and the last patient last visit date was July 31, 2015, the clinical database lock date for this study. The table below summarizes the total number of subjects enrolled in the study and the number of subjects in each of the analyses population considered in this study.

Table 7: Analyses populations (EORTC 26101)

Analysis Populations	Lom	Bev+Lom	Total
Enrolled Subjects # patients who did not consent to share data			437 5
Randomized subjects (ITT)*: #patients who did not receive the study dose	149 2	283 5	432 7
Treated/Per protocol population: (All randomized subjects who received at least one dose of study drug.)	122	243	365
ORR population (Patients with measurable disease at baseline)	139	260	399
QoL population	136	267	403

*The baseline demographics and efficacy analyses are performed using ITT population.

Patient Disposition

Of the 437 enrolled patients, 5 were not randomized, and 7 patients from the randomized group were not treated due to withdrawal of consent (n=3), hospitalization due to epilepsy (n=1), no treatment being given prior to disease progression (n=1), clinical deterioration (n=1), and screen failure (n=1). The table below also summarizes the number of patients who were continuing the study treatment at the time of database lock date.

Table 8: Disposition of patients (EORTC 26101)

Subject Disposition, n	**Lom**	**Bev+Lom**	**Total**
Enrolled			437
Randomized(ITT)	149	283	432
Treated	147	278	425
Not Treated	2	5	7
At clinical cut-off			
#Subjects continuing treatment	3	23	26
#subjects followed for survival	33	45	78
Lost-to-follow-up	0	1	1
Deaths	113	214	327
Reason for withdrawal from study treatment	120	201	321
Disease Progression	15	37	52
Study drug toxicity (+Toxic death)	1	5	6
Withdrawal of consent by patient	2	2	4
Investigator's decision	-	1	1
Death not due to malignant	8	14	22
Other			

Baseline Demographic and disease characteristics

The demographic and disease characteristics at baseline of the subjects are summarized by treatment arm in **Table 9**. In general, the distribution of the demographic characteristics and baseline disease characteristics appear to be balanced between the treatment arms

Table 9: Demographic and baseline disease characteristics (EORTC 26101)

n (%)		Lom N-149	Bev+Lom N=283
Gender	Female	58 (38.9%)	112 (39.6%)
	Male	91 (61.1%)	171 (60.4%)
Age (in years)	Mean	57.2	56.2
	SD	10.67	10.67
	Median	59.0	57.0
Age Group I	<65	109 (73.2%)	216 (76.3%)
	>=65	40 (26.8%)	67 (23.7%)
Age Group II	<50	30 (20.1%)	67 (23.7%)
	50-59	46 (30.9%)	107 (37.8%)
	60-69	57 (38.3%)	78 (27.6%)
	>=70	16 (10.7%)	31 (11.0%)
MGMT Gene Promoter Status	Methylated	37 (24.8%)	64 (22.6%)
	Non-methylated	38 (25.5%)	85 (30.0%)
	Missing	74 (49.7%)	134 (47.3%)
Corticosteroid intake at baseline	No	75 (50.3%)	140(49.5%)
	Yes	74 (49.7%)	143 (50.5%)
Surgery/Biopsy for 1st Progression	No	121 (81.2%)	225(79.5%)
	Yes	28 (18.8%)	58(20.5%)
WHO Performance Status	0	48 (32.2%)	100 (35.3%)
	1	83 (55.7%)	151 (53.4%)
	2	18 (12.1%)	32 (11.3%)
GBM Histology	Confirmed	147 (98.7%)	281 (99.3%)
	Not confirmed	2 (1.3%)	2 (0.7%)
Largest Lesion Diameter (mm) at Baseline	<=40	85 (57.0%)	159 (56.2%)
	>40	64 (43.0%)	124 (43.8%)
Prior Therapy for GBM	Prior chemotherapy and prior Irradiation	149 (100%)	283 (100%)
Anti-convulsant Treatment at Baseline	No	45 (30.2%)	103 (36.4%)
	Yes	104 (69.8%)	180 (63.6%)

6.1.3 Analysis results of primary and key secondary efficacy endpoint(s)

Study EORTC 26101

In this section, the efficacy results for the primary and key secondary endpoints of the study based on clinical cutoff date of 31 July 2015 are presented to compare the Bev+Lom arm with Lom arm alone.

As of the clinical cutoff date, a total of 327 deaths were observed and the median duration of survival follow-up was similar between the two treatment arms (8.08 months in the bevacizumab + Lom arm vs. 8.11 months in the Lom arm).

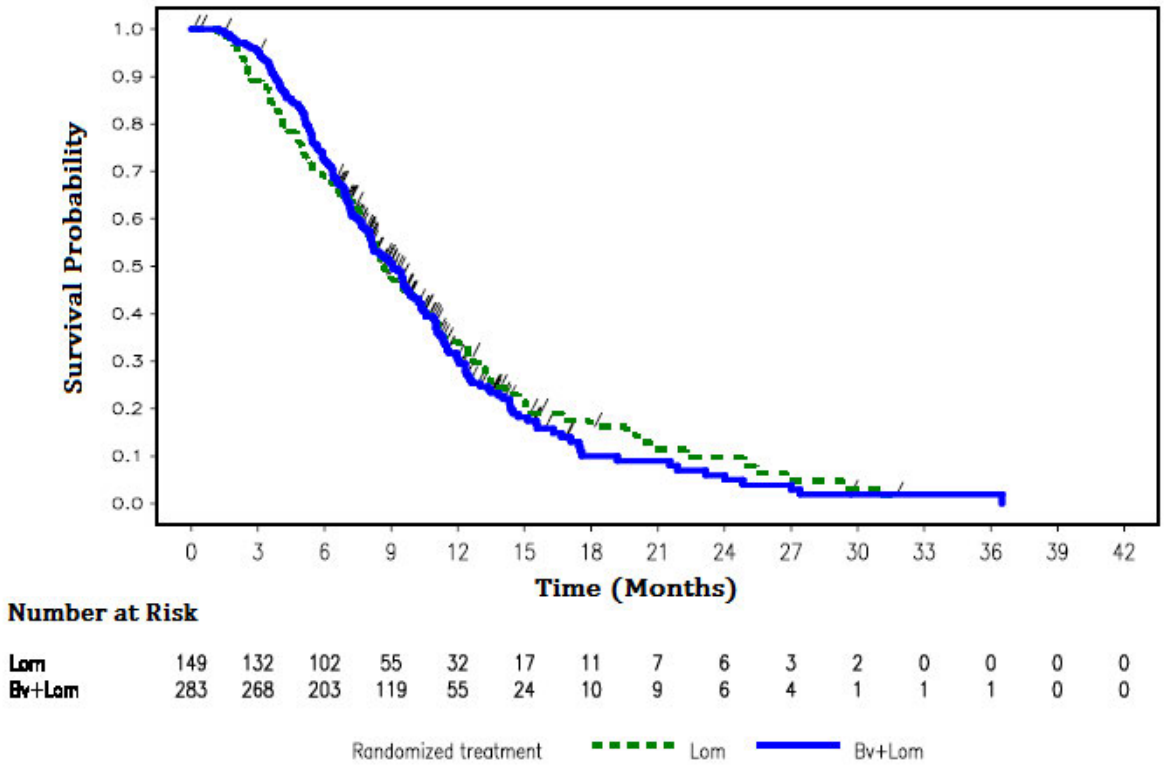
Primary (OS) endpoint analysis results
No statistically significant improvement in OS was observed in the Bev+Lom arm compared to Lom alone arm based on the primary analysis methods and the sensitivity analyses methods. The results for overall survival are presented in the table below.

Table 10: OS Efficacy Results (EORTC 26101)

	Bev+Lom N=283	**Lom N=149**
Deaths (%)	214 (75.6)	113 (75.8)
Median in mons (95% CI)	9.1 (8.1, 9.9)	8.6 (7.6, 10.4)
Adjusted HR [a] (95% CI)	0.91 (0.72, 1.16)	
p-value[b]	0.4578	

[a] Hazard ratio calculated using cox proportional hazards model with treatment group as a single covariate and stratified by WHO Performance Status, Steroids Administration, Largest Lesion Diameter and Phase II/III enrolment
[b] Based on stratified log-rank test

Figure 4: Kaplan-Meier plot of Overall Survival (EORTC 26101)



Based on the RPSFT method, performed as part of a sensitivity analyses to account for the 33% of the patients in the control arm who were crossed over to receive the subsequent bevacizumab treatment, the HR was 0.86 (95% CI: 0.57, 1.29) indicating no difference between the treatment arms.

Key secondary endpoints analysis results

Because the OS results were insignificant, the key secondary endpoints of PFS, ORR, and NDFS are analyzed descriptively and the results are presented in the below table.

Table 11: Efficacy Results for key secondary endpoints (EORTC 26101)

	Bev+Lom N=283	Lom N=149
Investigator assessed PFS per modified RANO criteria		
N	283	149
Events (%)	256 (90.5 %)	143 (96.0 %)
Median in mons (95% CI)	4.2 (3.6, 4.2)	1.5 (1.5, 2.5)
Adjusted HR [a] (95% CI)	0.52 (0.41, 0.64)	

	Bev+Lom N=283	Lom N=149
Confirmed ORR as assessed by Investigator using modified RANO criteria		
N[b]	283	149
# Responders (%)	68(24%)	8 (5.4%)
(95% CI)	(19.2, 29.4)	(2.4, 10.3)
N[c]	260	139
# Responders (%)	68 (26.2 %)	8 (5.8 %)
(95% CI)	(20.9, 31.9)	(2.5, 11.0)
Median DoR in mons (95% CI)	5.6 (4.2, 7.0)	5.6 (3.5, 8.3)
Clinical/Neurological DFS		
N	283	149
Events (%)	149 (52.7 %)	67 (45.0 %)
Median in mons (95% CI)	6.1 (5.7, 7.2)	5.7 (3.8, 8.7)
Adjusted HR [a] (95% CI)	0.76 (0.56, 1.03)	

[a] Hazard ratio calculated using cox proportional hazards model with treatment group as a single covariate and stratified by WHO Performance Status, Steroids Administration, Largest Lesion Diameter and Phase II/III enrolment
[b] Number of patients in ITT population; ORR based on the randomized population and those who had measurable disease at baseline
[c] Number of patients with measurable disease at baseline and the corresponding ORR; pre-specified analysis population for ORR analysis per protocol.

Corticosteroid Use

Half of patients enrolled in Study EORTC 26101 were receiving corticosteroids at baseline (217/432); among these patients, those on the bevacizumab plus lomustine arm were more likely to decrease or stop corticosteroids than in the lomustine alone arm. Among patients who were not receiving corticosteroids at baseline, time to initiation of corticosteroids was twice as long in the bevacizumab with lomustine arm than in the lomustine arm.

Table 12: Corticosteroid use Study EORTC 26101

	Bevacizumab + lomustine (n=283) N (%)	Lomustine (n=149) N (%)
Patients receiving corticosteroids at baseline	143 (50.5%)	74 (49.7%)
• Median dose of corticosteroids	4.5 mg	4.0 mg
• Reduced corticosteroids during the study	91/143 (63.6%)	27/74 (36.5%)
• Reduced corticosteroids by ≥ 50%	73/143 (51.0%)	19/74 (25.7%)
• Discontinued steroids	33/143 (23.1%)	9/74 (12.2%)
Patients not receiving corticosteroids at baseline	140 (49.5%)	75 (50.3%)
• Initiated corticosteroids during the study	53/140 (37.9%)	29/75 (38.7%)
• Median time to corticosteroid initiation (range)	3.02 months (1.2–22.1 months)	1.48 months (0.6−12.7 months)

Compared with the lomustine alone arm, a greater proportion of patients in the bevacizumab with lomustine arm had a decrease in their steroid dose by ≥ 50% (51.0% vs. 25.7%) or discontinued corticosteroids (23.1% vs. 12.2%).

Of the patients who were not receiving corticosteroids at baseline, corticosteroids were initiated during the study in 37.9% of patients in the bevacizumab with lomustine arm and 38.7% of patients in the lomustine arm. Among these patients, the median time to initiation of corticosteroids in the combination arm was twice that in the lomustine arm (3.02 vs. 1.48 months, respectively).

Of the patients who had a confirmed objective response and were receiving corticosteroids at baseline in the bevacizumab plus lomustine arm, 96.2% had dose reduction (including 42.3% discontinuing corticosteroids). In the lomustine arm, a single patient with confirmed objective response was receiving corticosteroids at baseline. This patient was able to discontinue corticosteroid use.

Discontinuation of corticosteroids is an important clinical outcome given the toxicities associated with corticosteroid use. A higher percentage of patients in the bevacizumab-containing arm discontinued corticosteroids during the study. In addition, of the patients who discontinued corticosteroids, 20% (28/143) discontinued for ≥ 12 weeks (3 months).

Table 13 Discontinuation of corticosteroids

	Bevacizumab + lomustine (n=283) N (%)	**Lomustine (n=149) N (%)**
Patients receiving corticosteroids at baseline	143 (50.5%)	74 (49.7%)
Patients who discontinued corticosteroids	33/143 (23.1%)	9/74 (12.2%)
• Discontinued for ≥ 6 and < 12 weeks	3 (2.1%)	3 (4.2%)
• Discontinued for ≥ 12 and < 18 weeks	13 (9.1%)	4 (5.4%)
• Discontinued for ≥ 18 and < 24 weeks	7 (4.9%)	1 (1.4%)
• Discontinued for ≥ 24 weeks	8 (5.6%)	0 (0%)

Health-related quality of life and Neurocognitive function

The reviewers consulted the FDA Clinical Outcome Assessment (COA) staff to provide input on understanding the validity and reliability of the following secondary outcome measures:

- Patient-Reported Outcome (PRO) or health-related quality of life (HRQL) as measured by EORTC QLQ-C30/BN-20
- HVLT-R, TMT, COWA, Performance Outcome (PerfO), neurocognitive functioning

The reviewers also consulted the Division of Neurology Products (DNP) for input on the validity and reliability of neurocognitive outcome assessments and interpretation of the results.

The COA review concluded that the selected tools may be reasonable to assess some aspects of HRQL (e.g., physical function, role function) and neurocognitive functioning in the target patient population; however, these instruments have limitations. In addition, contrary to Genentech's assertion that stable HRQL was observed in the EORTC 26101 study, the COA review concluded that the PRO results are uninterpretable and subsequently cannot provide any conclusive evidence of clinical benefit due to the following limitations:

- high attrition and dropout rates
- high floor effects at baseline
- no meaningful improvement or deterioration observed among various domains/symptoms of the PRO instrument
- open-label clinical trial design and other methodological issues (e.g., infrequent assessments, absence of an assessment before withdrawal of trial)
- reliability of self-report in a cognitively impaired patient population

The pre-specified threshold (i.e. 10-point change on the 0-100 points transformed scale) is clinically meaningful. Ten-point (10) change does not represent a possible within-patient response (i.e., improvement/deterioration) because the smallest response corresponding to a 1-category change on the 1-4 scale would be 33 points on the 0-100 points scale for a single item domain.

EORTC 26101 study PRO Results

In this section, in addition to the sponsor reported analysis of global health status (GHS), cognitive functioning and pain as measured by the instrument EORTC QLQ-C30, the reviewer has conducted an independent analysis of PRO data from EORTC QLQ-C30 questionnaire. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. Patients' data on each item were collected at baseline and every 12 weeks thereafter.

Table 14 below presents completion rates for the QLQ-C30 assessments in patients receiving treatment at each visit. The completion rate was defined as the number of patients who fill out the instruments over the number of eligible patients based on the same window definitions in each time point.

Table 14: Completion rates for QLQ-C30 assessments for study EORTC 26101

Visit	Lom N=149			Bev+Lom N=283		
	# Patients in study	#Completed questionnaire	Completion rate	# Patients in study	#Completed questionnaire	Completion rate
BASELINE	102	102	100%	207	207	100%
WEEK 12	87	65	74.7%	252*	228	90.5%
WEEK 24	24	23	95.8%	115	94	81.7%
WEEK 36	10	6	60%	51	42	82.4%
WEEK 48	1	0	0%	18	18	100%
WEEK 60	0			9	8	88.9%
WEEK 72	0			4	4	100%
WEEK 84	0			2	2	100%
WEEK 96	0			1	1	100%

*49 patients in Lomustine arm were treated with subsequent Bevacizumab therapy.

As presented in **Table 7**, there were 403 (267 and 136, respectively) patients included in the PRO analysis. Table 15 presents the descriptive analysis of GHS, cognitive functioning and pain as pre-specified in the key secondary endpoints.

Table 15: Analysis of Time to deterioration in GHS, cognitive functioning and pain in study EORTC 26101

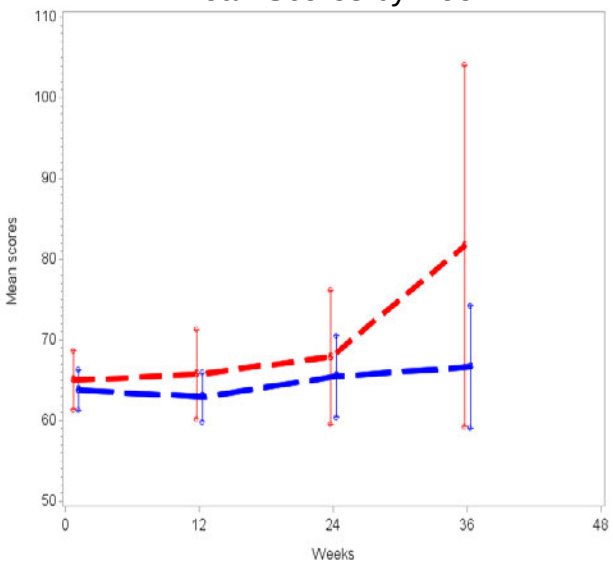
	Bev+Lom N=267	Lom N=136
Global Health Status		
Events (%)	252 (94.4 %)	132 (97.1 %)
Median in mons (95% CI)	3 (2.9, 3.6)	1.5 (1.5, 2.5)
Adjusted HR [a] (95% CI)	0.55 (0.44, 0.70)	
Cognitive functioning		
Events (%)	249 (93.3 %)	131 (96.3 %)
Median in mons (95% CI)	3 (3, 3.7)	1.5(1.5, 1.9)
Adjusted HR [a] (95% CI)	0.55 (0.43, 0.69)	
Pain		
Events (%)	253 (94.8 %)	131 (96.3 %)
Median in mons (95% CI)	3.1 (3, 3.6)	1.5 (1.5, 2.4)
Adjusted HR [a] (95% CI)	0.54 (0.43, 0.67)	

[a] Hazard ratio calculated using cox proportional hazards model with treatment group as a single covariate and stratified by WHO Performance Status, Steroids Administration, Largest Lesion Diameter and Phase II/III enrolment

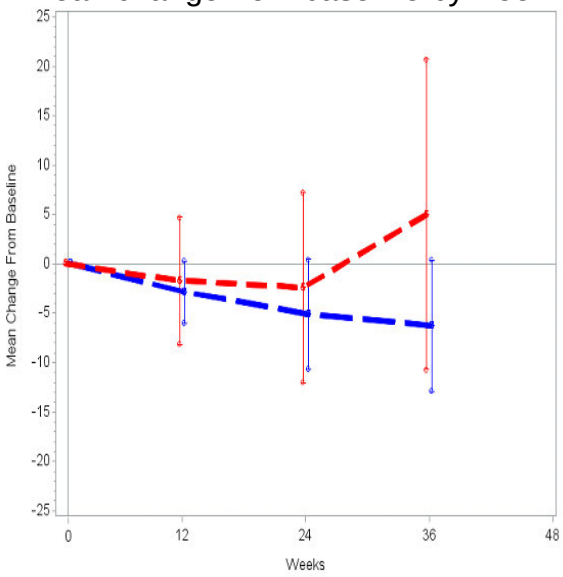
Figure 5: Mean Scores and Mean Changes from Baseline in QLQ-C30 Global Health Status, Cognitive function and Pain scores

Global Health Status

Mean Scores by week

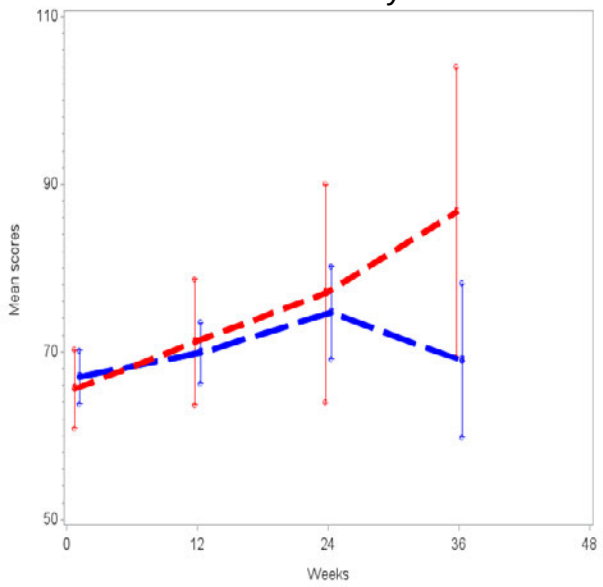


Mean change from baseline by week



Cognitive functioning

Mean Scores by week



Mean change from baseline by week

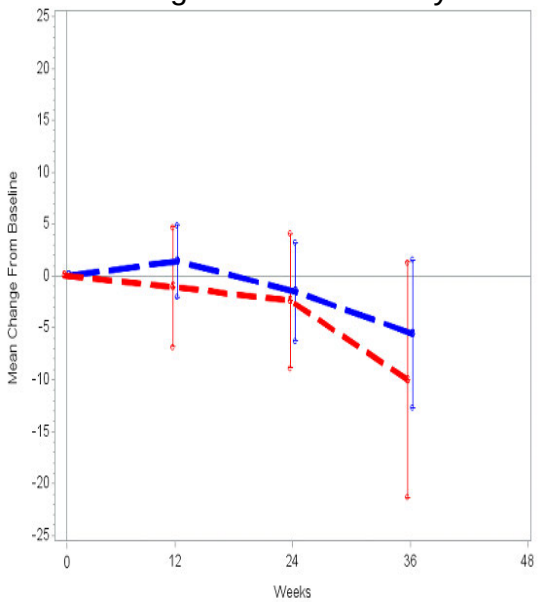
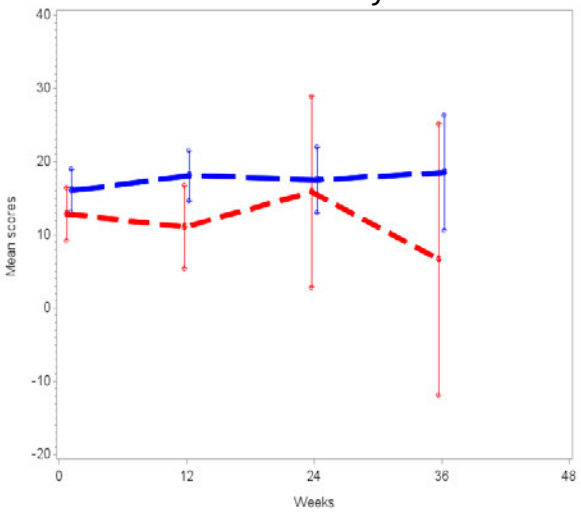


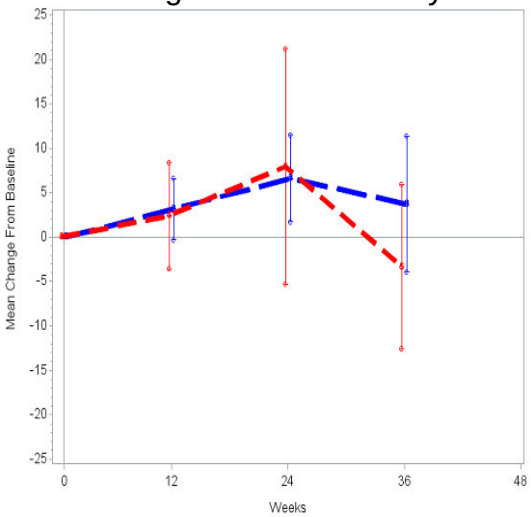
Figure 5 (Continued): Mean Scores and Mean Changes from Baseline in QLQ-C30 Global Health Status, Cognitive function and Pain scores

Pain

Mean Scores by week



Mean change from baseline by week

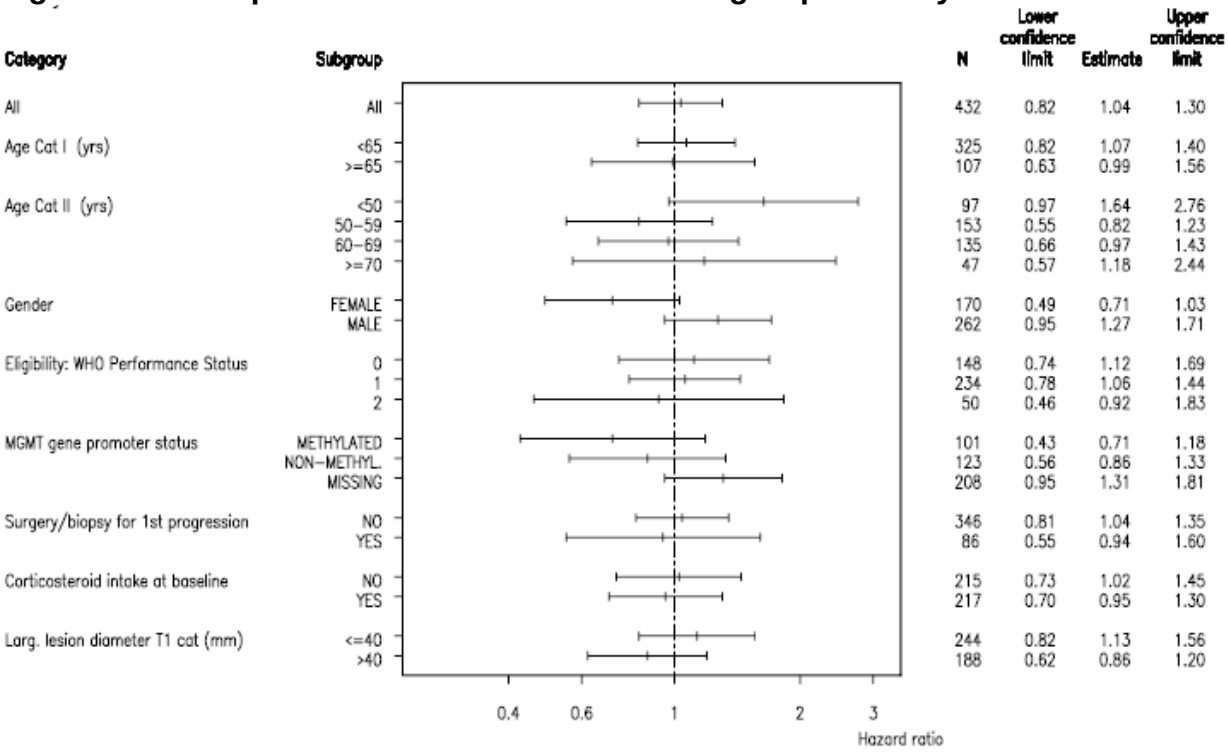


Reviewer comment: The results should be interpreted with caution due to the significant attrition and dropout rate at week 12 (40% in the treatment arm and 20% in the control arm) in addition to concerns related to high floor effects at baseline, the open-label clinical trial design and reliability of self-reporting in the target patient population. Individual component scores are not presented in this review because they are considered uninterpretable due to high levels of missing data.

6.1.6 Subpopulations

The overall survival results in the subgroups were consistent with the primary analysis results of OS in the ITT population. The figure below presents the forest plot of the OS hazard ratios for the subgroups in EORTC-26101 study as specified in Section-5.

Figure 6: Forest plot of OS hazard ratios for subgroups in Stuyd EORTC 26101



6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

No formal dose finding studies were performed by Genentech to explore the optimal dose of bevacizumab for treatment of patients with recurrent GBM. Doses ranging from 1-20 mg/kg every 1-3 weeks have been used in clinical trials.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Assessments of response over time were not performed.

6.1.9 Additional Efficacy Issues/Analyses

As stated earlier, Studies AVAglio and RTOG 0825 were similar in design, patient population, and primary endpoints. Key outcomes from both studies are summarized in Table 16.

Table 16: Comparison of results from AVAglio and RTOG 0825

	AVAglio	RTOG 0825
Randomized (ITT)	921 patients	637 patients
• **SoC + bevacizumab** • **SoC + placebo**	458 463	320 317
Open to accrual	May 2009	April 2009
Median age (years) • **SoC + bevacizumab** • **SoC + placebo**	 57 56	 59 57
Male • **SoC + bevacizumab** • **SoC + placebo**	 62% 64%	 57.1% 62.8%
Gross total resection • **SoC + bevacizumab** • **SoC + placebo**	 41% 42%	 63.1% 58.6%
MGMT methylated • **SoC + bevacizumab** • **SoC + placebo**	 26% 26%	 28.8% 27.5%
Primary endpoints		
• **OS (HR)**	0.88 (95 % CI:0.76,1.02) p 0.0987	1.13 (95% CI:0.93,1.37) p 0.11
• **KM median (months)**	16.7 (Soc + placebo) 16.8 (Soc + bevacizumab)	16.1 (Soc + placebo) 15.7 (Soc + bevacizumab)
• **PFS (HR)**	0.64 (95% CI:0.55,0.74) p < 0.0001[a]	0.79 (95% CI: 0.66,0.94) p 0.004
• **KM median (months)**	6.2 (SoC + placebo) 10.6 (SoC + bevacizumab)	7.3 (SoC + placebo) 10.7 (SoC + bevacizumab)

ITT: intent to treat; SoC: standard of care; PFS: progress-free survival; MGMT: O6-methylguanine–DNA methyltransferase; IRF: independent review facility; KM: Kaplan Meier; OS: overall survival; CI: confidence interval; HR: Hazard ratio
a: investigator assessed

Neither trial demonstrated an OS benefit; however, PFS was prolonged in both studies as summarized in the table above.

6.1.5 Other Endpoints
N/A

7 Review of Safety

Safety Summary

Three studies were evaluated to assess the safety of bevacizumab for the treatment of patients with GBM: EORTC 26101, AVAglio, and RTOG 0825. In each of the studies the safety of the bevacizumab-containing regimen observed was consistent with the previous experience of bevacizumab in patients with GBM, and with the known safety profile of. No new or unexpected adverse events (AEs) were observed in any of the studies. In this review, the safety profile of bevacizumab for the treatment of GBM is

characterized by exposure data from approximately 1000 patients across the three clinical studies.

The overall incidences of Grade ≥ 3 AEs, deaths, serious AEs (SAEs), and AEs leading to discontinuation of study treatment were more frequent in the bevacizumab-containing arms compared with the comparator arms. Most of the increases in AE incidence in the bevacizumab-containing arm were attributable to events with a known association with bevacizumab treatment. and were reported in patients treated for a longer duration as a result of prolonged PFS time. In the EORTC trial, AEs of hypertension, epistaxis, fatigue, headache, and decreased weight occurred with a ≥ 10% higher incidence in the bevacizumab + Lom arm compared with the Lom arm. In the AVAglio trial, AEs that occurred with at least a 10% higher incidence in the bevacizumab +RT/T arm compared with the Pl+RT/T arm were hypertension, epistaxis, and proteinuria. The incidence of patients with AEs of special interest (AESIs), as assessed in studies EORTC 26101 and AVAglio, was higher in the bevacizumab -containing arms than in the comparator arms; this was not an unexpected finding as the AEs considered as AESIs were those known to be associated with bevacizumab treatment. The incidence of patients with AESIs in the bevacizumab -containing arms was generally in line with previous experience except for the difference in the incidence of arterial thromboembolic event (ATEs) observed in AVAglio (5.9% in the bevacizumab + RT/T arm, 1.6% in the Pl + RT/T arm). In EORTC 26101, the incidence of ATEs in the bevacizumab + Lom arm was comparable with that in the Lom arm, although it was higher than expected (11.5% of patients compared with 10.9% in the Lom arm) and higher than the incidence in the AVAglio study.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For the purposes of this review, safety was evaluated in three separate studies, EORTC 26101, AVAglio, and RTOG 0825. EORTC provides comparative safety data of the addition of bevacizumab to Lom compared to Lom alone in patients with relapsed or refractory GBM. AVAglio and RTOG 085 provide comparative safety data for the addition of bevacizumab to chemoradiotherpay in patients with newly diagnosed GBM. There are key differences in the study designs, line of treatment, and data collection in the three studies which do not allow pooling of the safety data; therefore, the three studies are presented sequentially. Limited datasets for RTOG 085 were provided in this submission as Roche/Genentech was not the sponsor. The results from this study are supportive and the review with regards to safety will primarily focus on the results from EOTC 26101 and AVAglio.

7.1.2 Categorization of Adverse Events

Safety parameters evaluated in Study EORTC 26101 included all adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), AEs leading to dose modification/interruption, AEs leading to treatment discontinuation, deaths due to toxicity, standard blood and urine laboratory parameters, vital signs (body weight and body surface area), and 12-lead ECGs. AEs graded according to National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 or New York Heart Association (NYHA) functional classification for events of congestive heart failure. For classification purposes, lower level terms were assigned to the original terms from the case report form (CRF), using Medical Dictionary for Regulatory Activities (MedDRA) v18.0 terminology for AEs and diseases and the Roche International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for medications and treatments.

Safety parameters evaluated in AVAglio included AEs that were collected throughout all trial treatment phases and up to 90 days after the last dose of trial treatment. Patients who did not receive at least one dose of trial treatment were excluded from the safety analysis AESIs were collected up to 6 months after the last dose of trial treatment, and SAEs considered related to trial treatment by the investigator were to be reported indefinitely. AEs were graded according to the NCI-CTCAE, version 3. For classification purposes, lower level terms/preferred terms were assigned by the Sponsor to the original terms entered on the CRF, using the most up-to-date version of the MedDRA v16.0 terminology for AEs and diseases and the Roche INN Drug Terms and Procedures Dictionary for treatments.

Reviewer Comment: In AVAglio, 4 patients randomized to the Pl+RT/T arm and 6 randomized to the bevacizumab +RT/T arm did not receive at least one dose of treatment and were excluded from the safety analysis. A further 9 patients randomized to the PI+RT/T arm incorrectly received at least one dose of bevacizumab instead of placebo and for the purposes of safety reporting, are included in the bevacizumab +RT/T arm.

The incidence, seriousness and severity of the following known AESIs of interest for bevacizumab were also analyzed for both EORTC 26101 and AVAglio:

- Hypertension
- Proteinuria
- Gastrointestinal perforation, abscesses, and fistulae
- Wound healing complications
- Thromboembolic events: arterial thromboembolic events (ATEs) and venous thromboembolic events (VTEs)
- Bleedings: cerebral hemorrhages and gastrointestinal and other hemorrhages
- Congestive heart failure

- Non-gastrointestinal abscesses/fistulae
- Posterior Reversible Encephalopathy Syndrome (PRES)

In AVAglio, thrombocytopenia and infections were selected post hoc for further analysis because, apart from the AESIs, these were clinically relevant AEs that had a clearly increased overall incidence in the bevacizumab plus chemoradiotherapy arm of the study.

Safety parameters evaluated in RTOG 0825 included AEs were evaluated weekly during the Concurrent Stage and on Day 28 (±3 days) of each cycle during the Adjuvant Stage. AEs were graded for severity according to the NCI CTCAE, version 3.0. A special interim toxicity analysis was performed to monitor possible unacceptable increases in the incidence of the following Grade ≥3 AEs (performed after 20 patients had entered the bevacizumab + RT/T arm and again after 40 patients had entered the bevacizumab + RT/T arm):

- Hemorrhage/bleeding, any term
- Wound complication, non-infectious
- Leukoencephalopathy (radiographic findings) and encephalopathy
- Thrombosis/thrombus/embolism and thrombosis/embolism (vascular access-related)
- Myelosuppression (Grade 4-5 neutrophils or platelets)

In addition, dose reduction of TMZ (<80% of the protocol-defined dose) when given with radiation was also evaluated as an indirect measure of toxicity, and patient tolerance was considered as an AE for this analysis.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A, See Section 7.1.1

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

EORTC
In the bevacizumab + Lom arm, the majority of patients (76.3%) completed ≥ 90% of the planned bevacizumab doses. The mean duration of treatment was 20.3 weeks and the median dose intensity, defined as the ratio between planned and received dose, was 99.7%. While similar proportions of patients in the bevacizumab+ Lom arm (82.0%) and

Lom arm (83.0%) completed ≥ 90% of the planned Lom doses, patients in the bevacizumab + Lom arm received more doses and had a longer duration of treatment than patients in the Lom arm (14.2 weeks verses 7.7 weeks, respectively). The median cumulative Lom dose was higher in the bevacizumab +Lom arm (460.0 mg) than in the Lom arm (200.0 mg).

AVAglio
The majority of patients (approximately 89%) received all four planned doses of bevacizumab/placebo over the 6 weeks of the Concurrent Phase. More patients in the bevacizumab +RT/T arm than in the Pl +RT/T arm entered the Maintenance Phase (87.4% versus 80.0%, respectively) and the Monotherapy Phase (59.7% vs. 34.0%, respectively). More patients discontinued treatment in the Pl+RT/T arm than the bevacizumab+RT/T arm, with the primary reason for the difference between the treatment arms being progressive disease (PD). Subsequently, the overall duration of treatment and exposure to bevacizumab/placebo was greater in the bevacizumab +RT/T arm (median number of doses across all phases: 19.0 doses) than in the Pl+ RT/T arm (12.0 doses). The dose and duration of RT exposure was similar in the two treatment arms. At least 95% of patients in each arm completed ≥ 90% of the planned dose.

The majority of patients in both treatment arms received the planned dose and duration of TMZ treatment during the Concurrent Phase (90% of patients in each arm received ≥90% of the planned dose). More patients completed the planned 6 cycles of TMZ in the Maintenance Phase in the bevacizumab +RT/T arm (64.6%) than in the Pl + RT/T arm (36.9%), primarily due to patients discontinuing earlier for PD in the Pl +RT/T arm. Relatively few patients discontinued TMZ for toxicity in either arm (bevacizumab +RT/T: 5.2%, Pl +RT/T: 6.0%). The proportion of patients who were able to escalate their TMZ dose (from 150 to 200 mg/m2) during the Maintenance Phase was higher in the bevacizumab +RT/T arm (41.3%) than the Pl + RT/T arm (34.8%).

RTOG
In the bevacizumab+ RT/T arm, 294 patients received at least one dose of bevacizumab in the Concurrent Stage and 222 patients received at least one dose of bevacizumab in the Adjuvant Stage. The median (range) bevacizumab dose was 2315 mg (485- 4445 mg) in the Concurrent Stage and 7000 mg (530 -34,080 mg) during the Adjuvant Stage. No information regarding exposure to radiotherapy was provided in the submission.

7.2.2 Explorations for Dose Response
Dose response explorations were not conducted as part of the review of this supplement.

7.2.3 Special Animal and/or In Vitro Testing
No special animal and/or In Vitro Testing was conducted.

7.2.4 Routine Clinical Testing

The following safety evaluations were performed at baseline and throughout the on-treatment period of EORTC:

- Complete medical history
- Prior cancer therapy (including prior chemotherapy and radiation therapy)
- Physical examination including but not limited to height, weight, vital signs (blood pressure to collect possible hypertension) and neurological evaluation
- World Health Organization (WHO) performance status
- 12 lead ECG
- Specific concomitant medications (anti-epileptic agents, anti-hypertensive agents, anticoagulants and corticosteroids - only concomitant medications actually taken by the patient at the time of study start were recorded)
- Steroid intake
- Adverse events grading according to CTCAE 4.0; NYHA criteria for congestive heart failure
- Laboratory tests, including complete blood counts (hemoglobin, hematocrit, white blood cells and differentiate - neutrophils and lymphocytes -, platelets) and serum chemistry: sodium, potassium, calcium, phosphates, chloride, creatinine, ASAT, ALAT, total bilirubin, alkaline phosphatases, total protein, albumin, INR and aPTT
- Urine dipstick
- Serum or urine pregnancy test for premenopausal female patients within 72 hours prior to treatment start

The following safety evaluations were performed at baseline and throughout the on-treatment period of AVAglio:

- Hematology: Hemoglobin, platelet count, WBC count, neutrophils
- Coagulation: INR or PT (secs), and aPTT
- Blood Chemistry: Including total bilirubin, AST, ALT, alkaline phosphatase, serum albumin, urea (BUN), serum creatinine, and electrolytes (sodium, potassium, calcium, magnesium)
- Urinalysis: A 24-hour urine collection should be performed in the event of proteinuria ≥ +2 by urine dipstick test) and must demonstrate ≤ 1.0 g of protein in 24 hours. OR Urine protein/creatinine ratio (UPC) must be ≤ 1.0.
- Other: Medical History, physical exam, neurological examination (including MMSE), vital signs (blood pressure, body temperature), pregnancy test, performance status, concomitant medications. ECG at baseline and thereafter as medically indicated.
- Adverse events (NCI-CTC, version 3.0)

The following safety evaluations were performed at baseline and throughout the on-treatment period of RTOG 0825:

- History and Physical, Vitals, including blood pressure
- PT/PTT, INR
- EKG
- Serum pregnancy
- Steroid dose documentation
- Performance status
- Labs: CBC, BUN/Cr, Urine protein ratio, Bilirubin, AST/ALT, CD4 Count
- Adverse events
- Quality of Life and Neurocognitive Function

7.2.5 Metabolic, Clearance, and Interaction Workup
No metabolic, clearance, and drug interaction workup was conducted during any study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
Not applicable for this supplemental BLA.

7.3 Major Safety Results

7.3.1 Deaths

EORTC26101
The number of deaths was similar between treatment arms in the safety population, 75.9% (n=211) and 76.2% (n=112) in the bevacizumab+Lom arm and the Lom arm, respectively. The main cause of death in both arms was disease progression (**see Table 17 below).** Death from other causes was also similar between treatment arms. One patient in the bevacizumab+Lom was reported to have died from progressive deterioration of health after an admission for Grade 3 arthralgia; an MRI was not done and progressive disease could not be excluded; no autopsy was done.

Reviewer Comment: Four patients are included in the DIED.xpt raw dataset but not included in the death analysis as they did not receive study treatment (Patient (b) (6) due to seizure, Patient (b) (6) due to herpes zoster infection, Patient (b) (6) withdrew consent and Patient (b) (6) due to progressive disease).

The incidence of fatal AEs was higher in the bevacizumab + Lom arm (n=5, 1.8%) than in the Lom arm (n=1, 0.7%). The investigators did not consider these Grade 5 AEs to be related to study treatment and therefore these deaths were reported in the CRF as death due to “other causes” and not due to toxicity related to study treatment. The five

fatal AEs reported in the bevacizumab + Lom arm were myocardial infarction (2 patients), intracranial hemorrhage, large intestine perforation, and sepsis (summarized below). In the Lom arm, a fatal event of lung infection was reported.

- Intracranial hemorrhage: A 49-year-old male patient in the bevacizumab + Lom arm (Patient (b) (6)) died on Study Day 396 following a fall at home. He presented with a traumatic intracranial bleed (noted in a computed tomography scan). The last dose of study treatment was administered on Study Day 379. The patient was also receiving concomitant heparin at that time. The patient had confirmed PD prior to death.
- Myocardial infarction: *(1)* A 51-year-old male patient in the bevacizumab + Lom arm (Patient (b) (6)) died on Study Day 53 with confirmed PD prior to death. The patient only received one dose of study treatment administered on Study Day 29. *(2)* A 68-year-old male patient in the bevacizumab + Lom arm (Patient (b) (6)) died on Study Day 364. The patient had a history of hypertension. The patient presented with seizures and was admitted to hospital. His clinical condition deteriorated during hospitalization and the patient's family declined active treatment. It was suspected that he suffered a myocardial Infarction and he died the following day. The last dose of study treatment was administered on Study Day 336.
- Large intestinal perforation: A 64-year-old female patient in the bevacizumab + Lom arm (Patient (b) (6)) died on Study Day 99 with confirmed PD prior to death. The patient presented with abdominal distension and was diagnosed with intestinal perforation 40 days after her last dose of bevacizumab (received a total of 2 cycles). The patient's family declined intervention, and after receiving palliative care only, the patient died at home. Confounded by dexamethasone.
- Sepsis: A 65-year-old male patient in the bevacizumab + Lom arm (Patient (b) (6)) died on Study Day 159. The patient had a history of several prior episodes of Grade ≥ 3 respiratory tract infections (the last one being within 1 month of the start of study treatment). Following admission to hospital with seizures, confirmed pneumonia, and urosepsis, the patient died as a result of complications. The last dose of study treatment was administered on Study Day 156.

The patient in the Lom arm who died (Patient (b) (6)) was a 51-year-old male. He died on Study Day 376 due to a lung infection that was deemed unrelated to study treatment. The last dose of study treatment was administered on Study Day 169.

Reviewer comments: Narratives were reviewed and were based on reported information; the reviewer agrees that with the exception of intestinal perforation, the fatal AEs were not related to the study medication. The reviewer does not agree that there is sufficient information to determine that the event "large intestinal perforation" is not related to study medication.

Table 17 Cause of Death (EORTC 26101)

	Lom N=147 No. (%)	Bev +Lom N=278 No. (%)
Total number of deaths	112 (76.2)	211 (75.)
Progressive disease	102 (69.4)	196 (70.5)
Progressive disease and toxicity	--	1 (0.4)
Fatal Adverse Event^	1 (0.7)	5 (1.8)
Other	2 (1.4)*	3 (1.1)$
Unknown	7 (4.8)	6 (2.2)

^ The investigators did not consider these Grade 5 AEs to be related to study treatment
* Infection of ventricles after surgery, thrombotic microangiopathy after further anti-tumor therapy with bevacizumab
$ euthanasia, sepsis due to pancreatitis, possible progression not confirmed by MRI
Bev=bevacizumab, Lom=Lomustine

AVAglio

The number of deaths was similar between the two treatment arms (75% PI +RT/T vs. 73% bevacizumab+RT/T). The majority of deaths were due to progression of disease (305/450 [68%] in the PI+RT/T arm vs. 305/461 [66%] in the bevacizumab+RT/T arm). A comparable number of non-progressive disease deaths occurred in both arms (n=32 [7.1%] Pl+RT/T vs. n=30 [6.5%] bevacizumab+RT/T). In both treatment arms, the leading cause of non-PD death was events in the Infection and Infestations SOC (14/405 [3.1%] Pl+RT/T vs. 10/461 [2%] bevacizumab+RT/T). In three cases of death in patients treated with bevacizumab, death occurred several months following confirmed disease progression. There was no difference between treatment arms with respect to type of AE that led to a fatal outcome.

Reviewer Comment: No single cause of death was greater than 2% in either category. No major differences between treatment arms.

Table 18 Cause of Death, PD vs. Other (AVAglio, Safety Population)

	Pl+RT/T N=450 No. (%)	Bev+RT/T N=461 No. (%)
Total number of deaths	337 (75)	335 (73)
Progressive disease	305 (85)	305 (66)
Non-Progressive Disease	32 (7.1)	30 (6.5)
Infections and Infestations	14 (3.1)	10 (2.2)
Respiratory*	9 (2.0)	3 (0.7)

	Pl+RT/T N=450 No. (%)	Bev+RT/T N=461 No. (%)
Meningitis Chemical	1 (0.2)	0
Sepsis^	3 (0.7)	3 (0.7)
Bacteremia	0	1 (0.2)
Peritonitis	0	1 (0.2)
Pneumocystis Jiroveci	1 (0.2)	0
Wound Infection	0	1 (0.2)
Infection	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.6)	4(0.8)
Pulmonary embolism	2(0.4)	3(0.2)
Lung Disorder	0	1(0.2)
Respiratory Failure	1 (0.2)	0
Cardiac Disorder$	2 (0.4)	4(0.9)
Cardiac Arrest	2 (0.4)	3 (0.6)
Cardiovascular Disorder	0	1 (0.2)
General Disorders and Administration Site Conditions	1 (0.2)	3(0.6)
General Physical Health Deterioration	0	2 (0.4)
Drowning	1 (0.2)	1 (0.2)
Gastrointestinal Disorder	2 (0.4)	2 (0.4)
Gastrointestinal Hemorrhage	1 (0.2)	0
Intestinal perforation&	0	2 (0.4)
Acute Abdomen	1 (0.2)	0
Nervous System Disorder	2 (0.4)	2 (0.4)
Brain Edema	0	1 (0.2)
Cerebrovascular Accident	1 (0.2)	1 (0.2)
Cerebral Hemorrhage	1 (0.2)	0
Hepatobiliary Disorder	0	1 (0.2)
Drug-induced Liver Injury	0	1 (0.2)
Neoplasm Benign, Malignant and Unspecified	1 (0.2)	1 (0.2)
Metastases to Liver	1 (0.2)	0
Tumor Hemorrhage	0	1 (0.2)
Vascular Disorder	1 (0.2)	1 (0.2)
Embolism	1 (0.2)	0
Aortic Aneurysm Rupture	0	1 (0.2)
Other	6 (1.3)	2 (0.4)
Unevaluable	3 (0.6)	1 (0.2)
Death	3 (0.6)	1 (0.4)

*Respiratory is comprised of the following terms: Pneumonia, Lower Respiratory Tract Infection, Lung Infection, Pneumonia Aspiration, Pneumonia, Pneumonia Respiratory Syncytial Viral Respiratory Tract Infection
^ Sepsis is comprised of the following terms: Sepsis, septic shock

[$]Cardiac Arrest is comprised of the following terms: Cardiac arrest, Cardio-Respiratory Arrest, Myocardial Infraction.
[&] Intestinal Perforation is comprised of the following terms: Intestinal perforation, Large Intestinal Perforation.
Bev=bevacizumab, RT=radiotherapy, T=temozolomide

Table 19 Number of Patients with Grade 5 AEs treated with Bevacizumab (AVAglio, Safety Population)

ORGAN SYSTEM	PT TERM	PL +RT/T N=450 No.	%	BV + RT/T N=461 No.	%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY EMBOLISM	1	0.2	3	0.7
	LUNG DISORDER	0	--	1	0.7
NERVOUS SYSTEM DISORDERS	BRAIN OEDEMA	0	--	1	0.2
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	TUMOUR HAEMORRHAGE	0	--	1	0.2
INFECTIONS AND INFESTATIONS	PNEUMONIA	0	--	3	0.7
	SEPSIS	0	--	3	0.7
	BACTERAEMIA	0	--	1	0.2
	WOUND INFECTION	0	--	1	0.2
HEPATOBILIARY DISORDERS	DRUG-INDUCED LIVER INJURY	0	--	1	0.2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	GENERAL PHYSICAL HEALTH DETERIORATION	0	--	2	0.4
GASTROINTESTINAL DISORDERS	LARGE INTESTINE PERFORATION	0	--	1	0.2
CARDIAC DISORDERS	CARDIAC ARREST	0	--	1	0.2
	CARDIOVASCULAR DISORDER	0	--	1	0.2
	MYOCARDIAL INFARCTION	0	--	1	0.2

Bev=bevacizumab, RT=radiotherapy, T=temozolomide

Reviewer comment: The CSR (Table 49) for AVAglio states that there were 2 AEs of pulmonary embolism that lead to death in patients treated with bevacizumab vs. one patient treated with placebo. The reviewer identified three patients treated with bevacizumab who had an AE of pulmonary embolism that lead to death. The CSR correctly includes all three narratives and includes these patients in the section referred to for more detail which includes a table. The percentage difference between arms is still less than 1% and does not affect the assessment of safety for bevacizumab.

RTOG 0825
The number of deaths was similar between treatment arms. Similar to EORTC and AVAglio, the most common cause of death was due to progressive disease. The most common non-progressive disease cause of death was Infection.

Table 20 Number of Patients with Grade 5 AEs by Category and Term in the Concurrent Radiotherapy, Temozolomide and Bevacizumab/Placebo Stage (copied from RTOG CSR)

Category Term	Arm 1 (n=300)	Arm 2 (n=303)
Cardiac General	1	0
Myocardial ischemia	1	0
Death	2	3
Death	1	1
Disease progression	1	1
Sudden death	0	1
Gastrointestinal	0	1
Appendicitis perforated	0	1
Infection	3	1
Pneumonia (with unknown ANC)	1	0
Sepsis (with Grade 3-4 ANC)	0	1
Sepsis (with unknown ANC)	2	0
Neurology	1	2
Depression	1	0
Encephalopathy	0	2
Pulmonary/Upper Respiratory	1	2
Hypoxia	0	1
Pneumonitis	1	1
Vascular	1	0
Thrombosis	1	0
Note: Adverse events were graded with NCI CTCAE, Version 3.0. Source: Table 4.8 of RTOG 0825 Primary Analysis (page 281)		

Table 21 Number of Patients with Grade 5 Adverse Events, by Category and Term, in the Adjuvant Stage (copied from RTOG CSR)

Category Term	Arm 1 (n=233)	Arm 2 (n=260)
Death	5	9
Death	0	8
Disease progression	4	1
Sudden death	1	0
Hemorrhage/Bleeding	0	1
Intracranial hemorrhage	0	1
Infection	1	0
Urinary tract infection[with unknown ANC]	1	0
Neurology	1	1
Encephalopathy	1	0
Ischemia cerebrovascular	0	1
Vascular	0	1
Vascular access complication	0	1
Note: Adverse events were graded with NCI CTCAE, Version 3.0. Source: Table 4.8 of RTOG 0825 Primary Analysis (page 281)		

Reviewer comment: The reported causes of death across the three studies are consistent with the known risk profile of bevacizumab and with the known causes of death for patients with GBM.

7.3.2 Nonfatal Serious Adverse Events

EORTC
Non-fatal SAEs reported in >2% of patients in either treatment arm were seizure, (5.4% in the bevacizumab +Lom arm vs. 2.7% in the Lom arm), and pulmonary embolism (4.7% and 1.4%, respectively). Both and were reported at a higher frequency (>2% difference) in patients in the bevacizumab +Lom arm than in the Lom arm. None of the SAEs of seizures led to discontinuation of study treatment. No fatal SAE occurred in more than one patient except for cardiac infarction which occurred in two patients; deaths described above in Section 7.3.1.

Reviewer Comment: Seizures are not unexpected in this patient population. Pulmonary embolism is a known AE associated with bevacizumab and the incidence is in line with the expected frequency for patients treated with bevacizumab.

One patient (Patient (b) (6) in the bevacizumab + Lom arm) experienced a secondary malignancy. The patient had a history of Cowden's syndrome (cancer predisposition disorder characterized most commonly by multiple hamartoma) and the patient's sister had a history of Cowden's syndrome and breast cancer. A breast tumor was identified by routine mammogram on Day 36 of treatment; diagnosis confirmed by biopsy on Day 51 of treatment. Study treatment was delayed due to biopsy but was not discontinued. At the time of clinical data cut-off, the patient remained on treatment (Day 316 of Lom and Day 359 of bevacizumab) and was reported to be alive.

AVAglio
Non-fatal SAEs reported in >2% of patients in either treatment arm were pulmonary embolism, (2.6% in the bevacizumab +RT/T arm vs. 3.1% in the Pl +RT/T arm), thrombocytopenia (3.7% and 1.8%, respectively), and deep vein thrombosis (2.6% and 1.6%, respectively). No SAEs occurred at more than 2% difference between treatment groups.

Reviewer Comment: Pulmonary embolism and DVT are known AEs associated with bevacizumab and their incidence are in line with the expected frequency for patients treated with bevacizumab. Thrombocytopenia is discussed in Section 7.3.4.

Table 22 Summary of Most Frequent SAEs (Incidence ≥1% in Either Treatment Arm, Safety Population, AVAglio)

ORGAN SYSTEM	PT TERM	PL +RT/T N=450 No., %		Bev + RT/T N=461 No., %	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	THROMBOCYTOPENIA	8	1.8	17	3.7
	NEUTROPENIA	2	0.4	5	1.1
	PANCYTOPENIA	1	0.2	5	1.1
GASTROINTESTINAL DISORDERS	VOMITING	5	1.1	5	1.1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	PYREXIA	3	0.7	8	1.7
INFECTIONS AND INFESTATIONS	PNEUMONIA	6	1.3	7	1.5

ORGAN SYSTEM	PT TERM	PL +RT/T N=450 No., %		Bev + RT/T N=461 No., %	
METABOLISM AND NUTRITION DISORDERS	HYPERGLYCAEMIA	5	1.1	1	0.2
NERVOUS SYSTEM DISORDERS	CONVULSION	6	1.3	6	1.3
	BRAIN OEDEMA	5	1.1	1	0.2
	CEREBROVASCULAR ACCIDENT	1	0.2	8	1.7
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY EMBOLISM	14	3.1	12	2.6
VASCULAR DISORDERS	DEEP VEIN THROMBOSIS	7	1.6	12	2.6

Bev=bevacizumab, RT=radiotherapy, T=temozolomide

RTOG
Serious AEs were not summarized separately in this study.

7.3.3 Dropouts and/or Discontinuations
EORTC
AEs leading to discontinuation of any component of study treatment were more frequent in the bevacizumab + Lom arm (36/278, 12.9% of patients) than in the Lom arm (8/147, 5.4%). The higher proportion of patients experiencing events leading to discontinuation in the bevacizumab + Lom arm was mainly driven by patients who experienced events of pulmonary embolism, which occurred in 2.5% of patients in this arm compared with 0 in the Lom arm as well as longer duration of treatment of patients in the bevacizumab arm. In all patients the events were reported to have resolved. The percentage of patients who discontinued due to toxicity when hematologic toxicity is included (not collected as an adverse event), the percentage increases to 21.9% in the bevacizumab plus Lom arm and 10.2% in the Lom arm. The only other AEs leading to treatment discontinuation reported in > 1% of patients in either treatment arm were epistaxis, which only occurred in the bevacizumab + Lom arm (3 patients [1.1%]), and fatigue (1 patient [0.4%] in the bevacizumab + Lom arm, and 3 patients [2.0%] in the Lom arm).

Reviewer comment: Other notable bevacizumab related AEs that led to treatment discontinuation included gastrointestinal perforation (n=1), large intestine perforation (n=1), wound complication (n=2), wound dehiscence (n=2), intracranial hemorrhage (n=2), hypertension (n=1), proteinuria (n=1), and embolism (n=2).

If embolism is grouped with pulmonary embolism, the total number of AEs occurred in 9 patients out of 278 (3.2%) verses none in the Lom alone treatment arm.

Table 23 Summary of Most Frequent Adverse Events Leading to Discontinuation of Study Treatment in Either Treatment Arm by Preferred Term (EORTC Safety Population)

System Organ Class	PT Term	Lom (N=147) No., %		Bev+Lom (n=278) No, %	
CARDIAC DISORDERS	CARDIAC FAILURE CONGESTIVE	1	0.7	0	--
	LEFT VENTRICULAR DYSFUNCTION	0	--	1	0.4
EYE DISORDERS	BLINDNESS UNILATERAL	0	--	1	0.4
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	0	--	1	0.4
	DIARRHOEA	1	0.7	0	--
	DUODENAL ULCER	0	--	1	0.4
	GASTROINTESTINAL PERFORATION	0	--	1	0.4
	INGUINAL HERNIA STRANGULATED	0	--	1	0.4
	LARGE INTESTINE PERFORATION	0	--	1	0.4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	3	2.0	1	0.4
	MALAISE	0	--	1	0.4
HEPATOBILIARY DISORDERS	PORTAL HYPERTENSION	0	--	1	0.4
INFECTIONS AND INFESTATIONS	ABSCESS SOFT TISSUE	0	--	1	0.4
	ANORECTAL INFECTION	0	--	1	0.4
	SEPSIS	1	0.7	1	0.4
	SOFT TISSUE INFECTION	0	--	1	0.4
	UPPER RESPIRATORY TRACT INFECTION	0	--	1	0.4
	WOUND INFECTION	0	--	1	0.4
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	BRAIN CONTUSION	1	0.7	0	0.0
	WOUND COMPLICATION	0	--	2	0.7
	WOUND DEHISCENCE	0	--	2	0.7
INVESTIGATIONS	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	0.7	2	0.7
	WEIGHT DECREASED	1	0.7	0	--
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	0	--	1	0.4
	PAIN IN EXTREMITY	0	--	1	0.4

System Organ Class	PT Term	Lom (N=147) No., %		Bev+Lom (n=278) No, %	
NERVOUS SYSTEM DISORDERS	CEREBRAL ISCHAEMIA	0	--	1	0.4
	DEPRESSED LEVEL OF CONSCIOUSNESS	1	0.7	0	--
	HAEMORRHAGE INTRACRANIAL	0	--	2	0.7
RENAL AND URINARY DISORDERS	PROTEINURIA	0	--	1	0.4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	EPISTAXIS	0	--	3	1.1
	PNEUMONITIS	1	0.7	0	0.0
	PULMONARY EMBOLISM	0	--	7	2.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY FIBROSIS	1	0.7	0	--
VASCULAR DISORDERS	EMBOLISM	0	--	2	0.7
	HYPERTENSION	0	--	1	0.4

Bev=bevacizumab, Lom=lomustine

Overall, a higher proportion of patients in the bevacizumab + Lom arm (22.3%) than in the Lom arm (4.8%) required dose modification (dose reduction or delay) to any component of treatment (i.e., bevacizumab or Lom, as applicable) because of AEs. The higher proportion of patients experiencing events leading to dose modification in the bevacizumab + Lom arm was mainly driven by patients who experienced the following events that only occurred in the bevacizumab + Lom arm: seizure (7 patients [2.5%]), embolism (6 [2.2%]), and pyrexia (6 [2.2%]), hypertension (5 [1.8%]) and non-infective cystitis (3 [1.1%]).

AVAglio

Overall, a higher proportion of patients in the bevacizumab+RT/T arm (26.5%) than in the Pl+RT/T arm (13.6%) discontinued any component of treatment because of AEs. The most common AEs that led to withdrawal of treatment in both treatment arms were thrombocytopenia (3.3% in the PI+RT/T arm vs. 3.0% in the bevacizumab+RT/T arm) and pulmonary embolism (2.2% in the bevacizumab+RT/T arm vs. 1.8% in the Pl+RT/T arm). Proteinuria was the single preferred term that led to treatment discontinuation in the bevacizumab+RT/T arm only (3.5%). The overall increased incidence of AEs that led to treatment discontinuation in the bevacizumab+RT/T arm was attributable to events known to be associated with bevacizumab and included AEs in the following SOCs:

- Infections and infestations (21 [4.6%] vs. 8 [1.8%]) – including 6 wound infections in bevacizumab-treated patients vs. none in placebo-treated patients
- Nervous system disorders (17 [3.7%]) vs. 5 [1.1%]) – including 7 cerebrovascular accidents in the bevacizumab+RT/T arm vs. none in the Pl+RT/T arm. (See Section 7.3.5 for detail).
- Renal disorders (18 [3.9%] vs. none) – 16 proteinuria, 1 nephrotic syndrome, 1 acute renal failure
- General disorders (8 [1.7%] vs. none) – including pyrexia (3), fatigue (3)
- Neoplasm SOC (7 [1.5%] vs. 2 [0.4%]) – all 7 patients in the bevacizumab arm were included in this category based on the term "tumor hemorrhage." In the placebo arm, one patient was included based on tumor hemorrhage and one patients had liver metastasis
- Cardiac disorders (5 [1.1%] vs. none) – 3 myocardial infarction, 1 CHF, 1 coronary artery stenosis (See Section 7.3.5 for detail)

A low number of AEs led to discontinuation of radiotherapy (8 patients Pl+RT/T; 16 patients bevacizumab+RT/T), which led to discontinuation of all trial treatment for those patients in the Concurrent Phase of the study as per the protocol. These most commonly included infections in both treatment arms.

Overall, a higher proportion of patients in the bevacizumab+RT/T arm (52.5%) than in the Pl+RT/T arm (37.6%) modified any component of treatment (dose adjustment, interruption, delay) because of AEs. The most common reasons were hemotoxicity (primarily thrombocytopenia), vascular disorders (primarily hypertension), and infections, all of which led to dose modifications in a higher proportion of patients in the bevacizumab+RT/T arm. See Section 7.3.5 for more detail. Of the less common reasons (< 5% patients in either arm), proteinuria led to dose modification in notably more patients on bevacizumab treatment (4.6% vs 0.4%).

RTOG
Serious AEs were not summarized separately in this study.

7.3.4 Significant Adverse Events

See Section 7.3.2 for Serious Adverse Events. Summary of Adverse Events of special interest (AESIs) for EORTC and AVAglio will be reviewed in this section; see Section 7.3.5 for more detail of individual AESIs. AESIs were not summarized separately in RTOG.

EORTC
AESIs in this study were based on AEs known to be associated with bevacizumab treatment, including bleeding (both cerebral hemorrhages and bleeding at other sites),

ATEs, VTEs, wound healing complications, hypertension, proteinuria, gastrointestinal perforations, abscesses and fistulae, non-gastrointestinal abscesses and fistulae, congestive heart failure, and posterior reversible encephalopathy syndrome (PRES). The overall incidence of all-grade AESIs was higher in the bevacizumab + Lom arm (59.0%) than in the Lom arm (35.4%), with the largest relative increases in incidence (~3-fold or more) observed for epistaxis (14.4% vs. 1.4%), intracranial hemorrhage (2.5% vs. 0.7%), and wound-healing complications (4.7% vs. 0.7%). In the bevacizumab + Lom arm, 2.2% of patients experienced gastrointestinal perforations compared with 0% in the Lom arm.

The overall incidence of Grade≥ 3 AESIs was also higher in the bevacizumab + Lom arm (25.2%) compared with the Lom arm (10.2%), largely due to hypertension (15.1% in the bevacizumab + Lom arm vs. 4.8% in the Lom arm). There were also increases in the incidence of venous thrombosis events (VTEs), most of which were pulmonary embolisms (4.7% vs. 2.0%), wound-healing complications (1.8% vs. 0.7%), bleeding events (1.8% vs. 0.7%), and gastrointestinal perforations (1.4% vs. 0%) in the bevacizumab +Lom arm compared with the Lom arm.

The overall incidence of serious AESIs was also higher in the bevacizumab + Lom arm (13.3% of patients) than in the Lom arm (3.4%). The increased incidence in serious AESIs was largely due to VTEs (4.7% vs. 1.4% in the bevacizumab + Lom and Lom arms, respectively), which were all pulmonary embolisms (4.7% vs. 1.4%). There were also increases in the incidence of epistaxis (1.1% vs. 0%), ATEs (2.9% vs. 0%), wound-healing complications (1.8% vs. 0.7%), and gastrointestinal perforations (1.4% vs. 0%) in the bevacizumab + Lom arm compared with the Lom arm.

As described in Section 7.3.1, there were more fatal AESIs in the bevacizumab + Lom arm than the Lom arm (four vs. zero).

Reviewer Comment: The incidences for AESIs observed in the study were aligned with the known incidences reported in prior clinical studies with bevacizumab.

AVAglio

Similar to EORTC, AESIs in this study were based on AEs known to be associated with bevacizumab treatment. Additionally, thrombocytopenia and infections were selected post-hoc for further analysis since, apart from the AESIs, these were clinically relevant AEs that had a clearly increased overall incidence in the bevacizumab+RT/T arm in this study (see Section 7.3.5 for full review). AESIs for bevacizumab were collected if they started while on trial treatment and up to 6 months after the last dose of trial treatment.

The overall incidence of all-grade AESIs was higher in the bevacizumab+RT/T arm (75.7%) than in the Pl+RT/T arm (45.3%), with the largest relative increases in incidence (more than 2%) observed in hypertension (39.3% vs. 12.7%), bleeding

(37.1% vs. 19.5%), proteinuria (15.6% vs. 4.2%), thrombocytopenia (15.6% vs. 4.2%), arterial thromboembolic events (ATEs) (5.9% vs. 1.6%, mainly strokes), and wound healing complications (5.9% vs. 1.6%). Additionally, there were more GI perforations (including abscesses and fistulae) in the bevacizumab+RT/T arm compared to the Pl+RT/T arm (1.7% vs. 0.4%). Generally, the incidences for AESIs observed in the study were aligned with the known incidences reported in prior clinical studies with bevacizumab with the exception of ATE (See Section 7.3.5 for detail).

The incidence of Grade ≥ 3 AESIs was also higher in the bevacizumab+RT/T arm compared with the Pl+RT/T arm (32.5% vs. 15.8%). The increased incidence in Grade ≥ 3 AESIs was largely due to hypertension (11.3% vs. 2.2%), ATEs (5.0% vs. 1.3%), and proteinuria (5.4% vs. 0.0%). There was an increase in the incidence of wound healing complications (WHC; 3.3% vs. 1.6%), GI perforation (1.1% vs. 0.2%) and thrombocytopenia (15.2% vs. 10%) in the bevacizumab+RT/T arm compared with the Pl+RT/T arm. Other Grade ≥ 3 AESIs with a difference of > 1% between the bevacizumab+RT/T and Pl+RT/T arm were: cerebral hemorrhage, and 'other hemorrhages.' The only Grade ≥ 3 AESI which showed an increased incidence in the Pl+RT/T arm as compared to the bevacizumab+RT/T arm was VTEs, with 8.0% vs. 7.6% respectively.

As described in Section 7.3.1, there were more fatal AESIs in the bevacizumab+RT/T arm (3 Pl+RT/T vs. 7 bevacizumab+RT/T). The difference in arms was seen during the Concurrent Phase/Treatment Break with one AESI (GI hemorrhage) in the Pl+RT/T arm and four (2 pulmonary embolism, 1 GI perforation, 1 hemorrhage) in the bevacizumab RT/T arm.

7.3.5 Submission Specific Primary Safety Concerns

Details of adverse events of special interest (AESIs) for EORTC and AVAglio will be reviewed in this section by event type; see Section 7.3.4 for more summary. AESIs were not summarized separately in RTOG.

Cerebral Hemorrhage

EORTC
Cerebral hemorrhage events occurred more frequently in the bevacizumab + Lom arm (7/278, 2.5% of patients) than the Lom arm (1/147, 0.7%).

- The majority of patients who experienced cerebral hemorrhage events in the bevacizumab + Lom arm experienced Grade 1 or Grade 2 events (5/7 patients). There were no Grade 3 or Grade 4 events.

  - One Grade 5 event was reported, which occurred in the bevacizumab + Lom arm. The patient (Patient (b) (6)), who was receiving concomitant heparin, developed a traumatic intracranial bleed after experiencing a fall.
  - For one patient in the bevacizumab + Lom arm (Patient (b) (6)), the severity for the reported event of cerebral hemorrhage was not provided.
- One patient in each arm experienced an SAE of cerebral hemorrhage with the event in the bevacizumab + Lom arm being the aforementioned Grade 5 event.
- The events of cerebral hemorrhage were reported to have resolved in 1/7 patients (14%) in the bevacizumab + Lom arm and in 1/1 patient (100%) in the Lom arm.
- Two patients in the bevacizumab + Lom arm discontinued treatment as a result of cerebral hemorrhages. No patients in the Lom arm needed to have their treatment modified in response to cerebral hemorrhage events.

AVAglio
Events coded under 'cerebral haemorrhage' grouping occurred in more patients in the bevacizumab+RT/T arm (9 Pl+RT/T; 15 bevacizumab+RT/T). While the events in the bevacizumab+RT/T arm tended to be more severe (9 out of 15 events were Grade 4 while the remaining were Grade 1 and 2), the difference in the treatment arms was due to the occurrence of strokes (cerebrovascular accident), most of which were determined after medical review to be of ischemic origin and a majority of which resolved with or without sequelae. There was no fatal cerebral hemorrhage reported in the bevacizumab+RT/T arm compared to one fatal event of cerebrovascular accident that occurred in the Pl+RT/T arm.

Other Hemorrhage
EORTC
The incidence of all grade bleeding events other than cerebral hemorrhages was higher in the bevacizumab + Lom arm than the Lom arm (23.7% vs. 7.5%), as was the incidence of Grade ≥ 3 events (1.8% vs. 0.7%;). All grade bleeding events other than cerebral hemorrhage occurring with a higher rate in the bevacizumab + Lom arm compared with the Lom arm, and with a difference in incidence of ≥ 1%, were: epistaxis (14.4% vs.1.4%) and mouth hemorrhage (1.8% vs. 0%). Other events reported within the category of "Other hemorrhages" include: hematoma, hematuria, rectal hemorrhage, petechia, contusion, uterine hemorrhage, hemorrhoidal hemorrhage, purpura, subcutaneous hemorrhage, and thrombotic thrombocytopenic purpura (TTP).

- The majority of events reported in either arm were of Grade 1 or Grade 2 in severity, with the most common preferred term being epistaxis.
- Four patients (6%) with bleeding events experienced Grade 3 events in the bevacizumab + Lom arm, 3 of whom experienced Grade 3 epistaxis and 1 experienced Grade 3 hematuria. One patient in the Lom arm experienced a Grade 3 event of TTP. The Grade 3 events in the bevacizumab + Lom arm were

all reported to have resolved without sequelae, whereas the TTP event remained unresolved at the clinical cutoff date

- One patient in the bevacizumab + Lom arm experienced a Grade 5 event (intracranial hemorrhage), although note that this patient is actually the same patient ([redacted]) referred to above in "cerebral hemorrhage", due to an overlap in MedDRA preferred terms used to identify CNS and other hemorrhages (both sets of terms include the preferred term "hemorrhage intracranial"). There were no Grade 5 AEs in the Lom arm.
- Seven patients (11%) in the bevacizumab + Lom arm experienced "other hemorrhage" SAEs compared with 1 patient (9%) in the Lom arm.
- The hemorrhage events were reported to have resolved in 57/66 patients (86%) in the bevacizumab + Lom arm and 8/11 patients (73%) in the Lom arm.
- Five patients (8%) in the bevacizumab + Lom arm discontinued treatment and 2 (3%) required dose modifications as a result of hemorrhage events. No patients in the Lom arm needed to have their treatment modified in response to hemorrhage events.

AVAGlio

Overall, the increase in bleeding events seen in the bevacizumab+RT/T arm was primarily driven by Grade 1-2 events. Bleeding events at sites other than cerebral occurred more frequently in the bevacizumab+RT/T arm, with 171 patients (37.1%) reporting at least one AE related to 'Other haemorrhages' as compared to 88 patients (19.6%) in the Pl+RT/T arm. This increase was driven primarily by Grade 1-2 events, with Grade 1 events accounting for 91% and Grade 2 events 15% of patients with 'Other hemorrhages' (patients with multiple events having different grades were counted more than once). Of the total 'Other haemorrhages' events reported during the study, epistaxis was the most frequent reported term in the bevacizumab+RT/T arm. Grade 1 and 2 events of epistaxis accounted for 98% of the total epistaxis events reported in the bevacizumab+RT/T arm. Out of patients with 'Other hemorrhages' events, more patients in the Pl+RT/T arm (4.5%) experienced Grade ≥ 3 events compared with 3.5% in the bevacizumab+RT/T arm. One fatal event of tumor hemorrhage was reported in the bevacizumab+RT/T arm. Only two severe bleeding events of Grade ≥ 3 (both epistaxis) were associated with concomitant Grade ≥ 3 thrombocytopenia at the time of the event. These Grade ≥ 3 bleeding events were treated with platelet transfusions and subsequently resolved.

In total, overall there were three fatal bleeding events: two in the Pl+RT/T arm (cerebrovascular accident on Day 109, and GI hemorrhage on Day 67), and one in the bevacizumab+RT/T arm (tumor hemorrhage on Day 4) (See Section 7.3.5 for detail).

Arterial Thromboembolic Events (ATEs)
EORTC
The incidence of all grade ATEs was comparable in the bevacizumab + Lom arm and the Lom arm (11.5% vs. 10.9%). The most commonly reported ATE events (in > 1% of patients in either treatment arm) were hemiparesis (19 patients [6.8%] in the bevacizumab + Lom arm vs. 11 [7.5%] in the Lom arm) and embolism (11 [4.0%] vs. 3 [2.0%]). Embolism events were reported using NCI-CTCAE categories, which do not differentiate between ATEs and VTEs. Reports of "embolism" without further qualification or characterization by the investigator were categorized as ATEs according to Roche's coding conventions, and thus some of the embolism events recorded here may have been VTEs. The incidence of hemiparesis was similar in both arms (6.8% in the bevacizumab + Lom arm and 7.5% in the Lom arm).

The majority of patients who experienced ATE events in both arms were reported to have experienced Grade 1 or Grade 2 events. The incidence of Grade ≥ 3 ATEs was similar in the bevacizumab + Lom arm and the Lom arm (2.5% vs. 2.0%).

- Three patients in each arm experienced Grade 3 events (three events of hemiparesis in the bevacizumab + Lom arm and two events of hemiparesis and an event of TTP in the Lom arm).
- There were 2 patients with Grade 4 events in the bevacizumab + Lom arm (both embolisms) versus 0 in the Lom arm.
- There were 2 patients with Grade 5 events in the bevacizumab + Lom arm versus 0 in the Lom arm. Both Grade 5 events in the bevacizumab + Lom arm were events of myocardial infarction, which are described further in Section 7.3.1.
- The ATE events were considered to be serious in 8 patients in the bevacizumab + Lom arm and none in the Lom arm.
- A review of outcomes of Grade ≥ 3 ATE events indicated that at the cutoff date, two events of hemiparesis and one event of embolism remained unresolved in the bevacizumab + Lom arm, while two events of hemiparesis and the event of TTP remained unresolved in the Lom arm. One event of embolism had resolved with sequelae, and one event of hemiparesis resolved without sequelae in the bevacizumab + Lom arm

AVAglio
The overall incidence of ATEs (any grade) was higher in the bevacizumab+RT/T arm (5.9%) than in the Pl+RT/T arm (1.6%), as was the incidence of Grade ≥ 3 ATEs (5.0% vs. 1.3%). Medical review of all ATE events identified that most of the events can be grouped under the broad medical concept of 'stroke' or cerebrovascular accidents (19 of 27 patients in the bevacizumab+RT/T arm and 6 of 7 patients in the Pl+RT/T arm with an ATE experienced a stroke). A detailed review of all stroke cases revealed that a majority of the events in the bevacizumab+RT/T arm were of ischemic origin and only one event was confirmed to be a hemorrhagic stroke. Eleven stroke events occurred in patients < 65 years of age in the bevacizumab+RT/T arm, of which one event was

reported as Grade 1 in severity; 9 out of 11 events resolved; none was fatal; one case occurred > 2 months after confirmed disease progression and two cases were diagnosed as incidental findings on radiological scans with the patients being asymptomatic. In addition, 7 out of 11 events occurred in patients who tolerated the study treatment reasonably well and had been on study treatment without progression of the underlying disease for a time period ranging between 1.2 to 1.7 years.

The non-stroke ATE events included myocardial infarction (including acute myocardial infarction), peripheral arterial occlusive disease, embolism (later confirmed pulmonary embolism), stress cardiomyopathy, and thrombotic microangiopathy. One ATE event in each arm was fatal (cerebrovascular accident in the Pl+RT/T arm and myocardial infarction in the bevacizumab+RT/T arm). ATEs led to discontinuation of bevacizumab/Placebo therapy for more patients in the bevacizumab+RT/T arm (16 patients) than in the Pl+RT/T arm (1 patient). The majority of ATE events in the bevacizumab+RT/T arm resolved with treatment.

Among patients that experienced a Grade ≥ 3 ATE, 3/6 (50%) patients in the Pl+RT/T arm vs. 19/22 (86%) patients in the bevacizumab+RT/T arm were identified as having at least one or more co-morbidities or risk factors (e.g., history of hypertension, myocardial infarction, hypercholesterolemia, coronary artery disease, diabetes mellitus, smoking, atherosclerosis, or rheumatoid arthritis) or had experienced at least one AE of hypertension or increased blood pressure while on study treatment, that could have increased their risk for ATEs. The majority of Grade ≥ 3 ATEs (15 of 22 [73%]) resolved in the bevacizumab+RT/T arm while 3 of 6 (50%) resolved in the Pl+RT/T treatment arm.

Nine of the 22 Grade ≥ 3 ATEs in the bevacizumab+RT/T arm occurred in patients ≥ 65 years of age. None of the ATEs in the ≥ 65 years subgroup were fatal. Six of the 9 ATE events in patients ≥ 65 years of age in the bevacizumab+RT/T arm resolved. Five of 9 patients had a concomitant medical history of hypertension and 3 of those 5 patients also had a history of hypercholesterolemia. Two of 9 patients experienced ATE events more than 5 months after confirmed disease progression and 1.5 months after the last dose of bevacizumab.

Venous Thromboembolic Events (VTEs)
EORTC
In total, 16 patients experienced VTEs (all grades) in both arms, with a higher incidence in the bevacizumab + Lom arm (13/278 [4.7%]) than in the Lom arm (3/147 [2.0%]). All patients were reported to have experienced events that were Grade ≥ 3, thus the incidence of Grade ≥ 3 VTEs was also higher in the bevacizumab + Lom arm (4.7% vs. 2.0%). The VTE events reported were pulmonary embolism (in 13 patients [4.7%] in the bevacizumab + Lom arm vs. 3 [2%] in the Lom arm) and Deep vein thrombosis reported by 1 patient (0.4%) in the bevacizumab + Lom arm versus 0 in the Lom arm. Of note:

the incidence of patients with a history of pulmonary embolism at baseline was 1.8% in the bevacizumab + Lom arm and 4.0% in the Lom arm.

- In the bevacizumab + Lom arm, 9 patients experienced Grade 3 events and 5 experienced Grade 4 events. All reported events in the Lom arm were Grade 3. There were no Grade 5 VTE events.
- All 13 patients in the bevacizumab + Lom arm with VTEs and 2 patients in the Lom arm experienced serious events.
- Seven patients in the bevacizumab + Lom arm discontinued treatment and 1 required a dose modification as a result of VTEs. No patients in the Lom arm needed to have their treatment modified because of VTEs.
- A review of pulmonary embolism events showed that in the 3 patients in the Lom arm, the events remained unresolved in 2 patients and resolved without sequelae in 1 patient. In the 13 patients in the bevacizumab + Lom who developed a pulmonary embolism, the events were reportedly unresolved in 5 patients, resolved with sequelae in 5 patients, and resolved without sequelae in 3 patients.

AVAglio
The overall incidence of VTEs was similar across arms: (any grade) 9.6% and 8.2%; (Grade ≥ 3) 8.0% and 7.6% in Pl+RT/T and bevacizumab+RT/T arms, respectively. There were four fatal events of pulmonary embolism (1 Pl+RT/T and 3 bevacizumab+RT/T) (See Section 7.3.5 for detail). Similar numbers of patients discontinued bevacizumab/Placebo treatment or dose modified for VTE events in each arm. The VTE events resolved in a higher proportion of patients in the bevacizumab+RT/T arm (26/38; 68%) than in the Pl+RT/T arm (22/43; 51%).

Wound Healing Complications
EORTC
The incidence of all grade wound healing complications was higher in the bevacizumab + Lom arm than the Lom arm (4.7% vs. 0.7%), as was the incidence of Grade ≥ 3 events (1.8% vs. 0.7%). The wound healing complication events reported were: wound complication (8 patients [2.9%] in the bevacizumab + Lom arm vs. 0 in the Lom arm), wound infection (5 [1.8%] vs. 1 [0.7%]), wound dehiscence (4 [1.4%] vs. 1 [0.7%]) and pneumocephalus (1 [0.4%] vs. 0). Most all wounds were related to intracranial surgical resection. Further summary details were:

- Half of the reported wound healing complication events in either arm (9/18 in the bevacizumab + Lom arm and 1/2 in the Lom arm) were Grade 1 or Grade 2 in severity. Four patients experienced a total of five Grade 3 events in the bevacizumab + Lom arm versus 1 patient with one event in the Lom arm, and 1 patient experienced a Grade 4 event in the bevacizumab + Lom arm versus 0 patients in the Lom arm. There were no Grade 5 AEs in either arm.
- A review of outcomes in patients who experienced Grade ≥ 3 wound healing complication events indicated that in the bevacizumab + Lom arm, an event of wound complication remained unresolved in 1 patient, while an event of wound

infection in 1 patient resolved with sequelae and further events of wound complication (in 1 patient) and wound dehiscence (in 3 patients) resolved without sequelae In the Lom arm, one event of wound infection resolved without sequelae.

- Five patients in the bevacizumab + Lom arm experienced a total of six SAEs compared with one SAE in the Lom arm.
- Four patients in the bevacizumab + Lom arm discontinued treatment and 1 required a dose modification as a result of wound healing complications. No patients in the Lo arm needed to have their treatment modified in response to wound healing complications.
- The events were reported to have resolved in 11/13 patients (85%) in the bevacizumab + Lom arm and 1/1 patient (100%) in the Lom arm.

AVAglio
The definition of 'wound healing complications' that was used was expanded to include post-craniotomy complications as specified in the protocol. WHC including craniotomy complications were more frequently reported by bevacizumab-treated patients (6.9%) than Pl-treated patients (4.7%). Fifteen patients (3.3%) in the bevacizumab+RT/T arm reported Grade ≥ 3 WHC including craniotomy complication events compared with seven (1.6%) in the Pl+RT/T arm. The majority of WHCs, including craniotomy complication events, resolved with treatment.

There was one fatal wound infection in a bevacizumab-treated patient who had developed a post-operative cyst prior to study start. On Day 360, during the Monotherapy Phase of the study, the patient developed Grade 3 head wound infection leading to hospitalization and treatment with cefuroxime and methylprednisolone. The patient died on Day 384 reportedly after stopping antibiotic therapy and following discharge from the hospital. Nine patients discontinued therapy in the bevacizumab+RT/T arm compared with two in the Pl+RT/T arm due to WHC including craniotomy complications.

Hypertension
EORTC
The incidence of all grade hypertension was higher in the bevacizumab + Lom arm than the Lom arm (33.1% vs. 18.4%, as was the incidence of Grade ≥ 3 events (15.1% vs. 4.8%). Further summary details were:

- The majority of patients with hypertension experienced Grade 1 and Grade 2 events, although 46% of patients in the bevacizumab + Lom arm and 26% of patients in the Lom arm experienced Grade 3 events. No Grade 4 or Grade 5 events were reported.
- One of the events reported in the bevacizumab + Lom arm was considered serious compared with none of the events in the Lom arm.

- A review of Grade ≥ 3 events of hypertension indicated that in 35 patients (12.6%) in the bevacizumab + Lom arm the events remained unresolved, compared with 6 (4.1%) in the Lom arm. More patients in the bevacizumab + Lom arm than in the Lom arm had Grade ≥ 3 events that resolved without sequelae (2.5% vs. 0.7%). One patient in the bevacizumab + Lom arm discontinued treatment and 1 required a dose modification as a result of hypertension. No patients in the Lom arm needed to have their treatment modified in response to hypertension events.
- In 13% of patients with hypertension in the bevacizumab + Lom arm and 7% in the Lom arm the hypertension resolved after the patient had received treatment for hypertension, and in 48% and 37%, respectively, the event remained unresolved after the patient had received treatment for hypertension.

AVAglio
Hypertension was reported as an AE more frequently in the bevacizumab+RT/T arm than the Pl+RT/T arm (any grade 39.3% vs. 12.7% of patients; Grade 3, 11.3% vs. 2.2%, respectively). There were no Grade 4 or 5 events of hypertension reported in the study. Hypertension was reported as resolved in the majority (> 70%) of cases. Four patients required discontinuation of bevacizumab therapy due to hypertension.

Proteinuria
EORTC
Proteinuria in this study was monitored by means of laboratory values and is discussed further in Section 7.4.2, urinalysis. One patient in the study, in the bevacizumab + Lom arm (Patient 0343), was reported to have experienced a Grade 3 SAE of proteinuria, which 28 days later changed to a non-serious Grade 2 AE of proteinuria. The patient had concurrent Grade 3 portal hypertension. Treatment with bevacizumab was permanently discontinued due to proteinuria and Grade 3 portal hypertension. The Grade 2 proteinuria remained unresolved at the clinical cutoff date for the CSR. No AEs of proteinuria were reported in the Lom arm.

AVAglio
A higher proportion of patients reported proteinuria as an AE in the bevacizumab+RT/T arm than in the Pl+RT/T arm (any grade 15.6% vs. 4.2%; Grade 3/4, 5.4% vs. 0%, respectively). Proteinuria resolved without specific treatment in the majority of cases; however, 17 patients discontinued bevacizumab treatment due to proteinuria. One bevacizumab-treated patient developed Grade 4 nephrotic syndrome that resolved with treatment.

Non-Gastrointestinal Abscesses/Fistulae
EORTC
There were no reports of non-gastrointestinal abscesses or fistulae in either arm in this

study.

AVAglio
Five patients developed abscesses or fistulae: 3 patients had one Grade 3 event in the Pl+RT/T arm and two patients had one Grade 1, one Grade 3, and one Grade 4 event in the bevacizumab+RT/T arm. All the events resolved with treatment; two patients in the Pl+RT/T arm and one patient in the bevacizumab+RT/T arm withdrew from therapy for the events.

Gastrointestinal Perforation, Abscesses, and Fistulae
EORTC
Six patients in the bevacizumab + Lom (2.2%) and none in the Lom arm experienced gastrointestinal perforation events. The events (all grades) included large intestine perforation (in 3 patients), anal fistula (in 2 patients), gastrointestinal perforation (in 1 patient), and peritonitis (in 1 of the patients who experienced large intestine perforation).

- Four of 6 patients experienced events that were ≥ Grade 3 in severity: 1 patient experienced a Grade 3 event, 2 patients experienced Grade 4 events, and 1 patient experienced a Grade 5 event. This fatal event is described in more detail
- in Section 7.3.1.
- Four of the patients experienced serious gastrointestinal perforation events.
- Two patients discontinued treatment as a result of gastrointestinal perforation events.
- The events were reported to have resolved in 4 patients, but remained unresolved in 1 patient (who had a non-serious event of anal fistula; at the time of the clinical data cutoff for the CSR.

AVAglio
Eight (1.7%) patients in the bevacizumab+RT/T arm and two patients (0.4%) in the Pl+RT/T arm experienced a ‘GI perforation’ event (including GI abscesses and fistulae). Five of the 8 events in the bevacizumab+RT/T arm were Grade ≥ 3 (including one fatal large intestine perforation). Six of the seven non-fatal events resolved with treatment. One of the two events in the Pl+RT/T arm (large intestine perforation) was Grade 4 in severity; both events were unresolved

Congestive Heart Failure
The incidence of congestive heart failure was comparable in the bevacizumab + Lom arm and the Lom arm: 3 patients experienced congestive heart failure during the study, 2/278 patients (0.7%) in the bevacizumab + Lom arm and 1/147 patients (0.7%) in the Lom arm. The events reported were cardiac failure congestive (in 1 patient [0.4%] in the bevacizumab + Lom arm and 1 [0.7%] in the Lom arm), and left ventricular dysfunction (in 1 patient [0.4%] in the bevacizumab + Lom arm vs. 0 in the Lom arm) (Table 38).

- One patient in each treatment arm experienced a Grade 3 event. The remaining patient, in the bevacizumab + Lom arm, experienced Grade 2 congestive heart failure.
- All three events were considered to be serious.
- One of the patients in the bevacizumab + Lom arm (Patient (b) (6)) and the patient in the Lom arm discontinued treatment due to the congestive heart failure events.
- The congestive heart failure resolved with no sequelae in both patients in the bevacizumab + Lom arm, whereas the event in the Lom arm remained unresolved at the clinical cutoff date

AVAglio
Three patients had a CHF AE; 2 in the bevacizumab+RT/T arm and 1 in the Pl+RT/T arm. Both events in the bevacizumab+RT/T arm were Grade 3; a CTCAE grade was not assigned for the event in the Pl+RT/T arm. One patient in the bevacizumab+RT/T arm discontinued study treatment due to the event. The CHF resolved for the patient in the Pl+RT/T arm and for the patient who discontinued in the bevacizumab+RT/T arm. The CHF in the second bevacizumab-treated patient was unresolved.

Posterior Reversible Encephalopathy Syndrome (PRES)
EORTC
One event of PRES (Patient (b) (6) in bevacizumab + Lom arm) was reported during the study; however, this event was reported in the CRF in error. This error was not corrected at the time of database lock, therefore, this event was included in the data outputs.

AVAglio
There were no reports of PRES in either treatment arm.

Thrombocytopenia- AVAglio
There was an overall higher incidence of thrombocytopenia reported as AEs in the bevacizumab+RT/T arm (34.1%) than in the Pl+RT/T arm (27.3%). The incidence of Grade ≥ 3 thrombocytopenia AEs was also higher with bevacizumab than with Pl treatment (15.0% vs. 9.8%), but was not associated with clinically significant (Grade ≥ 3) bleeding events. Higher numbers of patients continue safety follow-up beyond 6 months in the bevacizumab+RT/T arm, and the greater exposure to TMZ in this arm is likely the cause of the greater number of events.

After 8 months, which is at the end of TMZ therapy in the Maintenance Phase, the curve for the bevacizumab+RT/T arm also reaches a plateau. Discontinuation of treatment because of thrombocytopenia was similar between the arms (bevacizumab+RT/T 3.0%; Pl+RT/T 3.3%). The number of patients with dose modification/interruption/delay due to thrombocytopenia was slightly increased in the bevacizumab+RT/T arm (24.5% vs.

17.8%). An analysis of time to onset of thrombocytopenia AEs indicates a similar incidence in both treatment arms over the first 3 months of the study. A sharp increase in rate occurs in both arms between Months 4 and 5 (period of dose escalation of TMZ) after which the curve reaches a plateau in the Pl+RT/T arm while some additional events occur in the bevacizumab+RT/T arm.

Infection- AVAglio
Overall there was a higher incidence of infections in the bevacizumab+RT/T arm than in the Pl+RT/T arm (all grade; 54.4% vs. 39.1%) and of Grade ≥ 3 infections (12.8% vs. 7.8%). The overall higher incidence of infections in the bevacizumab+RT/T arm was driven by Grade 1 or 2 infections occurring during the Maintenance Phase of the study. More patients in the bevacizumab+RT/T arm than in the Pl+RT/T arm had Grade ≥ 3 infections with an onset in the later phase of the study (after 6 months), possibly related to prolonged treatment and longer observation in bevacizumab+RT/T arm. The number of fatal (Grade 5) infection AEs (occurring during treatment or within 90 days of last dose) was similar in each group (8 patients bevacizumab+RT/T, 6 patients Pl+RT/T). The total number of fatal infections during the study including post-treatment survival follow-up was also similar in each group. The Grade ≥ 3 infection AEs included most commonly respiratory tract infections for which there was no clear overall imbalance across groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

EORTC
The majority of treated patients in both arms experienced at least one AE (97.1% of patients in the bevacizumab + Lom arm and 85.7% of patients in the Lom arm. The most frequently reported AEs (preferred terms occurring in ≥ 20% of patients) in the bevacizumab + Lom arm were fatigue, hypertension, headache, nausea, and seizure, while the most frequently reported AE in the Lom arm was fatigue (Table 24). Events of hypertension, epistaxis, fatigue, headache, and decreased weight occurred with a ≥ 10% higher incidence in the bevacizumab + Lom arm compared with the Lom arm. Events with a ≥ 5% higher incidence in the bevacizumab + Lom arm compared with the Lom arm additionally included nausea, seizure, constipation, diarrhea, decreased appetite, arthralgia, peripheral sensory neuropathy, pyrexia, stomatitis, myalgia, and toothache.

Reviewer comment: The denominator for AEs includes 4 patients in the bevacizumab arm who did not any reported AEs. Proteinuria is discussion in section 7.4.2.

Table 24 Summary of Adverse Events (All Grades) with an Incidence Rate of at Least 10% in Either Treatment Arm (EORTC, Safety Population)

Body System/ Adverse Event	Lom N = 147 No. (%)	Bv+Lom N = 278 No. (%)
NERVOUS SYSTEM DISORDERS		
HEADACHE	29 (19.7)	88 (31.7)
SEIZURE	26 (17.7)	66 (23.7)
DIZZINESS	15 (10.2)	30 (10.8)
PERIPHERAL SENSORY NEUROPATHY	2 (1.4)	28 (10.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	65 (44.2)	172 (61.9)
OEDEMA PERIPHERAL	16 (10.9)	24 (8.6)
GASTROINTESTINAL DISORDERS		
NAUSEA	25 (17.0)	68 (24.5)
CONSTIPATION	18 (12.2)	50 (18.0)
DIARRHOEA	10 (6.8)	44 (15.8)
VOMITING	13 (8.8)	31 (11.2)
VASCULAR DISORDERS		
HYPERTENSION	27 (18.4)	92 (33.1)
INVESTIGATIONS		
WEIGHT DECREASED	5 (3.4)	39 (14.0)
WEIGHT INCREASED	11 (7.5)	31 (11.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
MUSCULAR WEAKNESS	10 (6.8)	29 (10.4)
ARTHRALGIA	7 (4.8)	29 (10.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
EPISTAXIS	2 (1.4)	40 (14.4)
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	7 (4.8)	33 (11.9)

Bv=bevacizumab, Lom=lomustine

Reviewer Comment: The reviewer independently reviewed the data in Table 24. All data were confirmed. Minimal discrepancies were noted (<0.5% difference) that do not impact the evaluation of the safety profile of bevacizumab. Hypertension is a known and expected adverse event of bevacizumab.

Table 25 Summary of Grade 3-5 Adverse Events with an Incidence of at least 2% (EORTC, Safety Population)

Body System/ Adverse Event	Lom N = 147 No. (%)	Bv+Lom N = 278 No. (%)
VASCULAR DISORDERS		
HYPERTENSION	7 (4.8)	42 (15.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	3 (2.0)	13 (4.7)
DYSPNOEA	2 (1.4)	6 (2.2)
PNEUMONITIS	3 (2.0)	1 (0.4)
NERVOUS SYSTEM DISORDERS		
SEIZURE	4 (2.7)	17 (6.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	6 (4.1)	14 (5.0)
INFECTIONS AND INFESTATIONS		
LUNG INFECTION	3 (2.0)	6 (2.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
MUSCULAR WEAKNESS	3 (2.0)	3 (1.1)

Bv=bevacizumab, Lom=lomustine

Reviewer Comment: The reviewer independently reviewed the data in Table 25. All data were confirmed. Only one Grade 3-5 adverse event was reported with greater than 5% difference in the Bevacizumab+Lom arm (hypertension, 15.1% vs 4.8%). Hypertension is a known and expected adverse event of bevacizumab.

AVAglio

The most commonly reported AEs by individual preferred term with at least a 10% higher incidence in the bevacizumab+RT/T arm compared with the Pl+RT/T arm were those with a known association with bevacizumab treatment [hypertension (26.8%) , epistaxis (16.4%) and proteinuria (11.4%)]. Those that occurred with at least 5 % higher

incidence are outlined in table 27 below. The most commonly reported AEs with an incidence of >10% in either treatment arm are summarized in Table 26.

Table 26 Summary of Adverse Events (all Grades) with an Incidence of ≥10% in Either Treatment Arm (Safety Population, AVAglio)

Body System/ Adverse Event	Pl+RT/T N = 450 No. (%)	Bv+RT/T N = 461 No. (%)
GASTROINTESTINAL DISORDERS		
NAUSEA	191 (42.4)	223 (48.4)
CONSTIPATION	137 (30.4)	178 (38.6)
VOMITING	102 (22.7)	149 (32.3)
DIARRHOEA	70 (15.6)	96 (20.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	178 (39.6)	191 (41.4)
ASTHENIA	63 (14.0)	86 (18.7)
PYREXIA	28 (6.2)	47 (10.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
ALOPECIA	162 (36.0)	180 (39.0)
RASH	61 (13.6)	77 (16.7)
PRURITUS	37 (8.2)	54 (11.7)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
THROMBOCYTOPENIA	123 (27.3)	157 (34.1)
NEUTROPENIA	55 (12.2)	66 (14.3)
LEUKOPENIA	41 (9.1)	56 (12.1)
NERVOUS SYSTEM DISORDERS		
HEADACHE	130 (28.9)	174 (37.7)
DIZZINESS	54 (12.0)	46 (10.0)
VASCULAR DISORDERS		
HYPERTENSION	51 (11.3)	178 (38.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
EPISTAXIS	22 (4.9)	98 (21.3)
COUGH	46 (10.2)	55 (11.9)
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	76 (16.9)	116 (25.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA	30 (6.7)	71 (15.4)
PAIN IN EXTREMITY	22 (4.9)	48 (10.4)
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	26 (5.8)	63 (13.7)
URINARY TRACT INFECTION	29 (6.4)	50 (10.8)
PSYCHIATRIC DISORDERS		
INSOMNIA	42 (9.3)	53 (11.5)
RENAL AND URINARY DISORDERS		
PROTEINURIA	19 (4.2)	72 (15.6)

Bev=bevacizumab, RT=radiotherapy, T=temozolomide

Reviewer Comment: The reviewer independently confirmed the table above with the expectation that the incidence of "convulsions" occurred at more than 10% in the placebo group vs. the bevacizumab-containing arm (10.2% vs. 8.9%, respectively. . Convulsions are expected in this disease population and there is less 2% difference between the treatment groups. This does not impact the risk-benefit profile of bevacizumab.

Table 27 Summary of Adverse Events (all Grades) that occurred at more than 5% in the BV+RT/T arm compared to the Pl +RT/T arm (AVAglio, Safety Population)

ORGAN SYSTEM	PT TERM	PL +RT/T N=450 (No., %)		BV + RT/T N=461 (n, %)		% Difference
BLOOD AND LYMPHATIC SYSTEM DISORDERS	THROMBOCYTOPENIA	123	27.3	157	34.1	6.7
GASTROINTESTINAL DISORDERS	CONSTIPATION	137	30.4	178	38.6	8.2
	GINGIVAL BLEEDING	6	1.3	36	7.8	6.5
	NAUSEA	193	42.9	223	48.4	5.5
	VOMITING	104	23.1	150	32.5	9.4
INFECTIONS AND INFESTATIONS	NASOPHARYNGITIS	28	6.2	63	13.7	7.4
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	77	17.1	116	25.2	8.10
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	30	6.7	71	15.4	8.7
	MUSCULOSKELETAL PAIN	12	2.7	41	8.9	6.2
	PAIN IN EXTREMITY	22	4.9	48	10.4	5.5
NERVOUS SYSTEM DISORDERS	HEADACHE	130	28.9	176	38.2	9.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	DYSPHONIA	7	1.6	42	9.1	7.6
	EPISTAXIS	23	5.1	99	21.5	16.4
RENAL AND URINARY DISORDERS	PROTEINURIA	19	4.2	72	15.6	11.4
VASCULAR DISORDERS	HYPERTENSION	53	11.8	178	38.6	26.8

Bev=bevacizumab, RT=radiotherapy, T=temozolomide

More patients experienced at least one Grade ≥ 3 AE in the bevacizumab+RT/T arm (66.8%) than in the Pl+RT/T arm (51.3%). Some of the imbalance was attributable to events with a known association with bevacizumab treatment (e.g. hypertension and proteinuria) and an increase in cardiac events included ATEs (3 myocardial infarction) and two congestive heart failure (CHF) events, all of which occurred in the bevacizumab+RT/T arm. Events

Table 28 Summary of Adverse Events (≥Grade 3) with an Incidence of at least 2% in Either Treatment Arm (AVAglio, Safety Population)

Body System/ Adverse Event	Pl+RT/T N = 450 No. (%)	Bv+RT/T N = 461 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
THROMBOCYTOPENIA	44 (9.8)	69 (15.0)
NEUTROPENIA	25 (5.6)	35 (7.6)
LYMPHOPENIA	25 (5.6)	20 (4.3)
LEUKOPENIA	13 (2.9)	19 (4.1)
VASCULAR DISORDERS		
HYPERTENSION	9 (2.0)	52 (11.3)
DEEP VEIN THROMBOSIS	19 (4.2)	14 (3.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	21 (4.7)	34 (7.4)
ASTHENIA	15 (3.3)	9 (2.0)
NERVOUS SYSTEM DISORDERS		
CONVULSION	13 (2.9)	9 (2.0)
SYNCOPE	5 (1.1)	10 (2.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY EMBOLISM	12 (2.7)	14 (3.0)
RENAL AND URINARY DISORDERS		
PROTEINURIA	-	24 (5.2)
INFECTIONS AND INFESTATIONS		
PNEUMONIA	6 (1.3)	11 (2.4)
GASTROINTESTINAL DISORDERS		
NAUSEA	10 (2.2)	6 (1.3)
METABOLISM AND NUTRITION DISORDERS		
HYPERGLYCAEMIA	12 (2.7)	2 (0.4)

Bev=bevacizumab, RT=radiotherapy, T=temozolomide

Reviewer Comment: The reviewer independently reviewed the data in Table 28. All data were confirmed. AEs that occurred at more than 5% in the BV=RT/T arm compared to the Pl +RT/T arm included hypertension (9.1%), thrombocytopenia (5.4%) and proteinuria (5.2%).

RTOG
The most common categories of AEs reported across stages of treatment were constitutional symptoms, dermatology/skin, metabolic/laboratory, and gastrointestinal. Limited detail was included in this submission. The overall incidence of AEs by severity grade was similar between the two treatment arms in the Concurrent Stage and the Adjuvant Stage.

7.4.2 Laboratory Findings

EORTC
In EORTC, hematological abnormalities were reported as lab values and not necessarily as AEs. The incidence of newly occurring NCI-CTCAE Grade 3 and Grade 4 laboratory abnormalities (including abnormalities in hematological and clinical chemistry parameters) was generally comparable between the two treatment arms. Low white blood cell values of Grade 3 or Grade 4 were less frequent in the bevacizumab + Lom arm (12% of patients with Grade 3, 1% with Grade 4) than in the Lom arm (17% Grade 3, 5% Grade 4), whereas low platelets of Grade 3 were more frequent in bevacizumab + Lom arm (22% vs. 16%). proteinuria was more prevalent in the bevacizumab + Lom arm than in the Lom arm (See section 7.3.5 for more detail).

Table 29 Summary of Urine Analysis Proteinuria (EORTC, Safety Population, copied from CSR)

	Number (%) of Patients	
NCI-CTCAE grade [a]	Lom (N=147)	Bv+Lom (N=278)
Total number of patients with an assessment	135	275
Grade 1	47 (34.8)	113 (41.1)
Grade 2	2 (1.5)	25 (9.1)
Grade 3	0 (0.0)	4 (1.5)

Bv=bevacizumab; Lom=lomustine; N=total number of patients; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Grade 1=dipstick +1 or 24 hours protein <1.0 g/24 hours; Grade 2=dipstick +2 & +3 or protein 1.0–3.4 g/24 hours; Grade 3=dipstick +4 or more or protein ≥3.5 g/24 hours. If two assessments were available in the same time window, the highest grade was selected.

AVAglio
The proportion of patients with Grade 4 thrombocytopenia was higher in the bevacizumab + RT/T arm (9%) than in the Pl + RT/T arm (4%), see Section 7.3.5 for more detail. The incidences of newly occurring Grade 3 or 4 abnormalities for other laboratory tests were similar between the treatment arms.

RTOG
Results of laboratory assessments were not included in this submission.

7.4.3 Vital Signs
EORTC
Hypertension is described in section 7.3.5. Mean changes from baseline in body weight and body surface area were minimal in both treatment arms.

AVAglio
Minor increases in blood pressure were observed in the bevacizumab + RT/T arm compared with no notable changes in the Pl + RT/T arm. In the bevacizumab + RT/T arm, the median change from baseline to the last visit was 1.0 mmHg for diastolic blood pressure and 4.0 mmHg for systolic blood pressure. In the Pl + RT/T arm, the median change from baseline was 0.0 mmHg for diastolic blood pressure and + 1.0 mmHg for systolic blood pressure.

RTOG
Vital signs data were not included for review in this submission.

7.4.4 Electrocardiograms (ECGs)
EORTC
ECGs were done at screening and then every 6 weeks during study treatment if clinically indicated. There were no clinically relevant findings in ECG assessments during the study. The following Grade 1 ECG abnormalities were reported as AEs: sinus tachycardia (1 patient in the bevacizumab + Lom arm and 3 in the Lom arm), and supraventricular arrhythmia, sinus bradycardia and ventricular arrhythmia (each in 1 patient in the bevacizumab + Lom arm). All of these events resolved and none were considered related to study treatment.

AVAgio
Of the patients who had post-baseline ECG measurements, 2.2% in the bevacizumab+RT/T arm and 2.4% in the Pl +RT/T arm had a change from a normal ECG assessment at baseline to an abnormal assessment at follow-up. One patient in the Pl + RT/T arm had an abnormal ECG assessment at the safety follow-up visit but was missing a baseline assessment. No patients in the bevacizumab + RT/T arm who

were missing a baseline ECG had an abnormal ECG during or at the end of study treatment. AEs related to arrhythmias were reported in a comparable number of patients in both treatment arms (bevacizumab +RT/T: 6 patients, Pl+RT/T arm: 4 patients), and the majority of events were Grade 1 - 2 and resolved.

RTOG
ECG assessments were not performed in Study RTOG 0825.

7.4.5 Special Safety Studies/Clinical Trials
There were no Special Safety Studies/Clinical Trials conducted with bevacizumab and included in this supplement.

7.4.6 Immunogenicity
No immunogenicity studies were included for review in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The same dose was used in EORTC, AVAglio, and RTOG; therefore, dose-dependency was not specifically addressed in this application.

7.5.2 Time Dependency for Adverse Events

Time-dependency was not specifically addressed in this application.

7.5.3 Drug-Demographic Interactions

EORTC
Key safety data, including the incidence of AEs, SAEs, Grade ≥ 3 AEs, and AESIs for bevacizumab, were reviewed and compared in elderly (age ≥ 65 years) and younger patients (< 65 years). In both treatment arms, there was a higher incidence of SAEs and Grade ≥ 3 AEs in patient aged ≥ 65 years compared with those who were < 65 years old. This difference was noted in both treatment arms. In general, the safety profile of bevacizumab + Lom treatment was similar between elderly and younger patients in that the incidences of AEs, SAEs, Grade ≥ 3 AEs and AESIs for bevacizumab were all higher in the bevacizumab + Lom arm than in the Lom arm in both age groups.

A review of key safety data by gender did not show any impact of gender on the safety of the treatment regimen in either treatment arm.

AVAglio
In general, the safety profile of bevacizumab + RT/T treatment was comparable in elderly (age≥65 years) and younger patients (< 65 years) with a similar magnitude of bevacizumab-associated increases in AEs in both age subgroups. Overall, irrespective of treatment received, there was a higher incidence of Grade ≥ 3 AEs, SAEs, and fatal AEs in patients aged ≥65 years compared with patients aged ≥65 years). A possible exception was observed for strokes (coded under both ATEs and cerebral hemorrhage and determined upon medical review to be mainly of ischemic origin) for which the elderly appeared to be at higher risk with bevacizumab treatment relative to placebo.

Infections were reported in a higher proportion of patients overall in bevacizumab + RT/T arm than in the Pl + RT/T arm. In both the young and elderly subgroups, the proportions of patients with Grade ≥3 infection were higher in the bevacizumab + RT/T arm compared with the Pl +RT/T arm; however, the difference between treatment arms was larger (approximately 2-fold) in patients aged ≥ 65 years (17.0% in the bevacizumab + RT/T arm vs. 8.2% in the Pl +RT/T arm) than in patients aged ≥65 years (11.6% in the bevacizumab +RT/T arm vs. 7.7% in the Pl +RT/T arm).

Sex did not generally influence the safety profile of the bevacizumab + RT/T arm relative to that of the Pl +RT/T arm. As with age, the distribution of ATEs and cerebral hemorrhage (primarily stokes, most of which were determined upon medical review to be of ischemic origin) differed across subgroups; females in the bevacizumab + RT/T arm showed a greater increase of events relative to the Pl + RT/T arm than male patients; however, the numbers of patients with events were low and the data should be interpreted with caution. In both treatment arms a higher proportion of female patients than male patients (bevacizumab + RT/T arm: 74.4% vs. 62.1%, Pl +RT/T arm: 58.8% vs. 47.2%) experienced Grade ≥3 AEs. In the bevacizumab + RT/T arm, a higher proportion of female patients than male patients experienced SAEs (44.9% vs. 35.1%) and discontinued any treatment due to AEs (32.4% vs. 22.8%). This sex difference was not seen in the Pl +RT/T arm.

No safety analyses were performed by race because the size of the non-White subgroup (bevacizumab + RT/T: 45 patients, Pl+ RT/T: 44 patients) was too small in comparison with the White subgroup (bevacizumab + RT/T: 413 patients, Pl + RT/T: 419 patients) to enable a meaningful analysis.

No subgroup analyses was performed in Study RTOG 0825.

Reviewer Comment: The number of events in both treatment arms of each of these subgroup analyses were low, the data should be interpreted with caution.

7.5.4 Drug-Disease Interactions
N/A

7.5.5 Drug-Drug Interactions

No additional information on potential drug-drug interactions was obtained from Study EORTC 26101 or Study RTOG 0825.

Potential drug-drug interactions between bevacizumab and TMZ were explored in a sub-study of Study AVAglio. Twenty patients were recruited to the sub-study and provided PK data for analysis. Key findings include:

- The PK of bevacizumab in patients with newly diagnosed GBM was similar to the PK observed in other indications.
- Bevacizumab exposure did not appear to be influenced TMZ.
- TMZ exposure in both arms (bevacizumab + RT and TMZ and Placebo + RT and TMZ) was within published TMZ exposure variability for the initial dose regimen used in the Maintenance Phase (150 mg/m^2 once daily on Days 1 - 5).

Subgroups analyses by corticosteroid use at baseline showed that incidences of AEs were generally lower in patients not receiving corticosteroids at baseline compared with patients receiving corticosteroids at baseline, in particular for categories of more severe AEs, such as SAEs, Grade $\geq$ 3 AEs, or AEs leading to death or discontinuation of study treatment. These analyses are discussed in the Section 5 of the review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

There were no reported pregnancies in any of the patients in the studies. There was one pregnancy reported in a partner of a patient in Study AVAglio; however, no further information was available as the patient withdrew consent.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric patients were not included in any of the studies included in the sBLA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No additional information was obtained in the three clinical studies.

7.7 Additional Submissions / Safety Issues

No additional submissions regarding safety issues were reviewed.

8 Postmarket Experience

Since initial market approval in the United States on February 26, 2004 (i.e., international birth date [IBD]) and until the end of the February 2016, bevacizumab has been approved for use in over 100 countries. The Applicant states that estimated cumulative clinical study exposure to bevacizumab from the development international birth date (March 3, 1997) to February 2016 is 32,237 patients. Since the IBD, an estimated total of (b) (4) patients have received bevacizumab in the post-market setting. An estimated (b) (4) patients with GBM have received bevacizumab treatment worldwide. Overall, the safety profile of bevacizumab in GBM appears consistent with the known safety profile. No relevant new safety signals have been identified based on post-marketing data from patients treated with bevacizumab in combination with chemotherapy. The Applicant continues to monitor safety as part of the ongoing pharmacovigilance program.

The Empirica Signal data mining tool was used to identify potential safety signals not already described in the bevacizumab prescribing information. A data mining run was performed in an unrestricted patient population on October 27, 2017. No additional safety signals were uncovered through analysis of the Empirica Database.

9 Appendices

9.1 Literature Review/References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England journal of medicine 2005;352:987-96.
2. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1999;17:2572-8.
3. Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31:3212-8.
4. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:1168-74.
5. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:4733-40.
6. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:740-5.
7. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. The Lancet Oncology 2014;15:943-53.

9.2 Labeling Recommendations

Labeling review was ongoing at the time this clinical/statistical review was completed. Significant changes to streamline the safety data and information from clinical trials were proposed. Please see the package insert for Avastin.

9.3 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drug Advisory Committee

(ODAC) for this application as the safety profile is acceptable based on the indicated population and the efficacy outcome measures were considered acceptable. The Division requested advice from two special government employees (SGEs). At the time this clinical review was completed, discussions with the SGEs were pending.

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/s/

AMY K BARONE
11/30/2017

JOOHEE SUL
11/30/2017

SIRISHA L MUSHTI
11/30/2017

LISA R RODRIGUEZ
12/01/2017

SUZANNE G DEMKO
12/01/2017
I concur with the content and conclusions contained in this review, and am in agreement with the recommendation to approve this sBLA.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products
Center for Drug Evaluation and Research

Date: October 16, 2017

From: Billy Dunn, M.D.
Division Director

Subject: BLA 125085 (S-319)
Bevacizumab (Avastin)
Genentech
Study EORTC 26101/MO22968: Neuropsychological Test Results

To: Director
Division of Oncology Products 2

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

BLA (Serial Number)	**125085 (S-319)**
Sponsor:	**Genentech**
Product:	**Bevacizumab (Avastin)**
Indication:	**Glioblastoma**
Material Submitted:	**Consult (Efficacy Supplement)**
Correspondence Date:	**2/2/17**
Date Received By Reviewer:	**7/6/17**
Date Review Completed	**10/16/17**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This consultation request from the Division of Oncology Products 2 and the Clinical Outcomes Assessment staff is in regard to the validity, reliability, and clinical meaningfulness of the results seen on several neuropsychological tests in a clinical efficacy study of bevacizumab (Avastin) in patients with glioblastoma. Those neuropsychological tests were used as secondary efficacy measures in that study, the report of which was submitted as part of a supplemental Biological License Application (sBLA) (efficacy supplement; S-329) for Avastin.

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody to vascular endothelial growth factor, a regulator of angiogenesis. It is approved for a number of oncological indications including "*the treatment of glioblastoma as a single agent for adult patients with progressive disease following prior therapy*." Please see the following link for full details of the indications that Avastin is currently approved for and for the full Prescribing Information for that compound .

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125085s225lbl.pdf

The clinical efficacy study to which this consultation request pertains is EORTC 26101/MO22968.

The neuropsychological tests to which this consultation pertains are the following: the Hopkins Verbal Learning Test-Revised, Parts A, B, and C; the Trailmaking Tests A and B; and the Controlled Word Association Test.

In this review, the terms "neuropsychological test" and "cognitive test" are used synonymously, as are the names "Avastin" and "bevacizumab."

The approval of Avastin (bevacizumab) for the current glioblastoma-related indication was granted under the Accelerated Approval pathway (Subpart E; 21 CFR 601.41) in a letter dated May 5, 2009. That action was in response to a sBLA, an efficacy supplement (S-169) submitted under Biologics Licensing

Application (BLA) 125085 on October 31, 2008. The aforementioned Accelerated Approval letter required that the sponsor conduct a further efficacy study in support of the full approval of Avastin for the same indication, as a post-marketing requirement. Study EORTC 26101/MO22968 has been conducted, and the results submitted in the current sBLA on February 2, 2017, in fulfillment of that requirement, and in support of the full approval of Avastin for "*the treatment of glioblastoma with progressive disease in adult patients following prior therapy*."

2. Contents Of Consultation Request Package

This consultation request package contains a consultation request proper with a link to the contents of the submission to which the consultation pertains. The key text of the consultation request is copied verbatim below.

The Division of Oncology Products 2 and the Clinical Outcome Assessment Staff are requesting a DNP consult to help us better understand (1) the validity and reliability; and (2) clinical meaningfulness of the results of the following neuropsychological tests (performance outcome measures) administered in the pivotal study EORTC (MO 22968) to assess cognitive functioning in patients with glioblastoma.

- Hopkins Verbal Learning Test (HVLT) (Parts A, B, and C)
- Trail Making Test (TMT) (Types A and B)
- Controlled Oral Word Association (COWA)

3. Contents Of Review

The contents of this submission have been reviewed under the following main headings and in the same consecutive order as below.

- Outline of Study EORTC 26101/MO22968.
- Outline of neuropsychological (cognitive function) tests conducted during Study EORTC 26101/MO22968 and their analysis.
- Reviewer's summary comments.
- Response to consultation request.

Please note that this consultative review has been narrowly focused on the topic outlined in the consultation request. This review does not attempt to address whether the results of Study EORTC 26101/MO22968 merit the grant of full approval for Avastin (bevacizumab) for the indication proposed in this sBLA.

4. Outline Of Study EORTC 26101/MO22968

The elements of the final protocol for Study EORTC 26101/MO22968 that are essential to this consultation are summarized below. An in-depth review of that

protocol was not considered necessary to enable completion of this consultation. Please refer to the full protocol for further information.

(The abbreviation "EORTC" stands for "European Organization for the Research and Treatment of Cancer").

4.1 Primary Objective

To investigate whether the addition of bevacizumab to lomustine improved overall survival in patients with recurrent glioblastoma.

4.2 Design, Dose, Sample Size, And Duration

This was, in its final form, a Phase 3 randomized, open-label, parallel- and two-arm study.

The two arms of the study were as follows:

Arm 1: Lomustine 90 mg/m^2 every 6 weeks PLUS bevacizumab 10 mg/kg every 2 weeks

Arm 2: Lomustine 110 mg/m^2 every 6 weeks.

Patients were randomized in a 2:1 ratio to Arms 1 and 2, respectively.

This study began as a randomized, four-arm Phase 2 study. The original four arms of the study were as follows:

Arm 1: Lomustine 90 mg/m^2 every 6 weeks PLUS bevacizumab 10 mg/kg every 2 weeks.

Arm 2: Lomustine 110 mg/m^2 every 6 weeks until disease progression, followed by (switch to) bevacizumab 10 mg/kg every 2 weeks.

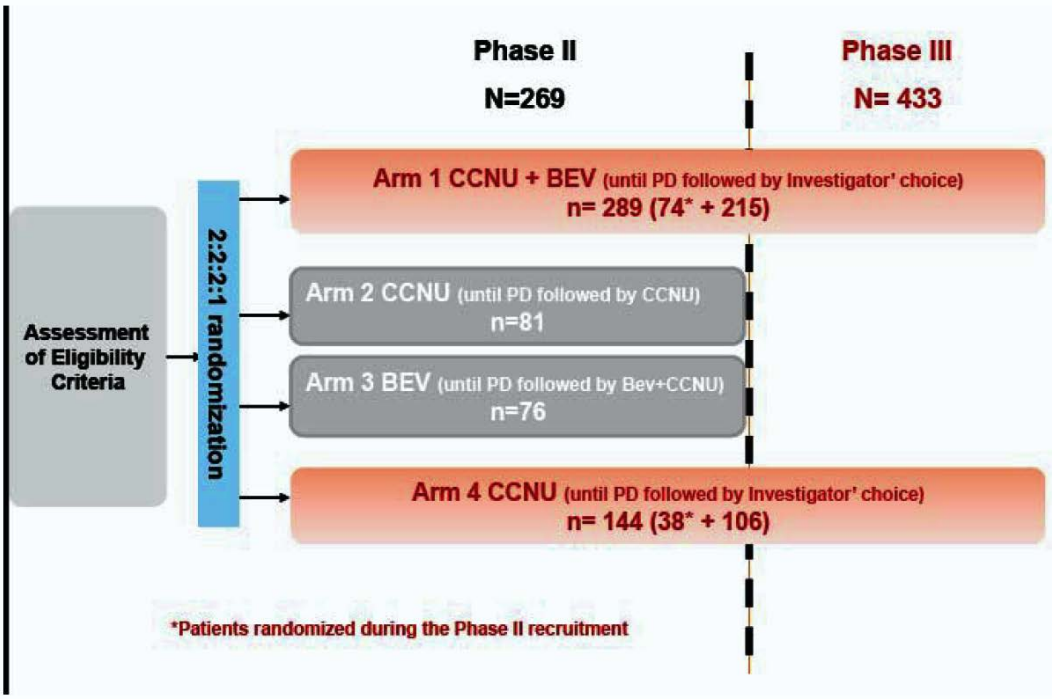
Arm 3: Bevacizumab 10 mg/kg every 2 weeks until disease progression, followed by bevacizumab 10 mg/kg every 2 weeks plus lomustine 90 mg/m^2 every 6 weeks.

Arm 4: Lomustine 110 mg/m^2 every 6 weeks. (This was considered the control arm)

The original primary endpoint was overall survival at 12 months.

After evidence emerged that the combination of bevacizumab and lomustine had a survival benefit compared with either lomustine or bevacizumab administered alone, the protocol was amended to the final two-arm study and the size of Arm 1 expanded. The amendment was implemented prior to any analysis of study data.

The amendment to this study is depicted in the following schematic that I have copied from the study report.



BEV = bevacizumab; CCNU = lomustine; N = total number of patients planned per study phase; n = number of patients per treatment arm; PD = progressive disease

---

4.3 Key Selection Criteria

4.3.1 Main Inclusion Criterion

First recurrence of glioblastoma occurring at least 3 months after standard chemotherapy-radiotherapy with temozolomide.

4.3.2 Main Exclusion Criterion

Prior treatment with nitrosoureas, bevacizumab, other vascular endothelial growth factor inhibitors, or vascular endothelial growth factor receptor signalling inhibitors.

4.4 Outcome Measures

4.4.1 Primary Efficacy Parameter

Overall survival*

*Overall survival was defined as the time from the date of randomization to death due to any cause or last date known to be alive for patients still alive at the clinical cut-off date.

4.4.2 Secondary Efficacy Parameters

- Progression-free survival as assessed by the investigator using the modified Response Assessment in Neuro-Oncology (RANO) criteria, at 6 months and 12 months.

- Response rates (objective response and median duration of response) based on the modified RANO criteria.

- Health-related quality of life. An entirely patient-rated outcome comprised of the EORTC Quality of Life Questionnaire C30 (Version 3) supplemented by a brain cancer-specific module (BN20), also from the EORTC. Further details of these instruments are in Section 4.4.2.1

- Clinical/neurological deterioration-free survival at 6 months and 12 months.

- Extent of steroid use.

- Cognitive function tests: Hopkins Verbal Learning Test-Revised; Trailmaking Tests Part A and B; and Controlled Word Association Test. (These are further described in Section 5).

- Overall survival at 6, 9, 12, and 24 months.

4.4.2.1 Further Details About Patient-Rated Quality Of Life Instruments

The components of that instrument that are rated are listed below in text copied from the study report.

EORTC QLQ-C30

- *Global health status/quality of life (items 29, 30)*
- *Physical functioning (items 1-5)*
- *Role functioning (items 6-7)*
- *Emotional functioning (items 21-24)*
- *Cognitive functioning (items 20 and 25)*
- *Social functioning (items 26 and 27)*
- *Fatigue (items 10, 12, 18)*
- *Nausea and vomiting (items 14, 15)*
- *Pain (item 9, 19)*
- *Dyspnea (item 8)*
- *Insomnia (item 11)*
- *Appetite loss (item 13)*
- *Constipation (item 16)*
- *Diarrhea (item 17)*
- *Financial difficulties (item 28)*

BN20 module of EORTC

- *Future uncertainty (items 31, 32, 33, 35)*
- *Visual disorder (items 36, 37, 38)*
- *Motor dysfunction (items 40, 45, 49)*
- *Communication deficit (items 41, 42, 43)*
- *Headaches (item 34)*
- *Seizures (item 39)*
- *Drowsiness (item 44)*
- *Itchy skin (item 47)*
- *Hair loss (item 46)*
- *Weakness of legs (item 48)*
- *Bladder control (item 40)*

The patient-rated quality of life instruments are addressed in a separate consultation by the Clinical Outcomes Assessment (COA) staff.

4.4.3 Safety Parameters

Adverse events, vital signs, safety laboratory tests, and electrocardiograms.

4.5 Selected General Aspects Of Statistical Analysis Plan

4.5.1 Primary Efficacy Analysis

The primary efficacy parameter was overall survival as defined in Section 4.4.1.

The primary efficacy analysis was to be performed on the intent-to-treat population, defined as all patients randomized with data available to the sponsor, regardless of whether they received any study drug or completed the full course of treatment. Patients were to be assigned to the treatment arm to which they were randomized for purposes of the analysis.

The difference in the duration of overall survival was to be compared between the two treatment groups using a stratified one-sided log rank test at an overall 0.025 level of significance. Stratification factors used in the model were those used for stratification at randomization (see below), except investigational site, and with an added variable indicating if the patient was recruited during the original Phase 2 period or the later Phase 3 period of the study. Further details of the primary efficacy analysis and of other analyses of the primary efficacy parameter are in the report of Study EORTC 26101/MO22968.

(Stratification factors used at randomization were investigational site, performance status, steroid administration, and largest lesion diameter).

4.5.2 Hierarchical Analysis Of Secondary Efficacy Endpoints

A hierarchical analysis of selected secondary efficacy endpoints was to be performed if the results of the primary efficacy analysis yielded a statistically significant treatment effect. An overall level of significance of 0.025 was to be maintained while performing that analysis.

The hierarchical analysis of selected secondary efficacy endpoints was to be performed in the following order.

- Progression-free survival as assessed by the investigator using the modified Response Assessment in Neuro-Oncology (RANO) criteria, at 6 months and 12 months.
- Objective response rates based on the modified RANO criteria.
- Health-related quality of life.
- Clinical/neurological deterioration-free survival.

Further details of the plan for this hierarchical analysis, including the method of controlling the overall Type 1 error, are in the report of Study EORTC 26101/MO22968.

5. Outline Of Neuropsychological (Cognitive Function) Tests Conducted During Study EORTC 26101/MO22968 And Their Analysis

5.1 Description Of Neuropsychological Tests

The neuropsychological tests that were performed serially as part of this study are described briefly below. These tests were performed by trained psychologists at baseline and then every 12 weeks until disease progression.

The description of these tests below is partly based on information provided in this submission.

5.1.1 Hopkins Verbal-Learning Test-Revised

This is a test of learning and memory. The subject is asked to learn and recall a list of 12 words consisting of three semantic categories of 4 words each. The test proceeds in the following numerical order through 3 parts, each of which is scored separately.

1. Part A. The subject is first read the aforementioned word list 3 times and is asked to recall as many words as possible after each reading. The total

number of words recalled yields a **raw** free recall score that ranges from 0 through 36.

2. Part B. After a delay of 20 minutes (following Part A), the subject is asked to recall the original list of 12 words a final time. The total number of words recalled yields a **raw** delayed recall score that ranges from 0 through 12.

3. Part C. The subject is then read a list of 24 words: this list includes all the 12 words in the original list together with 6 words that are related to the categories in the first list and 6 words that are not. After each word in the 24-word list is read, the subject is asked to state if the word then being read was in the original list of 12 words. A **raw** delayed recognition score is derived from the subject's responses and can range from -12 to 12.

In each part of the test, higher scores indicate better cognitive function.

5.1.2 Trailmaking Tests And B

These tests are intended to assess psychomotor speed and function, as well as attention, concentration, sequencing, and mental flexibility.

Part A requires the connection in proper order using pencil lines of 25 encircled numbers randomly arranged on a page. Part B requires the connection in proper order using pencil lines of a total of 25 encircled numbers and letters randomly arranged on a page; in this task, letters and numbers are to be connected in alternating sequence.

Raw scores will be determined by the total time to completion in seconds if both the sample and actual tests are completed. Raw scores range from 1 to 2750 for Part A, and from 1 to 3750 for Part B; higher scores indicate more cognitive impairment

5.1.3 Controlled Word Association Test

This is a standardized test of verbal fluency, specifically verbal association fluency. The subject is asked to generate a list of words beginning with each of 3 specified letters of the alphabet, each list being generated over a 1-minute period. The raw score for the Controlled Word Association test will be the sum of the 3 scores reported. Higher scores indicate better cognitive function.

5.2 Analysis Of Neuropsychological Test Scores

The raw scores for each of the cognitive tests above were to be normalized into z-scores using the following:

- Patient age at baseline for the Hopkins Verbal Learning Test-Revised and Trailmaking Tests.

- Gender for the Controlled Word Association Test.

The methods for converting raw scores into z-scores for each of the three instruments are further described in the submission. For the Trailmaking Tests A and B, z-scores were to be further multiplied by -1 so that negative scores represented performance below the mean.

Longitudinal data analysis was to be performed on the derived z-scores for each neuropsychological test to assess score trends over time using a linear mixed model. That model was to include treatment, time, and treatment-time interaction as fixed effects together with a random subject effect; in addition, baseline covariates such as performance status, age, and surgical status were to be explored as fixed effects.

A Reliable Change Index was to be calculated for each test so as to define cognitive decline, which in turn was defined for each test as a change in score that exceeded the Reliable Change Index. A formula for calculating the Reliable Change Index that used the observed standard error of the mean (for that measure) and normative data.

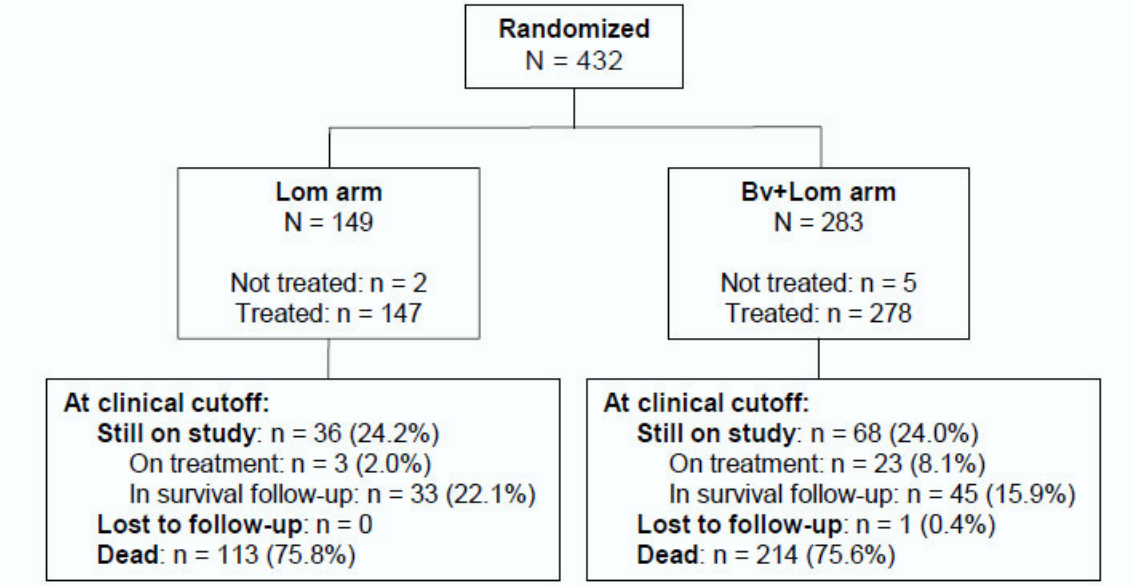
Cognitive decline was to be defined for each patient as a change in score that was a decline in excess of the Reliable Change Index threshold (for the Hopkins Verbal Learning Test-Revised and the Controlled Word Association Test) or a change in score that was an increase in excess of the Reliable Change Index (for the Trailmaking Tests A and B). Stable cognitive function was defined as a change in score that was within or included the boundaries of the Reliable Change Index (for that test).

The proportion of patients who had improved or remained stable versus those who had declined, in cognitive function was to be analyzed at each timepoint. Methods of handling missing data for the Trailmaking Tests are described.

Correlations were to be attempted between the analysis of the 3 cognitive tests described above and the cognitive component of the Health-Related Quality of Life Measures.

6. Overall Results Efficacy Analysis

Patient disposition in this study is summarized in the following sponsor schematic.



BEV = bevacizumab; Lom = lomustine; N = total number of patients planned per study phase; n = number of patients per treatment arm.

Note: Figure shows only patients whose data are available to Roche.

An overall summary of the analysis of the primary efficacy parameter and several secondary efficacy parameters is in the following sponsor table copied from the submission.

Parameter	Lom N = 149	Bv + Lom N = 283
Primary Efficacy Parameter		
Overall survival (KM est. median [months])	8.6	9.1
Hazard Ratio (stratified[a]) (95% CI)	0.91 (0.72, 1.16)	
	p[b] = 0.4578	
Secondary Efficacy Parameters		
PFS (Investigator) (KM est. median [months])	1.5	4.2
Hazard Ratio (stratified[a]) (95% CI)	0.52 (0.41, 0.64)	
	p[b] < 0.0001	
Landmark Survival Rates		
6-month overall survival rate[c] (95% CI)	69% (61, 76%)	73% (67, 77%)
Difference in overall survival rates (95% CI[d])	3.6% (−5.5, 12.7%)	
	p[b] = 0.439	
9-month overall survival rate[c] (95% CI)	47% (39, 56%)	51% (45, 57%)
Difference in overall survival rates (95% CI[d])	3.2% (−7.0, 13.5%)	
	p[b] = 0.537	
12-month overall survival rate[c] (95% CI)	34% (26, 43%)	31% (25, 37%)
Difference in overall survival rates (95% CI[d])	−3.5% (−13.8, 6.9%)	
	p[b] = 0.512	
24-month overall survival rate[c] (95% CI)	10% (4, 18%)	6% (3, 11%)
Difference in overall survival rates (95% CI[d])	−3.7% (−11.7, 4.3%)	
	p[b] = 0.361	
6-month PFS rate[c] (95% CI)	17% (11, 23%)	30% (24, 35%)
Difference in PFS rates (95% CI[d])	12.8% (4.7, 20.9)	
	p[b] = 0.002	
12-month PFS rate[c] (95% CI)	2% (0, 6%)	9% (6, 13%)
Difference in PFS rates (95% CI[d])	6.9% (2.4, 11.5)	
	p[b] = 0.003	
Best overall response		
Patients with measurable disease at baseline	N = 139	N = 260
Responders	8 (5.8%)	68 (26.2%)
Difference in response rates (95% CI)	20.40 (13.8, 27.0)	
	p[e] < 0.0001	
Duration of response in responders, KM est. median (95% CI) (months)	5.6 (3.5, 8.3)	5.6 (4.2, 7.0)
Number of responders without PFS event at clinical cutoff	0/8 (0%)	20/68 (29.4%)
Clinical/Neurological DFS (KM est. median [months])	5.7	6.1
Hazard Ratio (stratified[a]) (95% CI)[a]	0.56 (0.45, 0.70)	
	p[a] < 0.0001	
HRQoL GHS: Time to deterioration (KM est. median [months])	1.5	3.0
Hazard Ratio(stratified[a]) (95% CI)[a]	0.56 (0.45, 0.70)	
	p[a] < 0.0001	
Corticosteroid use		
Patients without corticosteroid treatment at baseline	N = 75	N = 140
Patients who initiated steroid use	29 (38.7%)	53 (37.9%)
Median time to initiation of corticosteroid treatment (days)	1.48	3.02

Parameter	Lom N = 149	Bv + Lom N = 283
Patients with corticosteroid treatment at baseline	N = 74	N = 143
Patients who decreased or discontinued their corticosteroid dose	27 (36.5%)	91 (63.6%)

Bv = bevacizumab; Lom = lomustine; DFS = deterioration-free survival; est. = estimated; GHS = global health status; HRQoL = health-related quality of life; ITT = intent-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; PS = performance status.

[a] Stratified by WHO PS, steroid administration, largest lesion diameter, and Phase II/III enrolment.

[b] Log-Rank p-value (stratified by WHO PS, steroid administration, largest lesion diameter, and Phase II/III enrolment).

[c] Kaplan-Meier estimate and 95% CI.

[d] 95% CI using Greenwood's formula.

[e] Cochran-Mantel-Haenszel; Stratified by WHO PS, Steroids Administration, Largest Lesion Diameter, and Phase II/III enrolment.

As the above table indicates, the addition of bevacizumab to lomustine did not result in a statistically significant improvement in overall survival in patients with recurrent glioblastoma as compared with lomustine alone. Sensitivity analyses confirmed the results of the primary efficacy analysis.

7. Results Of Neuropsychological Test Analysis

7.1 Neuropsychological Test Results At Baseline

The following is a sponsor table comparing the results of testing at baseline for each neuropsychological test or test component assessment. Numerical differences in baseline scores between treatment groups were more evident for the Hopkins Verbal Learning Test-Revised B and C mean scores and for the Trailmaking Test A and B mean scores; lower (more negative) scores were seen for the lomustine only group as compared with the lomustine plus bevacizumab group on those tests.

The sponsor has concluded that compliance with neuropsychological testing during Study EORTC 26101/MO22968 at baseline was high generally, but better for the Hopkins Verbal Learning Test-Revised and Controlled Word Association Test than for the Trailmaking Tests.

	Lom N = 138			Bv + Lom N = 270		
Test	n	mean (SD)	median	n	mean (SD)	median
HVLT-R A (Immediate Recall)	137	−2.4 (1.77)	−2.2	268	−2.1 (1.70)	−2.0
HVLT-R B (Delayed Recall)	135	−2.7 (2.03)	−2.7	267	−2.2 (1.84)	−1.9
HVLT-R C (Recognition)	135	−1.9 (2.48)	−1.3	262	−1.2 (2.08)	−0.6
Trail Making Test, Part A	116	−3.8 (6.37)	−2.0	227	−3.2 (3.71)	−2.0
Trail Making Test, Part B	95	−6.1 (12.97)	−3.2	193	−5.1 (12.50)	−3.1
COWA	137	−1.6 (1.39)	−1.7	268	−1.5 (1.34)	−1.6

BEV = bevacizumab; COWA = controlled word association; HVLT-R = Hopkins verbal learning test-revised; Lom = lomustine; N = total number of patients planned per study phase; n = number of patients.

7.2 Change In Neuropsychological Test Results During Progression-Free Survival Time

The following sponsor table summarizes changes in neuropsychological function test results during progression-free survival time in each treatment group.

Summary of Neurocognitive Function during Patients' Progression-Free Time (NCF Population)

Neurocognitive Function Scale	Lom (N=138)	Bv+Lom (N=270)
HVLT-R A (Immediate Recall)		
Number of patients stable/improved from baseline	47 (81.0%)	159 (81.1%)
Median duration (% progression-free time)	2.9 months (83.5%)	3.0 months (80.4%)
HVLT-R B (Delayed Recall)		
Number of patients stable/improved from baseline	51 (91.1%)	158 (81.9%)
Median duration (% progression-free time)	3.1 months (87.1%)	3.0 months (75.3%)
HVLT-R C (Recognition)		
Number of patients stable/improved from baseline	45 (78.9%)	138 (72.3%)
Median duration (% progression-free time)	3.1 months (96.5%)	3.0 months (81.6%)
Trail Making Test, Part A		
Number of patients stable/improved from baseline	36 (76.6%)	127 (78.9%)
Median duration (% progression-free time)	2.9 months (81.0%)	3.0 months (77.5%)
Trail Making Test, Part B		
Number of patients stable/improved from baseline	29 (70.7%)	98 (72.1%)
Median duration (% progression-free time)	2.9 months (100%)	3.0 months (69.6%)
COWA		
Number of patients stable/improved from baseline	48 (88.9%)	179 (92.7%)
Median duration (% progression-free time)	3.3 months (86.3%)	3.0 months (82.2%)

COWA=controlled word association; HVLT-R=Hopkins verbal learning test-revised; N=total number of patients.

Note: Stable NCF is defined as a change within (and including) the boundaries of the reliable change index (RCI), Improved neurocognitive function is defined as an increase in excess of the RCI threshold (HVLT-R and COWA) or decrease in excess of the RCI threshold (trail making tests).

The sponsor draws attention to the following as reasons for caution in interpreting the data in the above table.

- The neuropsychological tests were administered only every 12 weeks.
- A large proportion of patients had progressed based on the RANO criteria (see above) prior to the first post-baseline neuropsychological assessment (Week 12) and thus did not complete neuropsychological testing.
- At the first post-baseline neuropsychological testing timepoint (Week 12), the proportion of patients (of those randomized to each arm) with completed tests ranged as follows:
    - 67.2% to 74.1% for the bevacizumab plus lomustine arm.
    - 33.6% to 40.0% for lomustine only arm.

- At the second post-baseline neuropsychological testing timepoint (Week 24), the proportion of patients (of those randomized to each arm) with completed tests ranged as follows:

    - 28.6% to 38.8% for the bevacizumab plus lomustine arm.
    - 15.3% to 18.9% for the lomustine only arm.

8. Reviewer's Summary Comments

This consultation request from the Division of Oncology Products 2 and the Clinical Outcomes Assessment Staff is in regard to the validity, reliability, and clinical meaningfulness of the results seen on several neuropsychological tests in a clinical efficacy study of bevacizumab (Avastin) in patients with glioblastoma. These tests were used as secondary efficacy measures in that study.

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor, a regulator of angiogenesis. It is approved for a number of oncological indications, although not for the treatment of glioblastoma.

The clinical study to which this consultation request pertains is EORTC 26101/MO22968. This study in its final design was a randomized, open-label, parallel- and two-arm study. Patient with a recurrence of glioblastoma occurring at least 3 months after standard chemotherapy-radiotherapy with temozolomide were randomized and assigned to 2 treatment groups: Arm 1 consisting of lomustine 90 mg/m^2 every 6 weeks PLUS bevacizumab 10 mg/kg every 2 weeks; and Arm 2 consisting of lomustine 110 mg/m^2 every 6 weeks, administered alone. The primary efficacy parameter was overall survival defined as the time from the date of randomization to death due to any cause or last date known to be alive for patients still alive at the clinical cut-off date. A number of secondary efficacy parameters were proposed for the study consisting of progression-free survival as assessed by the investigator using the modified RANO criteria, at 6 months and 12 months; response rates (objective response and median duration of response) based on the modified RANO criteria; health-related quality of life; clinical/neurological deterioration-free survival at 6 months and 12 months; extent of steroid use; neuropsychological test results (see below); and overall survival at 6, 9, 12, and 24 months.

Neuropsychological testing, performed at baseline and every 12 weeks thereafter, during Study EORTC 26101/MO22968 consisted of the following: the Hopkins Verbal Learning Test-Revised (Parts A, B, and C); Trailmaking Tests Parts A and B; and the Controlled Word Association Test. For analysis purposes, raw scores for each test or test component were converted into z-scores, and used to determine whether each patient had exhibited cognitive decline or cognitive stability during the study according to a pre-specified method. While those neuropsychological test-based measures were considered secondary efficacy parameters for this study, their analysis was not included in the hierarchical scheme planned for the analyses of selected secondary efficacy

parameters and directed at preserving the overall study Type 1 error during those analyses; that sequential series of analyses were to be conducted only if a statistically significant treatment difference was seen on the analysis of the primary efficacy parameter.

In Study EORTC 26101/MO22968, 432 patients were randomized: 283 patients were randomized to the bevacizumab plus lomustine group and 149 patients were randomized to the lomustine only group. The results of the primary efficacy analysis failed to reveal a statistically significant treatment effect on overall survival. A high proportion of patients in both treatment groups progressed during the study and thus did not complete neuropsychological testing.

The Hopkins Verbal Learning Test-Revised, Trailmaking Tests (Parts A and B), and the Controlled Word Association Test have been widely used to assess selected aspects of cognition in a variety of clinical settings. Among the cognitive domains evaluated by one or more of these tests are the following: attention, memory (several aspects), executive function, and verbal fluency. In broad terms, these tests may considered both valid and reliable. The medical literature also indicates that the same tests (together with other similar tests and tests that evaluate other aspects of cognition) have been used on many previous occasions to evaluate the effect of therapeutic interventions on cognition in patients with glioblastoma, indicating that they may be widely accepted for that purpose. On that basis, those tests may be considered to have been appropriate for an exploratory evaluation of the restricted range of cognitive domains that they were directed at in Study EORTC 26101/MO22968.

In the report of Study EORTC 26101/MO22968, the sponsor has presented results of analyses comparing the change in neuropsychological function observed during progression-free survival period in each treatment group. However, for the reasons that follow, no inference regarding the effect of bevacizumab on cognition (when used in combination with lomustine as compared with lomustine alone) in the treatment of glioblastoma can be made based on those results:

- **Neuropsychological testing was not performed in a blinded manner in this study, a critical deficiency.**
- **Only a restricted range of cognitive domains was evaluated, not the broad spectrum of cognitive functions that would need to have been assessed in order to determine if an effect on cognition was seen in that study.**
- **A significant proportion of patients randomized to each treatment group did not complete neuropsychological testing even at the first post-baseline assessment.**

- **The analysis of the neuropsychological test results was intended to be exploratory and was not included in the pre-specified hierarchical analysis of secondary efficacy measures (that provided for an adjustment of the studywise Type 1 error).**

- **It is unclear if any of the reported changes in neuropsychological function seen in either treatment group were clinically meaningful; none of the other efficacy measures used in this study, including the quality of life measures, could have helped in evaluating whether the changes seen on those tests were clinically meaningful.**

- **The prespecified primary efficacy analysis for this study was negative for evidence of efficacy; thus any conclusions that are based on an analysis of secondary efficacy measures are questionable.**

9. Response To Consultation Request

Please see the text of the consultation request in Section 2 of this review. That text is addressed in the bolded comments in Section 8.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm
cc:
HFD-120
IND

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RANJIT B MANI
10/16/2017

WILLIAM H Dunn
10/16/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Template version: January 05, 2017

COA CONSULT TRACKING NUMBER	C2017089
BLA NUMBER	125085-319
REFERENCED IND FOR NDA/BLA	
ESTABLISHED NAME/TRADE NAME	Bevacizumab (AVASTIN)
APPLICANT	Genentech
INDICATION	Treatment of adult patients with glioblastoma following prior therapy
MEETING TYPE (A/B/C/WRO)	Not applicable
SUBMISSION NUMBER	2549
PDUFA GOAL DATE	December 2, 2017
DATE OF CONSULT REQUEST	March 29, 2017
REVIEW COMPLETION DATE	September 30, 2017
REVIEW DIVISION	Division of Oncology Products 2 (DOP2)
MEDICAL REVIEWER/TEAM LEADER (TL)	Amy Barone, MD
REVIEW DIVISION PM	Sharon Sickafuse
COA REVIEWER	Nikunj Patel, PharmD
COA TL/SECONDARY REVIEWER	Selena Daniels, PharmD, MS
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos, MD, MPH
COA TYPE	Patient-Reported Outcome (PRO); Performance Outcome (PerfO)
INSTRUMENT(S)	• EORTC-QLQC30 / BN20 • HVLT-R, TMT, COWA
ENDPOINT(S) CONCEPT(S)	HRQL; Neurocognitive functioning
INTENDED POPULATION(S)	Adult patients (≥18 years) with glioblastoma
Please check all that apply:	☒ Rare Disease/Orphan Designation ☐ Pediatric

Clinical Outcome Assessment Review
Nikunj Patel, PharmD
BLA 125085 / S-319
Bevacizumab (Avastin)
EORTC QLQ-C30 / BN-20 (HRQL); HVLT-R, TMT, COWA (Neurocognitive fx)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Oncology Products 2 (DOP2) regarding the sBLA 125085 (Supplement 319). The sBLA 125085 was originally approved to treat recurrence of glioblastoma under the accelerated approval pathway in 2009 based on improvement in objective response rate. The Applicant (Genentech) completed a confirmatory phase 3, open-label, randomized clinical trial (EORTC 26101) to support full approval of bevacizumab (Avastin) in (b) (4).

The Applicant is not seeking COA-related labeling claims.

The review division requested COA staff input to understand the validity and reliability of the following secondary outcome measures and corresponding results of the EORTC 26101 study to inform possible evidence of clinical benefit:

- *[1]EORTC QLQ-C30/BN-20, Patient-Reported Outcome (PRO), health-related quality of life (HRQL), See Appendix A for a copy of the instrument*
- *[2]HVLT-R, TMT, COWA, Performance Outcome (PerfO), neurocognitive functioning, See Appendices B and C for copies of the instruments*

The COA Staff, after consultation with the review division, requested additional PRO data analyses (See DARRTS Reference ID 4127265) for the EORTC QLQ-C30/BN-20 to examine item- and domain-level responses concerning relevant glioblastoma symptoms (e.g., headaches, vision, seizures, body weakness). The review division also consulted the Division of Neurology Products (DNP) based on discussion with the COA Staff to comment regarding the validity and reliability of neurocognitive outcome assessments and help interpret corresponding results.

This COA review concludes the proposed assessments may be reasonable choices to assess some aspects of HRQL (e.g., physical function) and neurocognitive functioning in the target patient population; however, these instruments have limitations (See Section C4 Content Validity). Contrary to Applicant's assertion that "stable HRQL" was observed in the EORTC 26101 study, PRO results are uninterpretable and subsequently cannot provide any conclusive evidence of clinical benefit because of high attrition and dropout rates[3],open-label clinical trial design, and other methodological issues (e.g., infrequent assessments, absence of an assessment before withdrawal of trial).

There is a possibility that cognitive deficits experienced in some glioblastoma patients may impact data interpretability. However, a published validation study of the PRO instrument has reportedly shown acceptable psychometric performance in a population of glioblastoma patients.

[1] EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; BN20=Brain cancer module
[2] HVLT-R=Hopkins Verbal Learning Test (-Revised); TMT=Trail Making Test; COWA=Controlled Oral Word Association
[3] Post-baseline assessment was only available for 42% of patients in the treatment arm and 20% in the comparator arm in the study EORTC 26101 due to a large portion of the patients had progressed within 12 weeks after baseline.

Refer to the DNP consult by Dr. Ranjit Mani for specific comments regarding neurocognitive outcome measures and corresponding results. Refer to the Clinical and Statistical reviews for additional presentation and analyses of relevant COA data.

We have the following suggestions to inform COA endpoint measurement strategy in future glioblastoma clinical trials:

- Increase COA assessments early in therapy to maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.
- Assess disease-specific signs and symptoms and functional impacts such as physical functioning, mobility, activities of daily living and cognition using well-defined and reliable instruments.
- Consider multi-pronged approach using combinations of various COA types (e.g., patient-reported outcomes, clinician-reported outcomes, caregiver- or observer-reported outcomes, and performance outcomes).
- There is a possibility that in some glioblastoma patients' cognitive deficits experienced may impact PRO data interpretability. A caregiver- or observer-report of patients' observable signs may complement self-report.

We refer readers to the following publications for additional suggestions on develop COA-based endpoint strategy in the target patient population.

- Armstrong, Terri S. et al. "Determining Priority Signs and Symptoms for Use as Clinical Outcomes Assessments in Trials including Patients with Malignant Gliomas: Panel 1 Report." Neuro-Oncology. 17 Mar. 2016.
- Blakeley, Jaishri O. et al. "Clinical Outcome Assessment in Malignant Glioma Trials: Measuring Signs, Symptoms, and Functional Limitations." Neuro-Oncology. 17 Mar. 2016.
- Gilbert, Mark R. et al. "Creating Clinical Trial Designs That Incorporate Clinical Outcome Assessments." Neuro-Oncology. 17 Mar. 2016.
- Helfer, J. L. et al. "Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA Clinical Trials Clinical Outcome Assessment Endpoints Workshop (October 15, 2014, Bethesda MD)." Neuro-Oncology. Mar. 2016

B. BACKGROUND

Gliomas are the most frequency primary brain tumors in adults. Glioblastoma is considered as a grade IV tumor. No curative treatment exists. Standard treatment consists of surgical resection followed by radiation and concomitant and adjuvant chemotherapy.

Materials reviewed:

- sBLA 125085-319 EORTC 26101 Clinical Study Report
- FDA Information Request (DARRTS Reference ID 4127265) and Applicant's response to FDA Information Request, sBLA125085, eCTD Submission Number 2666
- sBLA 125085-319 DNP Consult Review by Dr. Ranjit Mani (DARRTS Reference ID 4167941)

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

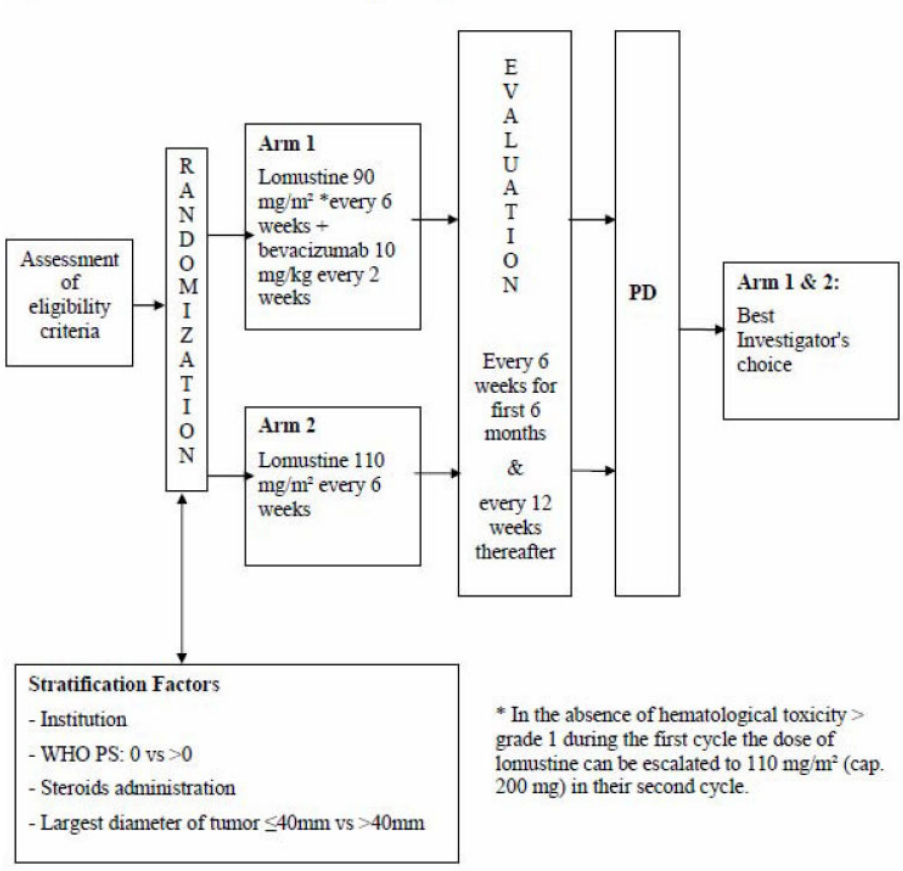
The EORTC 26101 study included adult patients (≥18 years) with histologically confirmed de novo glioblastoma with unequivocal first progression after radiotherapy concurrent/adjuvant chemotherapy at least 3 months after chemo-radiotherapy. The study included patients with World Health Organization Performance Status (WHO PS) 0 – 2.

Refer to the Clinical review for additional background.

1.2 Clinical Trial Design

The EORTC 26101 study was a randomized, two-arm, open-label, multicenter, phase 3 study to investigate the efficacy and safety of bevacizumab plus lomustine compared to lomustine. Refer to the Clinical and Statistical reviews for additional background.

Figure 1 Overview of Study Design and Treatment Schedule



(Source: **EORTC 26101 Clinical Study Report**, Page 7275)

Reviewer Comments: The open label nature of this clinical trial is a limitation to the interpretability of PRO data. Patients' knowledge of treatment assignment may lead to systematic overestimation of the treatment effect, the magnitude of which is currently unknown. However, open label trial design may not be a major limitation for using measures that may be more objective such neurocognitive battery.

1.3 Endpoint Hierarchy and Definition

The table below shows select efficacy endpoints (Source: Clinical Study Report, p7575-6)

Concept	Endpoint	Assessment
Primary Endpoint		
Overall Survival (OS)	--	--
Select Secondary Endpoint		
Progression free survival; objective response rate	--	--
Neurological deterioration-free survival (NDFS)	NDFS defined as the time between randomization and first documentation of clinical/neurological deterioration or death, whichever occurs first. Clinical/neurological deterioration is defined as a decrease in WHO performance status	WHO performance status
Health-Related Quality of Life (HRQL)	Time until HRQoL deterioration as the time from randomization until HRQoL deterioration or disease progression or death due to any cause. HRQoL deterioration for a specific scale is defined as a decrease of at least 10 points from baseline on the functional scales and global health status or an increase of at least 10 points from baseline on the symptom scales, neurological deficit scales and single items, without subsequent improvement.	EORTC QLQ-C30/BN-20 (v3)
Neurocognitive Function (NCF)	Descriptive statistics (mean, median, standard deviation, range, quartiles)	HVLT-R Types A, B, and C; TMT Part A and B; COWA

Refer to the Statistical and Clinical reviews for additional background on endpoint hierarchy and definitions.

Reviewer Comments: The Applicant did not perform hierarchical testing for the secondary endpoints because the primary endpoint was not achieved.

1.4 Labeling or promotional claim(s) based on the COA

The Applicant did not propose any COA-related labeling claims.

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest were health-related quality of life (HRQL) as assessed by EORTC QLQ-C30/BN20 and neurocognitive function assessed by a series of neuropsychological battery. Refer to the Appendices A, B, and C for copies of each specific instrument.

Domain/Neuropsychological Test	General Concepts of Interest
EORTC QLQ-C30 • *Global health status/quality of life (items 29, 30)* • *Physical functioning (items 1-5)* • *Role functioning (items 6-7)* • *Emotional functioning (items 21-24)* • *Cognitive functioning (items 20 and 25)* • *Social functioning (items 26 and 27)* • *Fatigue (items 10, 12, 18)* • *Nausea and vomiting (items 14, 15)* • *Pain (item 9, 19)* • *Dyspnea (item 8)* • *Insomnia (item 11)* • *Appetite loss (item 13)* • *Constipation (item 16)* • *Diarrhea (item 17)* • *Financial difficulties (item 28)*	Health-related quality of life
BN20 module of EORTC • *Future uncertainty (items 31, 32, 33, 35)* • *Visual disorder (items 36, 37, 38)* • *Motor dysfunction (items 40, 45, 49)* • *Communication deficit (items 41, 42, 43)* • *Headaches (item 34)* • *Seizures (item 39)* • *Drowsiness (item 44)* • *Itchy skin (item 47)* • *Hair loss (item 46)* • *Weakness of legs (item 48)* • *Bladder control (item 40)*	
Memory (HVLT-R Parts A, B, and C) • *Part A: Free recall* • *Part B: Delayed recall* • *Part C: Delayed recognition*	Neurocognitive functioning
Visual-motor scanning speed (TMT Type A)	
Executive function (TMT Type B)	
Verbal fluency (COWA)	

Reviewer Comments: The general concept of health-related quality of life appears reflective of various aspects of how patients feel or function in the target patient population. The EORTC QLQ-C30/BN20 may be a reasonable instrument to assess general domains of HRQL (e.g., physical function) in addition to disease specific signs, symptoms, and impacts, provided that

patients are not experiencing cognitive deficits that would impact the reliability of self-report. Furthermore, memory, executive function, and psychomotor processing speed are the most commonly impaired cognitive domains in the target patient population. More research is needed to determine the degree of cognitive impairment in this population and the impact on PRO assessments [4]

3 CLINICAL OUTCOME ASSESSMENT(S)

EORTC QLQ-C30/BN-20 (Version 3): The QLQ-C30 is a 30-item broad health-related quality of life PRO instrument that is consisted of a Global Health Status / quality of life scale, 5 functional scales (physical, role, cognitive, emotional and social), and another 9 scales on individual symptoms and financial impact. The first five items have no recall), while items 6-30 have a 7-day recall ("*during the past week*"). The BN20 is a disease-specific module designed to assess four multi-item scales (uncertainty, visual disorder, motor dysfunction, communication deficit) and seven single-item measures (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs) in the target patient population. All items in this module have a 7-day recall. See Appendix A for a copy of the instrument.

Neurocognitive Outcome Assessments:
The following neurocognitive tests are performance outcome instruments designed to assess executive functioning. See Appendix B and Appendix C for copies of the instrument and additional background on instrument administration.

- Hopkins verbal Learning Test-Revised (HVLT-R)
    - HVLT-R Part A (Free Recall Trial 1-3): This neurocognitive test is designed to assess learning and memory. A patient is asked to recall as many of the words as they can remember after the test administrator has read a list of words.
    - HVLT-R Part B (Delayed Recall): In this neurocognitive test, the administrator reads a list of words to a patient and the patient is asked to recall as many of the words as they can remember after 20 minutes. The raw score is the number of words that were correctly recalled.
    - HVLT-R Part C (Delayed Recognition): In this test, the test administrator reads a longer list of works that includes some words from the parts A/B and new words. A patient is asked to recognize words there were originally read to the patient in the parts A and B from the new worlds read in the part C. The score for this portion of the HVLT-R is the number of list words correctly identified minus the number non-list words incorrectly identified.
- Trail Making Test (TMT): The TMT test is designed to assess visual scanning and motor tracking requiring focused attention in addition to executive functioning.

[4] Blakeley, Jaishri O. et al. "Clinical Outcome Assessment in Malignant Glioma Trials: Measuring Signs, Symptoms, and Functional Limitations." Neuro-Oncology. 17 Mar. 2016.

  - TMT Type A: In this test, a patient is asked to draw a line connecting letters in order from "start" (1) to "end" (25) in an increasing numerical order. The raw score is the time to completion.
  - TMT Type B: In this test, a patient is asked to draw a line connecting numbers and alphabetical letters in order. For example, a patient is asked to start with "1" then draw a line to letter "A", then draw a line connecting "A" to "2" followed by the letter "B" and so forth until the end (which is number 13 and letter L).
- Controlled Oral Word Association (COWA): The COWA test is designed to assess lexical fluency. In this test, a patient is asked to say as quickly as they can all of the words that they can think of that begin with a specific letter told by the administrator. For example, if the administrator says "s", the patients could say "son", "sit", "shoe" or "slow."

Prior versions: Not applicable

User manual(s): The Applicant did not provide corresponding user manuals.

Timing, data collection method, and mode of administration: The COA instruments were administered at baseline, every 12 weeks until disease progression, death, loss of follow-up or patient's withdrawal of consent. Trained and certified healthcare professional at each site administered the cognitive function tests.

Reviewer comments: The assessment frequency for the COA instruments might not have been optimal for this drug development program. The general recommendation in cancer trials is to increase assessments early in therapy to maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early. Further, a last assessment should be administered prior to withdrawal from the clinical trial.

Training method/materials: The Applicant provided corresponding training materials for the neurocognitive outcome assessments. See Appendix C.

4 CONTENT VALIDITY

The Applicant cited relevant literature references to help content validity for the COA instruments.

To date, the following information has been submitted (check all that apply):

☒Literature review and/or publications
☐Documentation of expert input
☐Qualitative study protocols and interview guides for focus group or patient interviews
☐Chronology of events for item generation, modification, and finalization (item tracking matrix)
☐Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period

☐Qualitative support for meaningful change
☐Quantitative study summary with evidence to support item retention and scoring
☐Transcripts (if available)

Reviewer Comments:

EORTC QLQ-C30/BN20: The EORTC QLQ-C30 along with its brain cancer module BN20 is widely used PRO instrument to assess health-related quality of life (HRQL) and disease-specific symptoms, respectively, in the target patient population. The QLQ-C30 part of instrument appears to assess core aspects of HRQL in cancer patients.[5] The BN20 module, second part of the PRO instrument, appears to assess mostly disease-specific signs and symptom with the exceptions of few questions about distal concepts (e.g., uncertainly about the future, setbacks in your condition, disruption in family life, and outlook on the future). Improvement or deterioration in each of the EORTC QLQ-C30/BN20 domains/items may inform how patients are feeling or functioning because of illness and/or treatment. Of note, some of the HRQL concepts (e.g., social functioning, uncertainty about future, financial difficulties) might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect. We generally recommend sponsors to prioritize analyses of collected PRO data by the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment.

While QLQ-C30/BN20 may be a reasonable PRO instrument to assess some aspects of HRQL and symptomatic burden, there is a possibility that cognitive deficit experience in some glioblastoma patients may impact PRO data interpretability.

After discussion with the review division, this reviewer requested item- and domain-level analyses of the PRO instrument in the EORTC 26101 study, specifically to examine disease-specific symptoms from the BN20 module. According to the clinical reviewer, these relevant symptoms include headaches, vision, motor dysfunction, communication deficit, seizures, drowsiness, weakness of legs, and bladder control. The item- and domain-level analyses revealed significant floor effects for most of the symptoms at baseline and week 12, indicating patients remained asymptomatic and unchanged.[6] We observed 1-category deterioration (median group difference) for "unsteady on feet" question in the treatment arm at week 12 from baseline. Interestingly, we observed 1-category improvement (median group difference) for the "drowsiness" question in the control arm at week 12 from baseline. One should use caution when interpreting the PRO data because of significant attrition and dropout rate at week 12 (40% in the treatment arm and 20% in the control arm at week 12) in addition to concerns related to open-label clinical trial design and other methodological issues (e.g., infrequent assessments, absence of an assessment before withdrawal of trial).

[5] FDA PRO Guidance defines HRQL as a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.
[6] Applicant's response to FDA Information Request, sBLA 125085, eCTD Submission Number 2666

In summary, the PRO results appeared uninterpretable to demonstrate any conclusive evidence of treatment benefit because of high attrition and dropout rates, open label clinical trial design, and other methodological issues.

HVLT-R, TMT, and COWA: The HVLT-R, TMT, and COWA are widely used neurocognitive outcome measures and may be reasonable to implement in the target patient population to assess memory, visual-motor scanning speed, executive function, and verbal fluency. Memory, executive function, and psychomotor processing speed are the most commonly impaired cognitive domains in the target patient population.[7] However, the clinical meaningfulness of the neuropsychological tests remains unclear. This reviewer recommends consulting the Division of Neurology Products (DNP) for additional input on the reliability, validity, and clinical meaningfulness of using these tests in the target patient population in addition to input on interpretation of relevant results in the EORTC 26101 study. Refer to the DNP consult review by Dr. Ranjit Mani for additional comments and recommendations.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant did not conduct any psychometric evaluation of the COA instrument in the study. The Applicant referenced an article by Taphoorn et al (2010) to help support psychometric properties (reliability, validity, and ability to detect change) of the QLQ-BN20 module. The article discusses QLQ-BN20 psychometric results derived from pooled data from two clinical trials conducted ex-United States in patients with brain cancers (one trial conducted in anaplastic oligodendroglioma and anaplastic mixed oligoastrocytoma patients while the other trial was conducted in glioblastoma patients) (N=891). This reviewer summarizes relevant results below:

- The pooled patient population consisted of 891 patients with baseline median age of 53 years and 61% male. Majority of the patients has World Health Organization Performance Status (WHO PS) scores ≤2 (38% with PS of 0; 48% of patients with PS of 1; 14% of patients with PS of 2) at baseline. The median Mini Mental State Examination (MMSE) score was 29 at baseline (range 2-30; higher score indicates better functioning).
- Most patients appeared to be scoring at the lower end of scale at baseline (indicating few symptoms or functional problems), which may be due to the inclusion in clinical trials of patients with a relatively good performance status.
- The reliability (internal consistency) as assessed by Cronbach's alpha was ≥0.70 for all domains.
- Known group validity (degree to which the PRO instrument can distinguish among groups hypothesized to be different) was tested using WHO PS and MMSE scores. Patients with a better WHO PS (score of 0 or 1) reported significantly lower scores (i.e. fewer symptoms and less dysfunction) than those with poorer WHO PS (score of 2 or 3)

[7] Blakeley, Jaishri O. et al. "Clinical Outcome Assessment in Malignant Glioma Trials: Measuring Signs, Symptoms, and Functional Limitations." Neuro-Oncology. 17 Mar. 2016.

on the majority of QLQ-BN20 scales/items, including future uncertainty, visual disorder, motor dysfunction, communication deficit, drowsiness, weakness of legs and bladder control (all p-values <0.01) at both baseline and first follow-up. No statistically significant differences between WHO PS groups were observed for headaches, seizures, hair loss, or itchy skin. MMSE levels were significantly related to QLQ-B20 communication deficit, visual disorder, motor dysfunction, weakness of legs and bladder control scores at baseline (all p-values <0.01). Patients who scored below 27 on the MMSE reported greater difficulties on these scales than those who scores at least 27 ($p<0.001$).

- Ability to detect change (evidence that a PRO instrument can identify differences in scores over time in individual or groups who have changed with respect to their measurement concept) was tested based on changes in the WHO PS score. Patients whose WHO PS deteriorated from the baseline to first follow-up (scores shifting from 0-1 to 2-3) showed a significantly larger deterioration in motor dysfunction, drowsiness, visual disorder and bladder control than patients with a stable course of performance status over time. Significant differences were not found, however, for weakness of legs, seizures or headaches.

Taphoorn (2010) did not discuss any limitations related to PRO data interpretation because of cognitive impairment in some patients with advance forms of disease. Refer to Taphoorn (2010) article for additional background.

The Applicant did not provide any literature to support psychometric properties of the EORTC QLQ-C30 instrument, which is a generic HRQL measure commonly utilized in cancer clinical trials.

Reviewer Comments: Ideally this reviewer recommends psychometric evaluation be conducted in the target patient population; however, this reviewer acknowledges that some of the data discussed in the Taphoorn (2010) article came from patient with glioblastoma. Interestingly, most patients appeared to be either asymptomatic or scoring at the lower end of the QLQ-BN20 scales/items similar to the EORTC study results. This observation may be attributable to inclusion of those patients with a relatively good functioning at baseline. Overall, the results described in the Taphoorn (2010) article may be supportive of QLQ-BN20's psychometric properties in the target patient population.

The EORTC study conducted by the Applicant did not include MMSE assessment at baseline; therefore, it was not possible to conduct additional analyses to investigate PRO findings based on different levels of cognitive impairment.

6 SCORING ALGORITHMS

EORTC QLQ-C30/BN20:

The QLQ-C30/BN20 were scored according to its scoring manual (publicly available http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf). Items on both questionnaires were scaled and scored using the recommended EORTC procedure (Fayers et al. 2001).

For all scales, *RawScore* (RS) is defined as the mean of the component items: $RS = (I_1 + I_2 + \ldots + I_n)/n$, where n is the number of answered items in the scale.

If less than half of the items in the scale have been answered, scale score were set to missing.

A linear transformation was used to standardize the raw score, so that all scores for the scales and the single-item measures range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for global health status/QoL implies a high QoL, while a high score for symptom scale/neurological deficit scale/single-item represents a high level of symptomatology/problems. Therefore, the linear transformation was applied as follows:

- For functional scales → Score = [1 – (RS - 1)/range] × 100
- For symptom scale/neurological deficit scale/single-item and global health status/QoL → Score = [(RS - 1)/range] × 100

The range is the difference between the maximum possible value and the minimum possible value of the raw score, RS.

Neurocognitive Outcome Assessments (HVLT-R, TMT, and COWA):

For each of the 6 tests, for each patient and for each time-point, the reported scores will be converted to raw scores (RS).

- HVLT:
  - For the HVLT-R Part A (Free Recall) test, the raw score will be the sum of the 3 reported scores (one for each learning trial). The raw score can range from 0 to 36. A higher score is associated with better cognitive function.
  - For the HVLT-R Part B (Delayed Recall) test, the raw score will be the single score recorded. The raw score can range from 0 to 12. A higher score is associated with better cognitive function.
  - For the HVLT-R Part C (Delayed Recognition) test, the raw score will be the single score recorded (negative or positive). The raw score can range from -12 to 12. A higher score is associated with better cognitive function.
- TMT:

  - For the Trail Making Test A, the raw score will be the total time-to-completion, in seconds, if both the sample and actual tests were completed. If the actual test was not completed, the raw score will be adjusted, based on the last number correctly reached on the test, as follows (Heaton et. al 2004): raw score (RS) = 25*(total time-to- completion/last number correctly reached). Note that the actual test involves connecting circles with sequential numbers from 1 to 25. A higher score is associated with impaired cognition.
  - For the Trail Making Test B, the raw score will be computed in a similar way to that of Trail Making Test A. For the adjustment, instead of the last number reached, the number of circles completed will be used. Note that the actual test involves connecting circles with numbers from 1 to 13 and letters from A to L, with numbers and letters alternating (1-A-2-B…12-L-13). A higher score is associated with impaired cognition.
- For the COWA test, the raw score will be the sum of the 3 scores reported (one for each letter tested). A higher score is associated with better cognitive function.

For each time-point, the tests raw scores (as described above) were normalized into z-scores using patient's age (HVLT-R and TMT) at baseline or gender (COWA). Refer to the Statistical Analysis Plan in the Clinical Study Report (pp7687-7689) for additional background.

7 INTERPRETATION OF SCORES

EORTC QLQ-C30/BN20: The Applicant defined time until HRQL deterioration as the time from randomization until HRQL deterioration or disease progression or death due to any cause. HRQL deterioration for a specific scale is defined as a decrease of at least 10 points from baseline on the functional scales and global health status or an increase of at least 10 points from baseline on the symptom scales, neurological deficit scales and single items, without subsequent improvement. No imputation will be performed if a missing value is observed.

Neurocognitive Outcome Assessments: The Applicant provided descriptive statistics (mean, median, standard deviation, range, quartiles) for the neurocognitive function standardized scores and change from baseline of the standardized scores for each treatment arm, for each test at each defined time-point. The proportion of patients who have improved/remained stable vs. declined in neurocognitive function, as measured by the three tests, were analyzed at each time-point. Neurocognitive decline is defined for each patient as a change in score that has declined in excess of the Reliable Change Index (RCI) threshold (for HVLT-R and COWA) or increased in excess of the RCI threshold (for the Trail Making Tests). Stable neurocognitive function is defined as a change in score that is within (and including) the boundaries of the RCI, for each test.

Reviewer Comments: This reviewer does not agree that the pre-specified threshold (i.e. 10-point change on the 0-100 points transformed scale) is clinically meaningful. Ten-point (10) change does not represent a possible within-patient response (i.e., improvement/deterioration) because

the smallest response corresponding to a 1-category change on the 1-4 scale would be 33 points on the 0-100 points scale for a single item domain. In future trials, this reviewer recommends sponsors to pre-specify appropriate threshold that would constitute a clinically meaningful change in the target patient population. We generally recommend using anchor-based methods supplemented with cumulative distribution function (CDF) and probably distribution function (PDF) curves to derive specific threshold that is clinically meaningful.

The Applicant's definition for interpreting neurocognitive functioning using the RCI methodology appears purely statistically driven. There is no data in literature to support the RCI derived thresholds correspond to clinical meaningful improvement in in the target patient population. Additionally, the RCI was developed using a healthy control population.[8] This reviewer refers to the DNP Consult Review by Dr. Ranjit Mani for additional input on interpretation of neurocognitive outcome assessments.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The EORTC QLQ-C30/BN20 is available in multiple languages, which appears to comply with best practices for translation and cultural adaptation.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

10 REVIEW USER MANUAL

The Applicant did not provide corresponding user manuals.

11 KEY REFERENCES FOR COA

Benedict RHB, Schretlen D, Groninger L, et al. Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 1998;12:43-55.

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[8] Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression. Neuro Oncol. 2003;5:89–95.

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Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health related quality of life scores. J Clin Onc 1998;16:139–144.

Ruff RM, Light RH, Parker SB, et al. Benton Controlled Oral Word Association Test: reliability and updated norms. Arch Clin Neuropsychol 1996; 11:329–38.

Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, Stupp R, Mirimanoff RO, van den Bent MJ, Bottomley A; On behalf of the EORTC Quality of Life Group and Brain Cancer, NCIC and Radiotherapy Groups. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer. 2010; 46(6):1033-1040.

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/s/

NIKUNJ B PATEL
11/20/2017

ELEKTRA J PAPADOPOULOS
11/20/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s319

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121609

MEETING MINUTES

Genentech, Inc.
Attention: Timothy Burkoth, Ph.D.
Regulatory Program Management
1 DNA Way, MS #241B
South San Francisco, CA 94080

Dear Dr. Burkoth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Avastin (bevacizumab)."

We also refer to the meeting between representatives of your firm and the FDA on April 5, 2016. The purpose of the meeting was to discuss the results of Study EORTC 26101 entitled, "Phase 3 Trial Exploring the Combination of Bevacizumab and Lomustine in Patients with First Recurrence of Glioblastoma," and the format/content of a sBLA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-sBLA

Meeting Date: April 5, 2016

Application Number: IND 121609
Product Name: Avastin (bevacizumab)
Indication: Treatment of recurrent glioblastoma multiforme (GBM)
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Patricia Keegan
Meeting Recorder: Sharon Sickafuse

FDA ATTENDEES
Office of Hematology and Oncology Products
Division of Oncology Products 2
Suzanne Demko, P.A.-C.
Patricia Keegan, M.D.
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Sharon Sickafuse, M.S.
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Office of Biostatistics
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Dietmar Berger, M.D., Clinical Science
Tim Burkoth, Ph.D., Regulatory Affairs
Sunita Dhar, M.D., Safety Risk Management
Mika Derynck, M.D., Clinical Science
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Karen Jones, MSc, Regulatory Affairs
Nafsika Kronidou-Horst, Ph.D., Regulatory Affairs
Dorothy Leong, Ph.D., Regulatory Affairs
Alexandre Moreau, Ph.D., M.B.A., Global Product Leader

Cornelia Iri, Ph.D., Biometrics
Barbara Mueller, MSc, Biometrics
Elisabeth Piault-Louis, PharmD, Patient-Centered Outcomes Research

BACKGROUND

On January 19, 2016, Genentech submitted a meeting request (SDN 45) to discuss the results of Study EORTC 26101 entitled, "Phase 3 Trial Exploring the Combination of Bevacizumab and Lomustine in Patients with First Recurrence of Glioblastoma," and the content/format of a proposed sBLA for the following proposed indication:

> Bevacizumab is indicated for the treatment of GBM in adult patients with progressive disease following prior therapy as a single agent.

The meeting package was submitted on March 4, 2016, as SDN 46.

Regulatory History

On May 26, 2006, bevacizumab was granted Orphan Drug Designation for the treatment of malignant glioma.

On May 5, 2009, bevacizumab was approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) for treatment of recurrent GBM based on demonstration of durable objective response rate (ORR) in two trials; AVF3708g and NCI 06-C-0064E. The approval letter contained a PMR under 21 CFR 601 Subpart E to conduct studies to verify and describe the clinical benefit of bevacizumab for the treatment of GBM as follows:

> To submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling based on the results of study AVF4396g/BO21990 entitled "A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma," which was accepted under a Request for Special Protocol Assessment on December 29, 2008.

The clinical benefit of bevacizumab for patients with newly diagnosed GBM was investigated in Study AVF4396g (AVAglio). AVAglio was a multicenter, randomized, double-blind, placebo controlled trial evaluating bevacizumab in combination with radiation therapy (RT) and temozolomide (TMZ) in 921 patients with newly diagnosed GBM. The co-primary endpoints were progression free survival (PFS) assessed by investigator and overall survival (OS). The study did not demonstrate an improvement in survival; however, Genentech stated that the trial did demonstrate a statistically significant improvement in PFS for patients randomized to the bevacizumab plus standard therapy arm compared with those randomized to standard therapy (10.6 vs 6.2 months; HR 0.64 [0.55-0.74]). In addition, Genentech stated there was an improvement in health related quality of life (HRQoL).

The clinical benefit of bevacizumab for patients with newly diagnosed GBM was also investigated in Study RTOG 082; a randomized, double-blind, placebo controlled trial conducted in 621 patients with newly diagnosed GBM. The co-primary endpoints were OS and investigator-assessed PFS. The RTOG 0825 study demonstrated no improvement in OS and poorer HRQoL and cognitive function for patients randomized to the bevacizumab and standard therapy arm compared with standard therapy. The median PFS was 10.7 months for patients randomized to bevacizumab and standard therapy compared with 7.3 months for patients who received standard therapy; HR 0.79 (0.66, 0.94).

During the March 26, 2014, meeting, FDA provided feedback regarding the suitability of an ongoing randomized, multicenter trial in patients with recurrent GBM (EORTC 26101) to fulfill the PMR for bevacizumab. At that time, EORTC 26101 was an ongoing, open-label, randomized (2:1), multicenter trial to investigate the safety and efficacy of bevacizumab plus lomustine (bevacizumab/lomustine) versus lomustine alone in approximately 433 patients. Randomization used the minimization technique; was stratified by investigational site, performance status (0 versus > 0), steroid use (yes versus no), and largest tumor diameter (≤ 40 mm versus > 40mm).

The primary endpoint of the study was OS and the primary analysis was a stratified log-rank test performed on the intent-to-treat population. The stratification factors were those used at randomization (except investigational site) and a variable indicating if the patient was recruited in the Phase 2 or Phase 3 portion of the study. Assuming that the 9-month OS rates are 40% and 51.7% in the lomustine and bevacizumab/lomustine arms, respectively, a total of 327 events are needed to detect a hazard ratio of 0.72 (corresponding to median survivals of 6.8 months in the lomustine arm and 9.5 months in the bevacizumab/lomustine arm) with 80% power at a 1-sided alpha level of 2.5%.

Key secondary endpoints were investigator-assessed PFS and overall response rate (ORR) as determined by the Response Assessment in Neuro-oncology (RANO) criteria. Additional secondary endpoints included HRQoL (including global health status, cognitive function, pain scales assessed by the patient and caregiver using EORTC QLQ-30 and EORTC BN20); clinical/neurological deterioration free survival; steroid use; cognitive function; and 9-month and 24-month survival rates. A hierarchical procedure was proposed to adjust for multiplicity in testing the secondary endpoints in the order of PFS, ORR, clinical/neurological deterioration free survival, and HRQoL.

Key discussion during the meeting:

- FDA stated that study EORTC 26101 may be used to support a claim for (b) (4) and that the decision to grant conversion to regular approval will be based on the totality of the evidence including the results of the EORTC 26101, AVAglio, and RTOG 0825 studies. FDA also noted that efficacy of single agent bevacizumab in recurrent GBM will not be addressed in study EORTC 26101, and that several combination studies with chemotherapy or targeted agents plus bevacizumab (including the studies supporting accelerated approval) have not reported improved survival of combination treatment over bevacizumab monotherapy.

- For Study RTOG 0825, FDA agreed that a final CSR for OS, PFS, and safety accompanied by the corresponding raw and derived datasets, the protocol, protocol amendments, and publications by RTOG along with RTOG's tables and statistical outputs would be sufficient.

On July 24, 2015, a meeting was held to discuss the ongoing status of study EORTC 26101, and the content, format, and proposed statistical analysis plan for the efficacy supplement intended to fulfill the accelerated approval PMR.

Genentech argued that assessment of cognitive function and HRQoL are essential to evaluating the clinic benefit of PFS, and proposed that HRQoL as measured by EORTC QLQ C-30 and BN20 will be used to support the analysis of PFS in EORTC 26101. Patients on EORTC 26101 underwent neurocognitive testing every 12 weeks until disease progression. The following tests were included in the cognitive assessment:

- Hopkins Verbal Learning Test-Revised (HVLT-R)
- Trail Making Test (TMT) Part A and Part B
- Controlled Oral Word Association (COWA)

Three EORTC QLQ-30 scales were pre-specified as part of the testing hierarchy in the statistical analysis plan (SAP): global health status, cognitive function, and pain scales. These assessments occurred every 12 weeks until disease progression while radiographic and clinical evaluations occurred every 6 weeks.

At the time of the meeting, Genentech stated that accrual to EORTC 26101 was completed with 437 patients enrolled, and the final analysis (at 327 deaths) was projected to occur in the first quarter of 2016.

Key discussion during the meeting:

- FDA stated that the RANO criteria are acceptable to assess PFS and ORR in patients with recurrent GBM enrolled on EORTC 26101; however, because accurate assessment of radiographic response (even with RANO criteria) remains difficult to ascertain with the use of anti-angiogenic therapies, PFS and ORR will be considered supportive efficacy endpoints. FDA also stated that if Genentech intended to make labeling claims based on PFS, confirmation of the findings based on an independent radiologic review committee would provide greater confidence in the results. FDA stated that the central evaluation of response as part of EORTC 26101 where the reviewers are masked to treatment assignment and investigator assessment may be adequate to serve as an independent review of tumor based endpoints. Details of the procedure should be provided and a final decision on the acceptability of this approach to serve as independent verification of the investigator assessment would depend on the standard operating procedures and conduct.

- FDA stated that change in cognitive function and HRQoL are considered exploratory endpoints because these domains are not well-defined concepts and difficult to measure as they are likely influenced by multiple factors including patient variables, treatment effect, tumor location, concomitant medications, etc. Furthermore, the content validity of

the proposed cognitive testing measures has not been established in malignant brain tumors; therefore, the performance capabilities of these tests to detect clinically meaningful changes in GBM are unknown. Data on NCF and HRQoL may be considered in the final risk/benefit analysis of bevacizumab for recurrent GBM, but if Genentech intends to pursue a labeling claim in these areas, a comprehensive development and validation package for the use of the proposed instruments in this disease setting will be required.

- FDA did not agree that the analysis plan for NCF and clinical deterioration endpoints are adequate to support the assessment of clinical benefit. The cutoffs described for both the neurocognitive tests and HRQoL surveys have not been validated, and it is unclear that the changes in scores proposed will be able to measure a clinically meaningful benefit for patients. In addition, the HRQoL survey includes an assessment of cognitive functioning (patient reported outcome) that overlaps with the proposed neurocognitive battery of tests (clinician assessed outcome). These results should be analyzed to determine concordance between the two measures.

Background for this meeting

For Study EORTC 26101, Genentech states that there was no statistically significant difference in the primary efficacy variable of OS between the treatment arms; therefore, the addition of bevacizumab to lomustine did not significantly improve OS in patients with recurrent GBM compared with lomustine monotherapy. At the time of data cutoff, 76% of patients in either treatment arm had died. The stratified analysis resulted in an OS HR of 0.91 (95% CI: 0.72, 1.16; stratified log-rank p=0.4578; re-randomization test p=0.4577). The median OS was 9.1 months in the bevacizumab/lomustine arm and 8.6 months in the lomustine arm.

Genentech states that the totality of data supports a favorable benefit–risk profile of bevacizumab as a treatment for patients with GBM for the following reasons:

1. "The benefit of treatment with bevacizumab in GBM is reflected in the consistent and reproducible effect on PFS across multiple randomized controlled studies in patients with both newly diagnosed and recurrent GBM (i.e., Studies AVAglio, RTOG 0825, and EORTC 26101).

2. PFS is associated with maintenance of HRQoL, NCF, functional independence, and reduced steroid use in studies AVAglio and EORTC 26101.

3. While none of the studies demonstrated a survival benefit, all studies had high rates of salvage bevacizumab use following progression that may have impacted results. Furthermore, population level data from the United States Surveillance Epidemiology and End Results (SEER) registry showed longer survival following accelerated approval of bevacizumab for recurrent GBM in 2009.

4. The risks associated with bevacizumab use in GBM are consistent with the safety profile reported across other tumor types. These events have been well characterized in more

than 1000 clinical study patients with GBM treated in multiple randomized trials as well as post-marketing data from > than 50,000 patients with GBM treated since 2009."

Genentech presents the following data to support their interpretation of the clinical benefit of bevacizumab for the treatment of GBM:

Analysis of PFS:
Genentech presents data from three multicenter, randomized trials to support the reproducible effects on PFS for patients with GBM treated with bevacizumab (table modified from meeting package):

Study	***Treatment Arms***	***Median PFS (months***	***HR (95% CI)***	***Response assessment criteria***
AVAglio	Bevacizumab	10.6	0.64 (0.55, 0.71)	2D enhancing & non-enhancing disease
	Placebo	6.2		
RTOG 0825	Bevacizumab	10.7	0.79 (0.66, 0.94)	Macdonald criteria
	Placebo	7.3		
EORTC 26101	Bevacizumab/Lomustine:	4.2	0.52 (0.41, 0.64)	RANO criteria
	Lomustine	1.5		

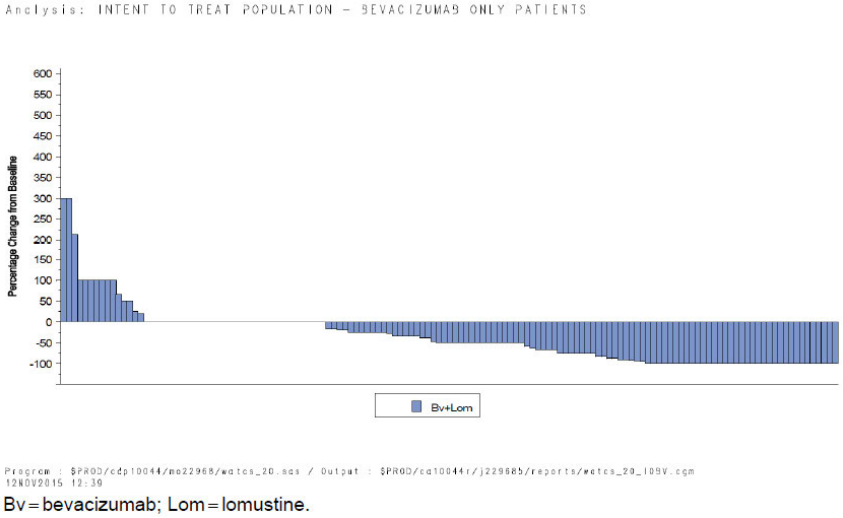
HR: hazard ratio, CI: confidence interval

Both AVAglio and EORTC 26101 incorporated evaluation of non-enhancing disease in tumor assessments to account for possible novel patterns of disease progrssion with bevacizumab use, while RTOG 0825 utilized more traditional Macdonald criteria that measured only enhancing disease when assessing response.

Genentech states that patients whose disease remained progression free had better QoL associated with stable disease symptoms compared with those with disease progression. In Study EORTC 26101, the majority of patients in both treatment arms had a high level of function at baseline as measured by WHO PS (~ 88% WHO PS ≤ 1). Similarly, both treatment groups self-reported a high level of HRQoL at baseline, consequently, the potential for improvement in the patient's health and functional status was limited, and therefore the maintenance of the global health and functional status during the progression-free time was examined as a measure of clinical benefit.

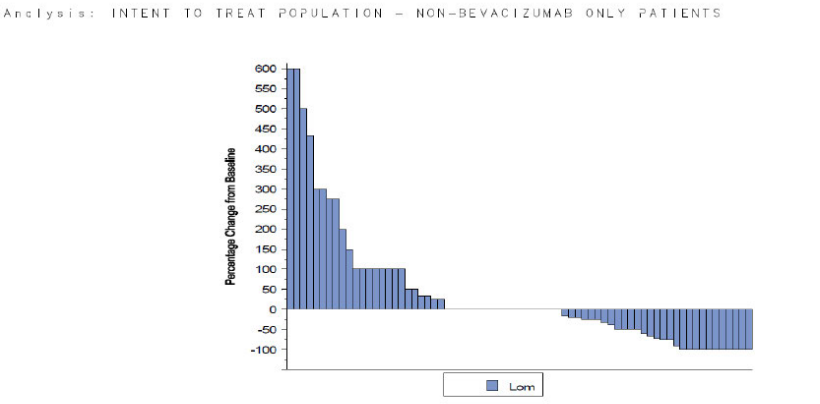
According to Genentech, while patients on study EORTC 26101 in either treatment arm were progression-free, WHO PS, NCF, and quality of life/physical functioning remained relatively stable. In addition, patients in the bevacizumab/lomustine arm had a diminished requirement for corticosteroids. Patients in the bevacizumab/lomustine arm taking corticosteroids at baseline (N=143 [50.5%]) were more likely to be able to decrease or stop taking corticosteroids compared to baseline (24.5% with discontinuation of corticosteroid intake, 40.6% of patients with a decrease in dose, whereas patients in the lomustine arm (N=74 [49.7%] taking corticosteroids at baseline) were less likely to decrease their corticosteroid dose (14.9% with discontinuation, 24.3% with a decrease).

Figure 4 Study EORTC 26101: Waterfall Plot of Percent Change of the Lowest Corticosteroid Dose from Baseline (Bv+Lom arm)



Bv = bevacizumab; Lom = lomustine.

Figure 5 Study EORTC 26101: Waterfall Plot of Percent Change of the Lowest Corticosteroid Dose from Baseline (Lom arm)



Lom = lomustine.

At the time of enrollment on the AVAglio study, the majority of patients in both study arms had a high functional status as measured by Karnofsky Performance Status (KPS) and reported a high HRQoL. While patients remained progression free, Genentech states that high baseline HRQoL was maintained in both arms with no significant difference over time; normal NCF at baseline (76% patients had a MMSE score of ≥ 27) was maintained in both arms; functional independence was maintained as evidenced by KPS ≥ 70 in 98% of patients for 96% of the progression-free time and time to deterioration in KPS was delayed in the bevacizumab arm. Evidence of deterioration of HRQoL and KPS is described at the visits where disease progression was determined, and not at prior visits. In addition, Genentech describes reduction in corticosteroid use in the bevacizumab arm on study AVAglio (reviewer table):

Corticosteroid Use	Patients on steroids at baseline		Patients not on steroids at baseline	
	Bevacizumab (n=187)	**Placebo (n=208)**	**Bevacizumab (n=269)**	**Placebo (n=253)**
Progression free time on 0 mg	66% of patients, median duration 195 days	47% of patients, median duration 170 days	94% of patients, median duration 330 days	92% of patients, median duration 155 days
Median time to initiation of corticosteroids	--	--	12.3 months	3.7 months
Rates of corticosteroid discontinuation (14 consecutive days)	61%	45%	--	--

While patients were on corticosteroids, lower average daily corticosteroid dose and greater reduction of corticosteroids in each treatment phase were reported for the bevacizumab arm.

In study RTOG 0825, HRQoL was assessed with EORTC QLQ-C30 and BN20; NCF (HVLT-R, TMT, and COWA test); and symptom burden assessed by MD Anderson Symptom Inventory-brain tumor tool (MDASI−BT). Study RTOG 0825 reported an increase in symptom burden, communication deficit, motor dysfunction, and neurocognitive decline with the addition of bevacizumab to SOC. Genentech notes that these changes were generally observed at later time points and postulates that the decline in functioning and HRQoL is due to the possibility that some patients had non-enhancing disease progression that was not captured using the Macdonald criteria for imaging response assessment.

Analysis of ORR and HRQoL:
On EORTC 26101, ORR was determined using the RANO criteria and required shrinkage of tumors by at least 50%, with stable or decreased corticosteroid dosing, absence of clinical progression, as well as confirmation of the response at least 4 weeks after the initial documentation of response. At the time of the data cutoff, in the population of patients with measurable disease at baseline, 68 patients (26.2%) in the bevacizumab/lomustine arm compared to 8 (5.8%) patients in the lomustine arm had radiographic response, with confirmation on at least two consecutive assessments. The resulting difference in ORRs between treatment arms was 20.4% (95% CI: 13.8, 27.0). The remaining patients with measurable disease had either stable disease (SD) (42.7% in the bevacizumab/lomustine arm vs. 26.6% in the lomustine arm), disease progression, or were not assessable.

According to Genentech, the median duration of response was 5.6 months in both treatment arms, and at the time of data cutoff, 29.4% of the responding patients in the bevacizumab/lomustine arm were continuing treatment while all patients with response in the lomustine arm had progressed. Genentech states that in exploratory analyses, responders generally showed better HRQoL at baseline and at each subsequent visit compared to non-responders and global health status improved in 31.6% of the responders. Responders also showed better NCF at baseline compared with non-responders, and these scores were largely maintained during treatment. Landmark survival analyses (at weeks 9, 18, and 26) were performed. Genentech states that patients who had a response in a given time period tended to have longer survival compared with non-responders and indicated that the median residual

survival among responders was higher than that of non-responders at each landmark, with no overlap of the CIs (see table below, copied from meeting package).

Table 4 Study EORTC 26101: Summary of Residual Survival by Response at 9, 18, and 26 Weeks

	All patients	
	Non-Responders [a]	Responders [a]
Until 9 weeks at risk		
No. of patients in analysis	363	54
No. of patients with event (n [%])	287 (79.1)	28 (51.9)
Median time to event (months) [b]	6.4	11.0
95% CI for the median	(5.8, 7.3)	(9.0, 13.5)
HR (95% CI) [c]	0.41 (0.27, 0.63)	
Until 18 weeks at risk		
No. of patients in analysis	293	70
No. of patients with event (n [%])	227 (77.5)	35 (50.0)
Median time to event (months) [b]	5.2	8.9
95% CI for the median	(4.4, 6.0)	(7.3, 11.5)
HR (95% CI) [c]	0.42 (0.28, 0.63)	
Until 26 weeks at risk		
No. of patients in analysis	230	75
No. of patients with event (n [%])	169 (73.5)	35 (46.7)
Median time to event (months) [b]	4.6	8.4
95% CI for the median	(3.6, 5.2)	(5.7, 11.1)
HR (95% CI) [c]	0.42 (0.28, 0.63)	

CI = confidence interval; HR = hazard ratio; n = number of patients in category; No. = number.
[a] Irrespective of treatment arm.
[b] Kaplan-Meier estimate.
[c] Analyses were adjusted for stratification factors at randomization (i.e., WHO PS, steroid use, largest lesion diameter) and Phase II/III enrolment.

OS analyses:
The OS results from AVAglio, RTOG 0825 and EORTC 26101 are presented below:

Study	***Treament Arm***	***Median OS (months)***	***HR (95% CI)***
AVAglio	Bevacizumab	16.8	0.88 (0.76, 1.02)
	Placebo	16.7	
RTOG 0825	Bevacizumab	15.7	1.13 (0.93, 1.37)
	Placebo	16.1	
EORTC 26101	Bevacizumab/lomustine	9.1	0.91 (0.72, 1.16)
	Lomustine	8.6	

Genentech states that although none of the above randomized studies demonstrated an OS benefit with bevacizumab use, all studies showed that there was no OS detriment with the addition of bevacizumab. Genentech also suggests that the use of bevacizumab treatment following progression might have confounded the primary analysis of OS. According to Genentech, although bevacizumab is not approved for GBM in the European Union (EU) where Study EORTC 26101 (and in part AVAglio) was conducted, it is currently used in clinical practice in most EU countries on the basis of local and European Association for Neuro-

Oncology (EANO) guidelines. As a result, in Studies EORTC 26101, AVAglio, and RTOG 0825, 48% to 55% of patients who received subsequent therapy in the control arms received bevacizumab post progression, compared with 25% to 34% in the bevacizumab-containing arms. In Study EORTC 26101, 122 patients (43%) in the bevacizumab/lomustine arm and 89 (60%) in the lomustine arm received at least one subsequent anti-cancer therapy. Among these patients, 55% (49/89 patients) in the lomustine arm versus 34% (42/122 patients) in the bevacizumab/lomustine arm received bevacizumab post-progression.

Genentech conducted several exploratory analyses for EORTC 26101 to evaluate the potential impact of bevacizumab use post-progression on the OS results seen in these studies (table copied from meeting package):

Overall survival analyses	Lom (N=149)	Bv+Lom (N=283)
No. of patients with an event (n [%])	113 (75.8)	214 (75.6)
Primary analysis [a]		
HR (95% CI)	0.91 (0.72, 1.16)	
RPSFT method [a]		
HR (95% CI [Bootstrap])	0.86 (0.57, 1.28)	
Discounting method assuming 33% benefit of subsequent bevacizumab [a]		
HR (95% CI)	0.77 (0.61, 0.99)	
Censoring for patients receiving subsequent lines of treatment		
HR (95% CI)	0.72 (0.51, 1.02)	
Patients with PD and no subsequent treatment [a]		
No. of patients in analysis	54	137
No. of patients with an event (n [%])	47 (87.0)	118 (86.1)
HR (95% CI)	0.77 (0.53, 1.12)	

Bv=bevacizumab; CI=confidence interval; CRF=case report form; HR=hazard ratio; Lom=lomustine; n=number of patients in category; N=total number of patients; PD=progressive disease; WHO PS=World Health Organization performance status.

[a] Analyses were adjusted for stratification factors at randomization as collected on the CRF (i.e., WHO PS [0, >0], steroid use [No, Yes], and largest lesion diameter [≤40, >40 mm]), and a variable indicating if the patient was recruited in the Phase II or Phase III portion of the study.

In the meeting package, Genentech presents similar analyses for the AVAglio study and argues that the OS hazard ratios from these additional exploratory analyses show a trend toward favoring the bevacizumab-containing treatment.

Genentech also provides epidemiologic data from US patients that suggest improved survival in patients with GBM since the accelerated approval of bevacizumab (reviewer table):

Reference	***Patient Population***	***Outcomes***
Johnson et al. 2013	5607 patients with GBM in the SEER database	Patients who died of GBM in 2010 had lived with the disease significantly longer than patients who died in 2008
Wachtel and Yang. 2014	20,879 patients diagnosed with GBM between 2000-2009 in the SEER database	concluded that TMZ positively impacted survival and adding bevacizumab further improved survival
Chen et al. 2015	159 bevacizumab-naive patients initiating 2nd line treatment between 2006-2010	OS reported to be significantly longer with bevacizumab-containing regimens (HR 0.51, 95% CI: 0.31, 0.82)

SEER: Surveillance Epidemiology and End Results

Genentech is performing ongoing analyses from the updated SEER registry as well as the linked SEER-Medicare database to further explore the role of bevacizumab in management of GBM based on population data.

Safety of bevacizumab:
Although Studies EORTC 26101, AVAglio, and RTOG 0825 differed in terms of population evaluated (recurrent vs. newly diagnosed GBM) and treatment-backbone (lomustine vs. RT/TMZ), Genentech states that the adverse reaction profile of bevacizumab was similar across all three studies and no new or unexpected adverse events (AEs) were observed. Genentech argues that the safety evaluation of bevacizumab in these studies should be considered in the context of the relatively longer exposure to study treatment in the bevacizumab containing arms.

In the EORTC 26101 study, for all AEs reported in at least 10% of patients incidence rates were higher in the bevacizumab/lomustine arm than in the lomustine arm (with the exception of peripheral edema). The most frequently reported AEs in the bevacizumab/lomustine arm (≥ 20% of patients) were fatigue, hypertension, headache, nausea, and seizure. Five patients (1.8%) in the bevacizumab/lomustine arm and one patient (0.7%) in the lomustine arm experienced Grade 5 adverse events; these adverse events were myocardial infarction (2 patients), intracranial hemorrhage, large intestine perforation, and sepsis in the bevacizumab/lomustine arm, and lung infection in the lomustine arm. Genentech states that these AEs were not considered by the investigator to be related to study treatment.

Overall benefit-risk analysis:
Genentech states that clinical benefit of treatment with bevacizumab is demonstrated by consistently prolonged PFS associated with maintenance of clinical condition, HRQoL, NCF and reduction of corticosteroid use. In addition, Genentech maintains that use of bevacizumab resulted in increased ORR that is indirectly associated with longer survival, and epidemiologic data suggest increased survival for patients with GBM since accelerated approval in 2009. Genentech argues that although bevacizumab is associated with an increase in toxicity, the safety profile observed is consistent across the studies in GBM, in line with its known safety profile across multiple indications, and remains manageable.

Central review of imaging:
According to Genentech, for Study EORTC 26101 all imaging data were reviewed independently by two different board-certified radiologists. The reviewers were blinded to the assigned treatment, the patient's clinical status and the local investigator's assessment for each patient. Discrepancies between the two radiologists resulted in a second review by the two reviewers, with consensus reached by discussion. Details regarding the processes and responsibilities involved in the central review of the imaging data are provided in the central review charter for Study EORTC 26101. The central radiology results will be exported to the clinical database and Genentech will complete the overall RANO assessment by combining the radiological review data with the patient's corticosteroid use and clinical status reported by the investigator.

Proposed contents of the sBLA:
Genentech anticipates the submission of the proposed sBLA at the end of the second quarter of 2016. Genentech states that the sBLA submission will include clinical study reports (CSR) for EORTC 26101, AVAglio and RTOG 0825 in Module 5. The proposed documentation for each study is provided in the table below (copied from meeting package):

Table 9 Clinical Study Report Documentation for the Studies Included in sBLA Submission

Study Documentation	EORTC 26101	AVAglio	RTOG 0825
Protocol and amendments, summary of changes	Included	Included	Included
List of IEC/IRBs	Included	Included	Included
Sample ICF	Included	Included	Included
Randomization scheme and codes	Included	Included	Not available
Audit certificates	Not available	Included	Not available
Statistical analysis plan	Included	Included	Included as statistical section of the protocol (no separate document)
Laboratory standards	Not available	Not available	Not available
Batch number of investigational product used	Included	Included	Included
Centralized Radiological Review Charter	A charter will be provided upon request.	Provided.	Not applicable
Imaging datasets	Available upon request.	Available upon request.	Not available
Patient Narratives	Patient narratives will be provided for the following categories (as was defined in AVAglio): SAE leading to death Related SAE AE leading to any treatment discontinuation CNS hemorrhage, any grade ATE, any grade Cranial wound- healing event and wound-healing event that required surgical intervention, any grade GI perforation, fistula, and intraabdominal abscess, any grade Hemorrhage, ≥ Grade 3		Patient narratives will not be provided.

	VTE, ≥ Grade 3 Hypertension, ≥ Grade 3 Proteinuria, ≥ Grade 3 Left ventricular systolic dysfunction, ≥ Grade 3 RPLS, any grade Any secondary malignancies Any case involving pregnancy or congenital anomaly		
Case Report Forms (deaths, SAEs, safety withdrawals)	eCRFs included for patient narrative categories	CRFs included for patient narrative categories	Not included
All Case Report Forms	Not included	Not included	Not included
List of Investigators and sites	Included	Included	Included
Bioanalytic Reports	Not included	Not included	Not included

AE = adverse event; ATE = arterial thromboembolic event; CNS = central nervous system; CRF = case report form; eCRF = electronic case report form; GI = gastrointestinal; ICF = Informed Consent Form; IEC = Institutional Ethics Committee, IRB = Independent Review Board; RPSL = reversible posterior leukoencephalopathy syndrome, SAE = serious adverse event; sBLA = supplemental Biologics License Application; VTE = venous thromboembolic event.

Genentech states that the sBLA will contain the financial disclosure, investigator qualifications, and disbarment certifications for the principal investigators that enrolled patients in Studies EORTC 26101 and AVAglio. In the case of Study EORTC 26101, Genentech notes that due to the nature of the consortium study, these data may be incomplete. Genentech will group the financial disclosures into three categories: (1) financial disclosure, (2) no disclosure, and (3) unable to obtain.

The Summary of Clinical Efficacy (SCE) will present the efficacy data from Studies EORTC 26101 and AVAglio, summarized based on the analyses described in the SAP of each study. Results will not be pooled due to the differences in patient and disease characteristics. (b) (4) . The efficacy results from the RTOG 0825 study (b) (4) but will be provided in the CSR. Individual efficacy datasets will be provided (in Module 5) for the key efficacy study and the two supportive studies separately.

Genentech proposes to submit the following SAS datasets as outlined below:

- Study EORTC 26101: raw datasets for all randomized patients available in generic data model (GDM) format and derived datasets that correspond to key variables used in the analyses of CSR outputs.
- Study AVAglio: raw datasets in GDM format and derived datasets that correspond to key variables used in the analyses of CSR outputs. Two sets of data will be provided: one with a clinical cutoff of March 31, 2012 for the final PFS analysis including data for all efficacy analyses except OS and one with a clinical cutoff of February 28, 2013, for the final OS analysis including data for all safety analyses.
- Study RTOG 0825: raw datasets in GDM format and derived datasets that correspond to key variables used in the analyses of OS, PFS and safety; based on data received from RTOG.

Genentech states they are not able to comply with CDISC standards; therefore, datasets will follow the Roche data model (GDM format). Analysis datasets will be generated from the GDM datasets. The datasets will be submitted as SAS transport files (.xpt) and will be accompanied by the following:

- A Reviewer's Guide, which will provide further information regarding the content of the eSubmission package and any complexities the reviewer should be aware of.

- A blank annotated case report form (CRF) showing the names of the SAS datasets and variables where the CRF captured data can be found.
- Define.pdf files to describe the list and contents of the raw and analysis (i.e. derived) SAS datasets that are being submitted.
- Additional specification document describing complicated pre-derivation for analysis datasets and lengthy derivations of analysis variables.

Due to the timing of the database locks, individual study results are reported using varying versions of the Medical Dictionary for Regulatory Activities (MedDRA).

FDA preliminary comments were emailed to Genentech on March 28, 2016.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical/Statistical

1. *Treatment of GBM patients with bevacizumab has consistently resulted in a substantial prolongation of PFS across multiple studies. This PFS extension has been associated with preservation of HRQoL and NCF, and a diminished requirement for corticosteroids. In addition, a substantial increase in the ORR was observed in EORTC 26101 (rGBM) and associated with preserved HRQOL and improved survival. Does the Agency agree that these improvements in ORR and PFS with associated clinically relevant outcome measures consistently observed across multiple studies in different lines of therapy demonstrate a clinically meaningful benefit for patients with GBM?*

   FDA Response:
   FDA agrees that the effect on PFS supported by evidence of a decrease in corticosteroid use and delay in time to initiation of corticosteroids reported for Study EORTC 26101 may be sufficient to verify the clinical benefit of bevacizumab for the second line treatment of GBM.

   As stated during the July 24, 2015, meeting, data on HRQoL and NCF may be considered in the final risk/benefit analysis of bevacizumab for recurrent GBM; however, if Genentech intends to pursue a labeling claim in these areas, provide data to support the validity and reliability of the HRQoL and NCF instruments used in EORTC 26101 in the recurrent GBM disease setting.

   FDA requests that the sBLA contain a thorough and comprehensive assessment of corticosteroid use in studies EORTC 26101 and AVAglio in the sBLA, based on all available data. In addition, rather than including corticosteroid use in the concomitant medications dataset, provide separate datasets for corticosteroid use in both studies in the sBLA. These datasets should include the specific corticosteroids administered (e.g., dexamethasone) and exact doses and schedules of corticosteroids administered. Finally, the sBLA should contain evidence to support a reduction in the incidence of morbidity attributed to corticosteroid use in the GBM patient population.

Genentech should be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by imbalances in assessment dates or missing data between treatment arms.

Please provide an additional PFS sensitivity analysis where the PFS data will be censored on the date of the last tumor assessment documenting absence of progression for patients:

- Who are alive, on study and progression-free at the time of the analysis,
- Who are given/change therapy other than the study treatment prior to observing progression,
- Who discontinue (due to personal preference or toxicity)/ withdraw or lost to follow-up; or,
- For whom documentation of disease progression or death occurs after ≥ 2 consecutive missed tumor assessments

As stated during the July 24, 2015, meeting, although the RANO criteria are acceptable to assess PFS and ORR in patients with recurrent GBM enrolled on EORTC 26101, accurate assessment of radiographic response (even with RANO criteria) remains difficult to ascertain with the use of anti-angiogenic therapies.

Discussion:
FDA stated that the review will focus on the totality of the evidence with AVAglio supporting EORTC 26101 for a second line indication; (b) (4)

Genentech summarized the types of corticosteroid data available. From AVAgio, Genentech can provide the type of corticosteroid, the dose and schedule, and the start and stop dates. For EORTC 26101, Genentech can provide the type of corticosteroid and the total daily dose, but not the schedule, or start and stop dates. Genentech agreed to provide a separate dataset for corticosteroid information that can be merged with the efficacy datasets for EORTC 26101, but not AVAglio. FDA stated that it would be appropriate to provide literature to support the clinical benefit of reduction of corticosteroid exposure as data on corticosteroid-induced adverse reactions was not collected in the clinical trials.

FDA and Genentech agreed that analysis of QoL would be supportive only.

2. *The widespread availability and clinical utilization of bevacizumab has resulted in a large proportion of patients receiving bevacizumab as a subsequent therapy following study treatment in AVAglio, RTOG 0825, and EORTC 26101. These studies did not show a statistically significant difference in OS; however using multiple and varied statistical methods to investigate the impact of subsequent bevacizumab treatment on the study outcomes indicate that the large proportion of patients in the control arm receiving bevacizumab as subsequent therapy might have impacted the OS endpoint. In this context does the Agency agree with the analysis and interpretation of the presented OS results?*

FDA Response:
No. Whether the OS sensitivity analysis results will support a determination of clinical benefit will be a review issue. Please provide the results of the discount method assuming a 10%-90% benefit as stated in the SAP V2 section 4.4.12.1.2.2. FDA acknowledges that cross-over to bevacizumab in the control arms of AVAglio, RTOG 0825, and EORTC 26101 may affect interpretation of treatment effects on OS.

Discussion:
Genentech did not have any questions or comments.

3. *The safety profile observed of bevacizumab in GBM is consistent with the well-established profile of bevacizumab and reflects the known safety risks of bevacizumab use. Does the Agency agree that the safety data from Studies EORTC 26101, AVAglio (BO21990), and RTOG 0825 are sufficient to characterize the safety profile of bevacizumab in GBM*?

FDA Response:
FDA agrees that the safety data from Studies EORTC 26101, AVAglio and RTOG 0825 are sufficient to permit a substantive review and to characterize the adverse reaction profile of bevacizumab in patients with GBM. Please confirm that safety narratives for all treatment-emergent serious adverse events (per 21 CFR 312.32), regardless of attribution, will be provided in the sBLA.

Discussion:
Genentech did not have any questions or comments.

4. *Does the Agency agree that the totality of the evidence including data from multiple studies (including AVAglio, EORTC 26101, and RTOG 0825) and epidemiologic data demonstrates a clinically meaningful benefit with manageable or acceptable risks and thus supports a positive benefit-risk profile of bevacizumab for the treatment of GBM?*

FDA Response:
FDA considers data from adequately designed, well-controlled trials to be the most credible and persuasive to support a positive benefit/risk assessment for a drug or biologic. The trials described in the meeting package (AVAglio, EORTC 26101, and RTOG 0825) appear to be adequately designed and well-controlled; however, determination that the results and the benefit/risk assessment of bevacizumab for the treatment of patients with GBM cannot be made until the totality of the evidence are reviewed in the context of the sBLA.

Discussion:
Genentech did not have any questions or comments.

Administrative/Regulatory

5. *Does the Agency agree that the data presented in this meeting package can support the conversion to full approval?*

FDA Response:
For biologics granted accelerated approval under 21 CFR 601.40-46, post-marketing confirmatory trial(s) are required to verify and describe the clinical benefit attributable to the product. Clinical benefit is evidenced by effects such as increased survival or reduction in disease-related symptoms. The data from the trials described in the meeting package may meet these criteria; however, determination that the results and the benefit/risk assessment of bevacizumab for the treatment of patients with GBM (including the wording of the indication) will be addressed during review of the application. Please also see FDA response to Question #4.

Discussion:
Genentech did not have any questions or comments.

6. *Does the Agency agree with the proposed structure and content of the application package?*

Study AVAglio included a pre-specified Independent Review Facility (IRF) (as per US Food and Drug Administration [FDA] guidelines) to substantiate the co-primary endpoint of investigator assessment of PFS. In contrast, the EORTC 26101 conducted their own central review to support the investigator assessment of PFS. In this context, does the Agency agree that the central review employed in Study EORTC 26101 is necessary and meets the criteria to be considered an independent central review to substantiate the PFS results for labeling?

FDA Response:
The approach to the structure and content of the clinical datasets for the proposed sBLA appear acceptable, with the exception of (b) (4). Please also see FDA response to Question #1.

Regarding the central review strategy for radiologic imaging employed in EORTC 26101, include in the sBLA a description of all cases where there was disagreement between the two radiologists and how these discrepancies were adjudicated.

The following comments apply to Studies EORTC 26101, AVAglio, and RTOG 0825:

- During the March 26, 2014, meeting, FDA agreed that for Study RTOG 0825, Genentech may submit a CSR containing the raw and derived datasets for OS, PFS, and safety accompanied by the protocol, protocol amendments, and summaries published by RTOG along with RTOG's tables and statistical output. In addition, FDA agreed that results of RTOG 0825 could be excluded from the SCE, based on lack of information on the conduct of this trial and its data integrity.

However, given that Genentech's arguments cited in the meeting package presented side-by-side comparisons for Studies EORTC 26101, AVAglio, and RTOG 0825 for OS and PFS, it appears appropriate that the summary results of RTOG 0825 should be included in the SCE and all three studies should be discussed in the SCE. As stated in ICH (M4), August 2015, "[T]he purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided." If you elect not to include the summary results of RTOG 0825 in the SCE, provide justification that the data are not considered relevant.

- FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the sBLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document" available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf.

- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.

- Provide executable SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets.

- Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

- Provide the SAS programs with adequate document(s) for the derived datasets and the analyses associated with the results presented in the proposed package insert.

Discussion:
FDA agreed with Genentech's proposal to include a description of (b) (4) EORTC 26101 in the clinical studies section of the package insert.

Regarding the central review strategy for radiologic imaging employed in EORTC 26101, Genentech stated that there was no documentation of the adjudication process when there were discrepancies between the radiologists. FDA recommended that Genentech

describe the adjudication process to identify the deviations from the ideal process and to provide a justification as to why the data are unlikely to be biased due to the procedures that were followed.

Regarding the need for an advisory committee, FDA stated that the complexity of the application may not lend itself well to specific voting questions and that FDA may not be able to do justice to the discussion of the application in the limited time allotted. However if a specific issue is identified during review for which ODAC's advice would be useful, FDA may elect to present at ODAC.

Genentech stated that they plan to submit the sBLA in Q1 2017 and not in Q3 2016 as originally planned. FDA advised Genentech to submit a letter to the BLA with the new milestone date along with a justification for the change.

FDA recommended that Genentech plan for an Applicant Orientation meeting for the sBLA. To facilitate scheduling, Genentech should contact FDA two months prior to the submission of the sBLA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

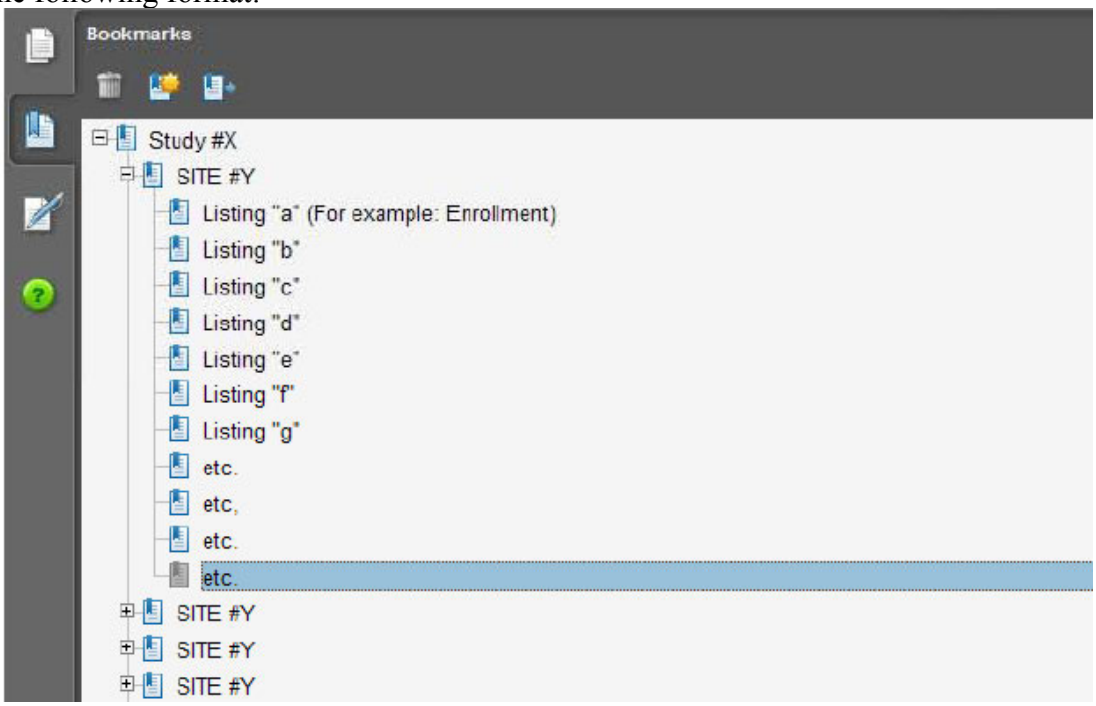
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON K SICKAFUSE
04/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 121609

MEETING MINUTES

Genentech, Inc.
Attention: Timothy Burkoth, Ph.D.
Regulatory Program Management
1 DNA Way MS#241B
South San Francisco, CA 94080

Dear Dr. Burkoth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Avastin (bevacizumab)."

We also refer to the meeting between representatives of your firm and the FDA on July 20, 2015. The purpose of the meeting was to "seek the Agency's input and agreement on the Sponsor's content, format, and proposed statistical analysis plan (SAP) for the efficacy supplement intended to fulfill the post-marketing requirement (PMR) as outlined in the relapsed GBM approval letter (BLA 125085/169) dated, May 5, 2009." In addition to provide verification of clinical benefit, the proposed efficacy supplement is intended to support the following indication:

> Avastin® (bevacizumab) (b) (4) is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-5890.

Sincerely,

{See appended electronic signature page}

Tina Ennis, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Other
Meeting Date and Time:	July 20, 2015, 12:00 PM-1:00 PM
Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 121609
Product Name:	Avastin (bevacizumab)
Indication:	Treatment of glioblastoma (GBM)
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	Patricia Keegan, M.D.
Meeting Recorder:	Tina Ennis, M.S.

FDA Attendees
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Division of Oncology Products 2

Patricia Keegan, M.D.	Division Director
Suzanne Demko, P.A.-C.	Medical Officer Team Lead
Joohee Sul, M.D.	Medical Officer
Kun He, Ph.D.	Biostatistics Team Lead
Janet Jiang Ph.D.	Biostatistics Reviewer
Tina Ennis, M.S.	Regulatory Health Project Manager

Genentech Attendees

Lauren Abrey, M.D.	Clinical Science
Tim Burkoth, Ph.D.	Regulatory
Dorothy Leong, Ph.D.	Regulatory
Alexandre Moreau, Ph.D., MBA	Project Leader
Barbara Mueller, MSc	Biometrics
Josep Garcia, Ph.D.	Clinical Science
Elisabeth Piault-Louis, Pharm.D	Patient-Centered Outcomes Research

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 20, 2015, between Genentech and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

FDA sent Preliminary Comments to Genentech on July 20, 2015.

BACKGROUND

On May 8, 2015, Genentech, Inc. (Genentech) submitted a meeting request (SDN 28) to "seek the Agency's input and agreement on the Sponsor's content, format, and proposed statistical analysis plan (SAP) for the efficacy supplement intended to fulfill the post-marketing requirement (PMR) as outlined in the relapsed GBM approval letter (BLA 125085/169) dated, May 5, 2009."

In the pre-meeting briefing package, received on June 19, 2015 (SDN 34), obtain FDA advice and agreement on the proposed statistical analysis plan (SAP) for study EORTC 26101, "Phase 3 Trial Exploring the Combination of Bevacizumab and Lomustine in Patients with First Recurrence of a Glioblastoma." Genentech also requested FDA advice on measuring and assessing the clinical significance of delaying tumor growth, and to discuss the content/format of the efficacy supplement intended to fulfill the post-marketing requirement (PMR) as outlined in the recurrent glioblastoma (GBM) accelerated approval letter dated May 5, 2009. The meeting package was submitted on June 19, 2015, as SDN 34.

Regulatory:
Bevacizumab was granted Orphan Drug Designation on May 26, 2006 for the treatment of malignant glioma.

On May 5, 2009, FDA granted bevacizumab was approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) for treatment of recurrent GBM based on demonstration of durable objective response rate (ORR) in two trials; AVF 3708g and NCI 06-C-0064E. The

approval letter contained a post-marketing requirement (PMR) under 21 CFR 601 Subpart E to conduct studies to verify and describe the clinical benefit of bevacizumab for the treatment of GBM as follows:

> To submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling based on the results of study AVF4396g/BO21990 entitled "A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma," which was accepted under a Request for Special Protocol Assessment on December 29, 2008.

Study AVF4396g/BO21990 (AVAglio) is a multicenter, randomized, double-blind, placebo controlled trial evaluating bevacizumab in combination with radiation therapy (RT) and temozolomide (TMZ) conducted in 921 patients with newly diagnosed GBM. The co-primary endpoints were PFS as assessed by investigator and overall survival. The study did not demonstrate a statistically significant improvement in survival, however Genentech states that it did demonstrate a statistically significant improvement in PFS for patients randomized to the bevacizumab plus standard therapy arm compared with those randomized to standard treatment (10.6 vs 6.2 months; HR 0.64 [0.55-0.74]; $p < 0.0001$). In addition, Genentech states that there was an improvement in health related quality of life (HRQoL) observed.

The clinical benefit of bevacizumab when administered combined with radiation and temozolomide for the first-line therapy of patients with newly diagnosed GBM was also investigated in Study RTOG 0825. Study RTOG is a randomized, double-blind, placebo-controlled trial conducted in 621 patients with newly diagnosed GBM. The co-primary endpoints were overall survival and investigator-assessed PFS. The RTOG 0825 study demonstrated no improvement in overall survival and poorer HRQoL and cognitive function for patients randomized to the bevacizumab, radiation, and temozolomide arm compared with radiation, temozolomide, and matching placebo.

On March 26, 2014, a Type B meeting was held to discuss the clinical development plan for the data package necessary to verify the clinical benefit of bevacizumab for the treatment of GBM, and Genentech requested feedback from the FDA regarding the suitability of an ongoing randomized, multicenter trial comparing lomustine alone to lomustine with bevacizumab in recurrent GBM (EORTC 26101) to fulfill the PMR for bevacizumab in the treatment of recurrent GBM. EORTC 26101 is an ongoing, open-label, randomized (2:1), multicenter trial to investigate the safety and efficacy of bevacizumab plus lomustine versus lomustine monotherapy in approximately 433 patients with recurrent GBM. Randomization used the minimization technique (Pocock and Simon, 1975); randomization was stratified by investigational site, World Health Organization (WHO) performance status (0 versus > 0), steroid use (yes versus no), and largest tumor diameter ($\leq$ 40 mm versus > 40mm).

As discussed during the meeting, and summarized by Genentech in the pre-meeting briefing package, Genentech stated that the data from study EORTC 26101 would provide direct evidence regarding the efficacy and safety of bevacizumab in the treatment of recurrent GBM

and the totality of evidence would allow for a more comprehensive verification of clinical benefit and support the conversion from accelerated approval to full approval for the approved indication for the treatment of GBM with progressive disease in adult patients following prior therapy.

This proposed plan is intended to fulfill the PMR required under 21 CFR 601 Subpart E as outlined in the recurrent GBM approval letter (May 2009). The FDA stated that the decision to grant conversion to full approval will be based on the totality of the evidence which will include the results of the EORTC 26101, AVAglio, and RTOG 0825 studies. For Study RTOG 0825, the FDA agreed that a final CSR for OS, PFS, and safety accompanied by the corresponding raw and derived datasets, the protocol, protocol amendments, and publications by RTOG along with RTOG's tables and statistical outputs would be sufficient.

At the request of FDA, a formal "PMR Correspondence" letter was sent on August 1, 2014 reiterating the submission plan, content, and describing a new timeline intended to fulfill the PMR. FDA acknowledged the correspondence on August 12, 2014.

The primary endpoint of the study is overall survival (OS). Assuming that the 9-month OS rates are 40% and 51.7% in the lomustine and bevacizumab plus lomustine arms, respectively, a total of 327 events are needed to detect a hazard ratio of 0.72 (corresponding to median survivals of 6.8 months in the lomustine arm and 9.5 months in the lomustine plus bevacizumab arm) with 80% power at a 1-sided alpha level of 2.5%. The primary analysis will be a stratified log-rank test performed on the ITT population. The stratification factors are those used at randomization (except institution) and a variable indicating if the patient was recruited in the Phase 2 or Phase 3 portion of the study.

Key secondary endpoints were investigator-assessed PFS and ORR as determined by the Response Assessment in Neuro-oncology (RANO) criteria; additional secondary endpoints include HRQoL (including global health status, cognitive function, pain scales assessed by the patient and caregiver using EORTC QLQ-30 and EORTC BN20); clinical/neurological deterioration free survival; steroid use; cognitive function; and 9-month and 24-month survival rates.

Genentech argues that assessment of cognitive function and HRQoL is essential to evaluating the clinical benefit of PFS. Patients on EORTC 26101 undergo neurocognitive testing every 12 weeks until progression of disease (POD). The following tests are included in the cognitive assessment:

- Hopkins Verbal Learning Test-Revised (HVLT-R)
- Trail Making Test (TMT) Part A and Part B
- Controlled Oral Word Association (COWA)

As stated in the analysis plan, changes from baseline in the cognitive functions score will be categorized as "improved, stable, or declined" using the Reliable Change Index (RCI) which

evaluates changes in test scores in the absence of intervention. The proportion of patients who are improved/stable or declined in neurocognitive function will be analyzed at each time-point together with the proportion of non-compliant patients. Neurocognitive decline is defined for each patient as a change in score that has declined in excess of the RCI threshold (HVLT-R and COWA) or increased in excess of the RCI threshold (Trail Making Tests).

Genentech also proposes that changes in HRQoL, as measured by EORTC QLQ C-30 and BN20, will be used to support the analysis of PFS in EORTC 26101. Three EORTC QLQ-30 scales are pre-specified as part of the testing hierarchy in the SAP: Global health status, Cognitive, and Pain scales. These assessments will also occur every 12 weeks until documented disease progression while radiographic and clinical evaluations occur every 6 weeks on EORTC 26101.

Since patients may not report clinical deterioration due to early progression, to avoid bias due to informative censoring in the time-to-event analysis of "clinical deterioration," Genentech states that analysis of clinical deterioration will include the following as "events:"

- Death occurring within 16 weeks of lastPRO assessment or disease progression at any time point in patients without documented HRQoL deterioration.

- A decrease of ≤ 10 points from baseline on the functional scales or global health status.

- An increase of ≥ 10 points from baseline on the symptom scales, neurological deficit scales or single items; without subsequent improvement.

A hierarchical procedure is proposed to adjust for multiplicity in testing the secondary endpoints in the order of PFS, ORR, clinical/neurological deterioration free survival, and HRQoL (global health status, cognitive functioning and pain scales).

Trial status
The study is conducted in Europe, where bevacizumab is not yet widely approved for use in this population. Accrual is completed with 437 patients enrolled. The final analysis (at 327 deaths) is projected to occur in the first quarter of 2016.

At the time when the study was amended with the intent to provide data to Genentech to support product registration, the Ethic Committees were informed and some countries requested the re-consenting of patients. The re-consent process in ongoing; thus far, three patients have not re-consented. However, the EORTC will be able to analyze the data from all patients enrolled on EORTC 26101 (including those who did not re-consent). Genentech proposes to provide this analysis as an appendix to the CSR once the results are publicly presented.

Genentech anticipates submission of the sBLA in the second quarter of 2016, and will request a meeting with FDA to discuss the preliminary results of Study EORTC 26101 upon completion of the study.

SPONSOR QUESTIONS AND FDA RESPONSES

Statistical

1. *On March 26 2014, the Sponsor received guidance on the overall type I error control and randomization process for study EORTC 26101. The statistical analysis plan (SAP) for this study was created and it addresses this feedback. The SAP is included in Appendix 6 of the meeting package. Does the Agency agree with the analysis plan, specifically with respect to the following elements?*

   a. *Overall type I error control adjusted based on the number of OS events which had occurred among patients randomized into the two treatment arms at the time the trial was converted from Phase 2 to Phase 3 (i.e., up to the time of protocol amendment) using the O'Brien-Fleming group sequential boundary function together with the Lan and DeMets (1983) α-spending function.*

   FDA Response: The proposed plan for control of overall Type I error is acceptable.

   Discussion During the Meeting: No further discussion.

   b. *Primary analysis of OS applying a stratified one-sided log-rank test at the overall 0.025 level of significance using the stratification factors collected at time of randomization on the eCRF except institution, (i.e., WHO PS, steroid administration and largest lesion diameter) and a covariate indicating if the patient was randomized during the Phase 2 or Phase 3 part of the trial.*

   FDA Response: No. FDA reiterates that a re-randomization test on the intent to treat (ITT) population will be considered the primary efficacy analysis for regulatory decision-making since the minimization technique was used in the randomization.

   Discussion During the Meeting: No further discussion.

   c. *The robustness of the results to the use of a minimization randomization algorithm will be evaluated by performing a re-randomization test on the primary efficacy analysis.*

   FDA Response: No further discussion.

2. *Are there any additional comments or feedback for the Sponsor on the SAP?*

   FDA Response: FDA has the following additional comments:

   a. The efficacy analyses of PFS and other time to event endpoints should be conducted with the re-randomization test on the ITT population.

b. The primary analysis of ORR should be based on the ITT population which consists of all randomized patients.

c. FDA is not clear whether the method proposed in SAP Section 4.4.12.2.2 is for a sensitivity analysis. For handling missing data in PFS analysis, please refer to the Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics at: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf).

Discussion During the Meeting: Genentech confirmed that the analysis referenced in FDA's response 2c to Genentech's Question 2 is a sensitivity analysis. FDA stated that the proposed sensitivity analysis is acceptable.

3. *Does the Agency agree with the proposed analyses accounting for the potential impact of cross-over from the control arm to bevacizumab treatment on the OS results? Does the Agency have any comments or further guidance?*

FDA Response: The proposed analyses may be performed as sensitivity analyses and will be considered as exploratory by FDA.

Discussion During the Meeting: FDA stated that the "weight" to be placed on the exploratory analyses of OS intended to adjust for administration of bevacizumab following disease progression for patients in the control arm should be revisited after the results are known and the extent of post-progression bevacizumab is known.

FDA further stated that consideration of the effects of post-progression bevacizumab on the observed survival outcome will likely be a review issue. Since FDA is unaware of a valid method for adjustment for post- progression therapy effects, FDA has no recommendations for specific exploratory analyses, however, FDA recommends all exploratory analyses be pre-specified in the statistical analyses plan.

Clinical

In recurrent GBM, tumor growth in the brain results in functional impairment and a decline in the health-related quality of the patient's life. In this disease, delaying tumor progression is of clinical relevance for the patients and caregivers as tumor growth is associated with inevitable decline. The Sponsor has the following questions related to measuring and assessing the clinical significance:

4. *Does the Agency agree that the RANO criteria used for the assessment of PFS and response in this study is acceptable criteria to evaluate the treatment effect in brain tumors?*

FDA Response: Yes. FDA agrees that the RANO criteria are acceptable to assess PFS and objective radiographic response in patients with recurrent GBM enrolled on EORTC

26101. However, since accurate assessment of radiographic response remains difficult to ascertain with the use of anti-angiogenic therapies (even with RANO criteria), PFS and ORR will be considered supportive efficacy endpoints. If Genentech intends to make labeling claims based on PFS, confirmation of the findings based on an independent radiologic review committee (IRRC) would provide greater confidence in the results.

Discussion During the Meeting: FDA stated the central assessment of response to be conducted in a centralized manner where the reviewers are masked to treatment assignment and investigator assessment as part of Study EORTC 26101 may be adequate to serve as an independent review of tumor based endpoints, however, details of the procedure should be provided and a final decision on the acceptability of this approach to serve as independent verification of the investigator assessment will depend on the standard operating procedures and conduct of this central assessment.

5. *Does the Agency agree that the maintenance of neurocognitive function will provide important evidence to document the clinical benefit?*

FDA Response: FDA agrees that assessment of neurocognitive function is an important component of GBM clinical trials and encourages the use of measures aimed at evaluating functional patient outcomes. However, FDA considers change in cognitive function to be an exploratory endpoint for the following reasons. Neurocognitive decline is not a well-defined concept and difficult to measure, as it is likely influenced by multiple factors including patient variables, treatment effect, tumor location, concomitant medications, etc. Furthermore, the content validity of the proposed cognitive testing measures has not been established in malignant brain tumors; therefore, the performance capabilities of these tests to detect clinically meaningful changes in GBM are unknown. Data on neurocognitive functioning may be considered in the final risk/benefit analysis of bevacizumab for recurrent GBM, but if Genentech intends to pursue a labeling claim in this area, a comprehensive development and validation package for the use of the proposed instruments in this disease setting will be required.

Discussion During the Meeting: Genentech will provide supportive evidence to address FDA's concerns regarding interpretation of the results of neuro–cognitive assessment and functioning.

6. *Does the Agency agree that documenting the impact of delay in tumor-growth on specific domains (i.e., cognitive, role and physical functioning, pain) of health-related quality of life (HRQoL) is important patient-relevant information to document clinical benefit?*

FDA Response: FDA agrees that evaluation of patient symptoms and functioning is an important component of GBM clinical trials and may provide supportive information to assess clinical benefit. However, FDA considers changes in HRQoL to be an exploratory endpoint for the following reasons. Similar to neurocognitive function, HRQoL is not well-defined and is subject to influence from multiple variables. Therefore, data on clinical deterioration may be considered in the final risk/benefit analysis of bevacizumab for recurrent GBM, but if Genentech intends to pursue a labeling claim in this area, a

comprehensive development and validation package for the use of the proposed instruments in this disease setting will be required.

Discussion During the Meeting: See response for Question #5.

7. *Does the Agency agree that the analysis plan for these endpoints support the clinical relevance of PFS?*

FDA Response: No. FDA does not agree that the analysis plan for neurocognitive function and clinical deterioration endpoints are adequate to support the assessment of clinical benefit. The cutoffs described for both the neurocognitive tests and HRQoL surveys have not been validated, and it is unclear that the changes in scores proposed will be able to measure a clinically meaningful benefit for patients.

In addition, the HRQoL survey includes an assessment of cognitive functioning (patient reported outcome) that overlaps with the proposed neurocognitive battery of tests (clinician assessed outcome). These results should be analyzed to determine concordance between the two measures.

Discussion During the Meeting: FDA stated that they will consider the totality of the evidence provided and the level of support from the neuro-cognitive assessment and function, which will likely be contingent on strength of the additional supportive information to be provided as discussed under Question #6 and the magnitude of the treatment effects observed.

8. *The sBLA submission will consist of three studies, EORTC 26101, AVAglio (BO21990/AVF4396g), and RTOG 0825. The results from the three studies will not be integrated or pooled together due to the differences in patient and disease characteristics. Therefore, no comparison data will be included in the submission. The efficacy and safety results from the RTOG 0825 study will not be summarized as agreed upon with FDA at the March 26, 2014 meeting, but provided in the CSR as defined in Section 12.4.1*

Does the Agency agree with the proposed contents of the application including the structure (modules 1, 2, and 5) and format of the electronic SAS datasets for the three GBM studies that will be provided to support a sBLA for the conversion of full approval as outlined in Section 12 of the meeting package?

FDA Response: This question is premature and should be revisited when the results of EORTC 26101are available. Please note, however, that in accordance with 21 CFR 314.50, an NDA should contain a description and analysis of each controlled clinical study pertinent to a proposed use of the drug, including the protocol and a description of the statistical analyses used to evaluate the study.

Discussion During the Meeting: FDA stated that additional supportive information in the form of published literature would be reasonable, however, FDA would not

encourage submission of a large meta-database. Genentech confirmed that the data package discussed in the March 26, 2014, meeting which includes the data (raw and derived datasets), but not analyses programs for the analyses from the AVAglio and RTOG studies would be provided in the proposed supplement. For the EORTC 26101 study, Genentech confirmed that the analyses programs will be provided.

9. *At the time when the study purpose was amended with the intent to provide data to the Sponsor for the purpose of product registration, the Ethic Committees were informed and some countries requested the re-consenting of patients. Only a few patients decided not to consent to allow the use of their data by the Company. Does the Agency agree that the proposed way of presenting the available data for EORTC26101 study is acceptable to support a sBLA for the conversion of full approval?*

FDA Response: The analysis based on all patients enrolled on EORTC 26101 who provide consent to allow the use of their data by Genentech. Genentech should provide a justification as for why the missing data from patients who do not provide consent for such use do not alter the conclusions from the study.

Discussion During the Meeting: Genentech acknowledge FDA's comment. No further discussion.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.
The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

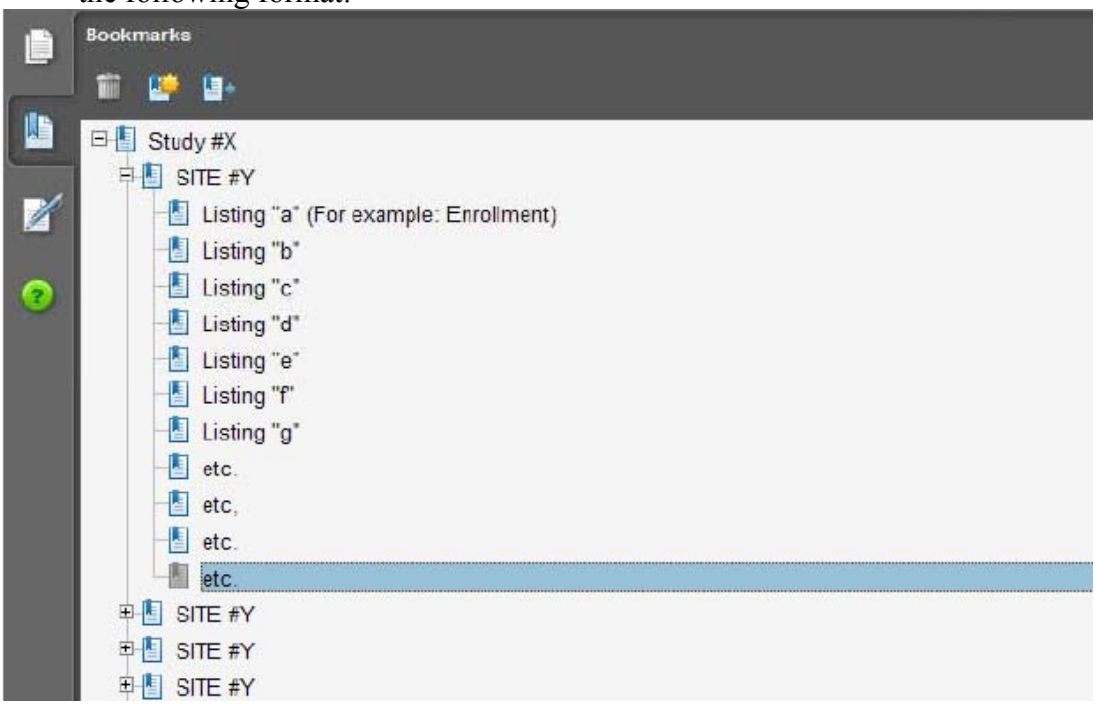
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

ACTION ITEMS: No action items.

ATTACHMENTS AND HANDOUTS: No attachments or handouts.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TINA M ENNIS
07/24/2015