



**FDA Briefing Document  
Oncology Drug Advisory Committee  
Meeting**

**March 31, 2009**

**BLA STN 125085/169  
Avastin® (bevacizumab)**

**Applicant: Genentech Inc.**

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## EXECUTIVE SUMMARY

The applicant seeks accelerated approval for Avastin® (bevacizumab), as a single agent for the treatment of patients with previously treated glioblastoma multiforme. Efficacy results from two single-arm, historically-controlled studies are submitted in support of the proposed indication.

AVF3708g is an open-label, multicenter, non-comparative, parallel group, Genentech-sponsored trial to evaluate the efficacy and safety of bevacizumab monotherapy and of bevacizumab plus irinotecan in patients with previously treated glioblastoma. A total of 167 patients were enrolled: 85 in the bevacizumab alone arm, 82 in the bevacizumab plus irinotecan arm.

The primary efficacy endpoint for regulatory purposes is objective tumor response as determined by an independent review facility. Tumor assessment was based on the modified WHO response criteria taking into account corticosteroid dosing. Because the contribution of irinotecan to the efficacy result can not be isolated in this study design, only efficacy data from the bevacizumab monotherapy arm can be used to support drug approval. Secondary efficacy endpoints are 6-month progression-free-survival, duration of response and safety.

Objective response rate was 25.9% (22/85; 97.5% CI 15.9, 37.8) in patients who received bevacizumab monotherapy. There were no complete responses (CR) per FDA assessment. Median duration of response was 4.2 months among the responders (95% CI 3.0, 5.7). The 6-month progression-free-survival was 36.0 % (97.5% CI 24.0, 48.0).

NCI 06-C-0064E was a single arm, single site, NCI-sponsored study of bevacizumab for the treatment of patients with previously treated gliomas. The study enrolled 56 patients with high-grade glioma. Objective response as determined by independent review was 19.6% (95% CI 10.9 %, 31.3%). Median duration of response was 3.9 months (95% CI 2.4, 17.4) among the responders.

Adverse events (AE) were reported in > 99% of the patients enrolled in AVF3708g. Serious AEs were reported in 26.2% of the subjects in the bevacizumab arm and 43% in the bevacizumab plus irinotecan arm. The most common AEs reported in the bevacizumab alone arm were fatigue (45.2%), headache (38.1%) and hypertension (29.8%). The most common bevacizumab associated toxicities were: bleeding/hemorrhage (41.1%), hypertension (32.5%) and venous/arterial thromboembolic event (14.0 %). Other serious AEs known to be associated with bevacizumab were also reported: wound-healing complications (6.1%), proteinuria (3.6%) and gastrointestinal perforation (1.8%). There were 2 deaths possibly related to bevacizumab: retroperitoneal hemorrhage and neutropenic infection.

Key issues of this application are:

1. Due to the hallmark histology of pseudopalisading necrosis of GBM, tumor size can not be accurately measured by MRI because of the irregular configuration. This difficulty is even greater for relapsed gliomas after prior surgery and radiation therapy, the target population for this application. Neither objective response rate nor objective progression can be satisfactorily assessed.

Since the accuracy of tumor measurement has been questionable in this disease setting, objective response has not been used as the basis for approval for GBM. It is unclear whether the response rate and duration of response seen in this application are of sufficient magnitude to support surrogacy for clinical benefit for the purpose of accelerated approval in the refractory glioblastoma.

2. Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and capillary permeability.

Based on the known mechanism of action of bevacizumab, it is unclear whether the responses observed in MRI are due to an anti-angiogenic effect on tumor vasculature or an effect on blood brain barrier disruption, leading to normalization of peritumoral edema with improvement of tumor contrast enhancement, resulting in a decrease in corticosteroid requirement in these patients. It is possible that bevacizumab therapy results in a significant reduction in tumor capillary permeability without producing a true antitumor effect.

## **PROPOSED INDICATION**

Avastin®, as a single agent, is indicated for the treatment of patients with previously treated glioblastoma.

## **DRUG DESCRIPTION**

Avastin® (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and subsequent tumor growth.

Avastin® is approved by the U.S. Food and Drug Administration (FDA) for use in:

- First-line (2004) and second-line (2006) treatment of patients with metastatic colorectal cancer in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy and FOLFOX-4 chemotherapy respectively.
- First-line treatment of patients with unresectable or metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel (2006).

Approval for both colorectal and lung cancer indications were based on randomized clinical trials demonstrating a statistically significant improvement in overall survival.

Accelerated approval based on improvement in progression free survival (PFS) was granted for Avastin® in combination with paclitaxel for the 1<sup>st</sup> line treatment of metastatic breast cancer (2008).

## **BIOPHARMACEUTICS**

The bevacizumab administered in the primary efficacy trial, AVF3708g was a product intended for investigational use and not the commercially marketed product. Information demonstrating the comparability between the product used in AVF3708g and the commercially marketed product has been requested.

The bevacizumab used in Study NCI 06-C-0064E was a commercially marketed product.

## **REGULATORY BACKGROUND**

### **FDA Approvals for Brain Tumor**

It is estimated that 21,810 new cases of cancer of the brain and other nervous system was diagnosed in 2008<sup>1</sup>. Glioblastoma multiforme counts for approximately 15 to 20 % of all brain cancers<sup>1,2</sup>. Median survival for glioblastoma from the time of diagnosis is estimated to be 9 - 12 months. Currently, only nitrosoureas (lomustine and carmustine), including Gliadel® Wafer (carmustine) as adjunct to surgery, are approved for use in previously treated GBM.

Following are the agents approved by the FDA for use in brain tumors.

**Table 1. FDA Approvals for GBM**

<b>Drug</b>	<b>Year</b>	<b>Endpoint</b>	<b>Population</b>
<b>Nitrosoureas</b>	1970's	Response Rate	Primary and metastatic brain tumors
<b>Gliadel® Wafer (carmustine)</b>	1996	Overall Survival	Recurrent GBM as adjunct to surgery
	2003	Overall Survival	1 <sup>st</sup> line high grade glioma as adjunct to surgery and radiation
<b>Temozolomide</b>	1996	Durable objective response (accelerated approval)	Refractory Anaplastic Astrocytoma
	2005	Overall Survival	1st line GBM concomitantly with radiotherapy and then as maintenance treatment

- Nitrosoureas are DNA alkylating agents capable of crossing the blood-brain barrier after systemic administration. Lomustine and carmustine were approved in 1970's based on tumor response.
  - Oral lomustine (CeeNU®) received approval in 1976 for use as single agent or in established combination therapy with other approved chemotherapeutic agents in patients with primary or metastatic brain tumors who have already received appropriate surgical and/or radiotherapeutic procedures.
  - Intravenous carmustine (BiCNU®) received approval in 1977 for use as single agent or in established combination therapy with other approved chemotherapeutic agents in brain tumors (glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors).
  
- Carmustine wafer (Gliadel) is a synthetic biodegradable polymer impregnated with carmustine.
  - Gliadel was first approved in 1996 for treatment of recurrent GBM as an adjunct to surgery. Approval was based on the results of a randomized, placebo-controlled trial in 222 gliomas patients who progressed following surgery and radiation. The primary endpoint was overall survival. Median survival for patients who received carmustine wafers was 7.4 months versus 5.5 months for those who received placebo.
  - In 2003, Gliadel was approved for 1<sup>st</sup> line treatment of high grade malignant glioma as an adjunct to surgery and radiation. Approval was based on an improvement in overall survival in a randomized, placebo-controlled study in 240 patients with newly-diagnosed, higher grade glioma undergoing resection craniotomy. Median survival was 13.9

months versus 11.6 months for the placebo arm (HR 0.73, 95% CI; 0.56-0.95), log-rank test p-value < 0.05).

- Temozolomide (Temodar) is an orally available alkylating agent chemically related to Dacarbazine.
  - Temodar was granted accelerated approval (AA) in 1999 on the basis of durable objective response in patients with anaplastic astrocytoma refractory to nitrosourea and procarbazine. Approval was based on a 22% response rate (12/54 patients) in AA patients who were refractory to both a nitrosourea and procarbazine. The complete response rate, in this group of patients, was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks). The median duration of complete response was 64 weeks (range of 52 to 114 weeks). Median progression free survival was 4.4 months and median overall survival was 15.9 months. Approval was not granted for refractory GBM based on data included in the same application.
  - Regular approval was granted in 2005 after confirmation of clinical benefit was obtained in a randomized trial of 573 patients with newly diagnosed GBM. Eligible patients following surgery were randomized to receive adjuvant radiation alone or radiation plus temozolomide followed by maintenance temozolomide for 6 months. Median survival was prolonged by 2.5 months in the temozolomide group (HR 1.59, 95% CI 1.33, 1.91, log-rank p-value < 0.001)

### **Regulatory Background Pertinent to this Application**

- |          |   |
|----------|---|
| May 2006 | Avastin received orphan drug designation for treatment of malignant glioma  |
| May 2006 | Genentech submitted protocol AVF3708g to IND 7203. AVF3708g is an open-label, multicenter, randomized, non-comparative trial to evaluate the efficacy and safety of bevacizumab alone or bevacizumab in combination with irinotecan in patients with previously treated glioblastoma. Patients who progressed on bevacizumab alone were eligible for cross-over to bevacizumab plus irinotecan arm. The proposed efficacy endpoints were 6-month PFS and objective response rate. |

The FDA provided the following comments in a letter on July 19, 2006:

- The proposed trial, as designed is not adequate to support regulatory approval because there is not internal comparison for the primary efficacy endpoint of 6-month PFS.

- The effect of bevacizumab is not isolated in the bevacizumab plus irinotecan combination arm.

January 2008 A meeting was held at Genentech's request to discuss the results of AVF3708g and a proposal for a confirmatory study.

Genentech reported 6-month PFS and objective response rates significantly higher compared with historical controls. Genentech indicated that they would like to submit a sBLA to request accelerated approval for relapsed GBM based on these findings.

The FDA provided the following comments:

- Genentech's proposal to submit a sBLA based on 6-m PFS based on comparison to historical control was not acceptable. Time to event endpoints must be evaluated in randomized, controlled clinical trials, as historically-controlled trials do not provide direct evidence of treatment effect.
- The effect of bevacizumab was not isolated in the bevacizumab plus irinotecan arm. The contribution of irinotecan to the efficacy finding could not be isolated based on the study design.
- Questions regarding potential surrogate endpoints in GMB are still unanswered, as discussed at the January 2006 Workshop on Brain Tumor Clinical Trial Endpoint ([http://www.fda.gov/Cder/drug/cancer\\_endpoints/#brain](http://www.fda.gov/Cder/drug/cancer_endpoints/#brain)) Appendix.
- FDA informed Genentech that FDA would consider the results of AVF3708g in support of a request for accelerated approval of bevacizumab monotherapy based on evidence of a clinically meaningful and durable objective tumor response. Tumor response should be determined by an independent radiographic review committee.
- Genentech should obtain and submit data from the single-arm, single-center study, conducted at NCI, by Dr. Howard Fine to support the application.
- Genentech should propose a confirmatory trial designed to demonstrate clinical benefit. The study should be ongoing and performed with "due diligence" at the time of the regulatory action.

September 2008 A pre-sBLA meeting was held. Agreement was reached regarding the sBLA content and the overall phase IV commitment trial design.

December 2008 Genentech submitted protocol AVF4393g/BO21990 under Special Protocol Assessment (SPA). Final agreement was reached regarding the regulatory endpoint and the statistical analysis plan.

AVF4396g/BO21990 is a randomized, placebo-controlled, study of bevacizumab in combination with radiotherapy and temozolomide for patients with newly diagnosed GBM. Following debulking surgery or biopsy, 920 eligible patients will be randomized to radiation therapy and temozolomide plus Avastin or placebo in the concurrent phase, followed by 6 months temozolomide plus Avastin or placebo, followed by Avastin or placebo until disease progression. Randomization will be stratified by recursive partitioning analysis (RPA) and by country. The study will be conducted world-wide, by Genentech's drug development partner, Hoffmann-La Roche Ltd. The study will enroll 920 patients with 683 events targeted at the time of final analysis. Although the proposed study has two co-primary endpoints, OS and PFS, agreement was reached that for U.S. FDA regulatory purposes, OS will be the primary regulatory endpoint. The 0.05 significance level is split between the two endpoints, with 0.04 allocated to OS and 0.01 to PFS. A formal interim analysis is planned for OS at the time of the PFS final analysis (when 492/683 events occurs). The primary analysis for OS will be based on the stratified log-rank test.

November 2008 Supplemental BLA was submitted for licensure of Avastin

## **CLINICAL REVIEW**

This sBLA is supported by two phase 2 studies: AVF3708g, sponsored by Genentech Inc. and NCI 06-C-0064E, sponsored by NCI.

### **AVF3708g**

#### **Study Design**

Study AVF3708g is an, open-label, multicenter, randomized, non-comparative trial to evaluate the efficacy and safety of bevacizumab monotherapy or of bevacizumab plus irinotecan in patients with previously treated glioblastoma. Patients were randomized to receive either:

- Arm 1 Bevacizumab 10 mg/kg by IV infusion once every 2 weeks
- Arm 2 Bevacizumab 10 mg/kg by IV infusion once every 2 weeks  
Irinotecan 340 mg/m<sup>2</sup> every 2 weeks (for patients receiving enzyme-inducing anti-epileptic drugs [EIAEDs]) or 125 mg/m<sup>2</sup> IV every 2 weeks (for patients not receiving EIAEDs)

Treatment continued until disease progression, unacceptable toxicity, or a maximum of 104 weeks. Patients in Arm 1 who experienced disease progression were permitted to be

transitioned to an optional post-progression phase to receive irinotecan plus bevacizumab at the discretion of the investigator and if they met eligibility criteria.

### **Study Population**

Adult patients ( $\geq 18$  years of age) with histologically confirmed GBM in 1<sup>st</sup> or 2<sup>nd</sup> relapse were eligible for the study. Patients must have received prior standard radiotherapy for GBM and prior temozolomide. Prior surgical procedure might have been biopsy, partial resection, or full surgical resection. Radiographic demonstration for progression following prior therapy, with bi-dimensionally measurable disease (minimum 1 cm in one diameter) was required. Patients may not have received more than two prior chemotherapy regimens. Patients must have had a Karnofsky performance  $\geq 70$ . If the patient was taking corticosteroids at baseline, steroids dose must have been stable or decreasing for  $\geq 5$  days prior to baseline MRI.

### **Efficacy Endpoints and Statistical Analysis**

#### **Per Genentech**

The primary efficacy endpoints, per Genentech, were IRF (Independent Radiologic Facility) assessed 6-month PFS and objective response rate for each treatment arm. Secondary endpoints were duration of response and safety.

Objective response is defined as a response of CR or PR which was confirmed at  $\geq 4$  weeks apart. In addition, the sponsor incorporated corticosteroid use in the response evaluation. To be considered as a CR, corticosteroids use can not exceed physiologically detectable level. To be considered as a PR, the corticosteroid dose at the time of the MRI scan response should not have increased from baseline. The baseline is defined as the maximum dose used in the first 6 weeks from treatment initiation.

Historical control assumptions (per applicant):

The analysis of response rate and 6-PFS were based on data from historical controls. The objective response rate of the historical control for bevacizumab alone arm is assumed to be 5% based on the estimate from the salvage chemotherapy. The objective response rate of the historical control for bevacizumab + irinotecan arm is assumed to be 10% based on the estimate from irinotecan alone treatment. The 6-month PFS of the historical control for each bevacizumab arm and bevacizumab + irinotecan arm is assumed to be 15%.

Statistical Analysis (per applicant):

All pair-wise tests of the experimental arm versus historical control will be performed at a two-sided 0.025 significance level.

The exact 97.5% confidence interval for ORR was presented based on the Blyth-Still-Casella method. The comparison of ORR between each treated arm versus the historical control was based on the normal approximation for comparing two proportions.

PFS is defined as the time from randomization to documented disease progression, as determined by the IRF using the modified WHO Response Evaluation Criteria, clear clinical progression in the absence of an MRI determination of progression, or death from any cause, whichever occurs first. Patients who did not have disease progression or died were censored at the last MRI assessment date. Patients who started to receive alternative anti-tumor therapy prior to disease progression were censored at the last tumor assessment date prior to receiving the alternative therapy. For patients who experience the first disease progression or die more than 42 days after the last dose of study drug, data was censored at the date of the last tumor assessment prior to the last dose of study drug plus 42 days.

Six-month PFS and the corresponding 97.5% CI were estimated based on the Kaplan-Meier method. The comparison of the 6-month PFS rate between each treated arm versus the historical control was based on normal approximation for comparing two proportions.

#### **Per FDA**

For regulatory purposes, objective response rate per independent radiological review is the primary endpoint that will be considered to support accelerated approval.

As previously stated as a general principle and in meetings with the applicant prior to the submission, time to event endpoints, such as PFS, must be evaluated in randomized, controlled clinical trials since historically controlled trials do not provide direct evidence of treatment effect.

Based on the study design, the contribution of bevacizumab in the bevacizumab plus irinotecan arm can not be isolated. Hence, efficacy data from arm 2 of the trial can not be used to support drug approval and is not analyzed by the FDA.

FDA's primary review focus is on the objective response rate and the duration of response for the bevacizumab monotherapy.

FDA performed a sensitivity analysis for 6-month PFS based on similar definition to that used in the sponsor's analysis (see definition above) except that: 1) the exact 6-month was used as the cutoff time point instead of 5.52 months used by Genentech and 2) the censoring rule (i.e. censor patients who had progression or died at 42 days post the last treatment date at the last MRC assessment date prior to the last treatment date plus 42 days) was not utilized for the analysis.

Genentech indicated that 5.52-months was used in the calculation because this time period is equal to 24 weeks [= 168 days] divided by 30.3475 days per month. Since 6-

month cutoff time point was specified in the protocol and statistical analysis plan, FDA believes that the exact 6-month cutoff date should be used for response assessment.

## Results

Study Period: June 30, 2006 to September 15, 2007

Data cut-off date: September 15, 2007

A total of 167 patients (85 patients in the bevacizumab arm and 82 in the bevacizumab plus irinotecan arm) were enrolled in 11 investigational sites in the United States.

Patient demographic and prior treatment characteristics are shown in tables 2 and 3. Almost 70% of the patients were male, median age 54 years, 90% were Caucasian. Half of the patients were on corticosteroids at baseline and approximately 1/3 of the patients were on EIAED treatment at baseline.

**Table 2. Patient Demographics and Characteristics**

Characteristics		Bevacizumab N=85 (%)	Bevacizumab + Irinotecan N=82 (%)
<b>Gender</b>	Male	58 (68)	57 (70)
	Female	27 (32)	25 (31)
<b>Age</b>	median (range)	54 (23 – 78)	57.0 (23 – 79)
	< 40 years	11 (13)	12 (15)
	41 - 64	63 (74)	52 (63)
	≥ 65 years	11 (13)	18 (22)
<b>Race</b>	White	77 (91)	73 (88)
	Black	3 (4)	2 (2)
<b>KPS</b>	70 - 80	47 (55)	51 (62)
	90 – 100	38 (45)	31 (38)
<b>Corticosteroids at Baseline</b>		43 (51)	43 (52)
<b>EIAEDs at Baseline</b>		18 (21)	30 (37)

**Table 3. Prior Cancer Treatment**

<b>Treatment</b>	<b>Bevacizumab N=85 (%)</b>	<b>Bevacizumab + Irinotecan N=82 (%)</b>
Surgery + RT + TMZ	85 (100)	82 (100)
Surgery		
Partial Resection	42 (49)	44 (54)
Complete resection	36 (42)	31 (38)
Biopsy Only	7 (8)	7 (9)
Systemic Therapy		
1st relapse	69 (81)	66 (81)
2nd relapse	16 (19)	16 (19)

### **Study Conduct**

Overall, the study was well-conducted with a small number of eligibility violations and protocol deviations. Tumor assessment was satisfactory with minimal missing data. One patient had missing tumor assessments as performed by investigator at wk 18 and 3 patients had missing assessments at week 36. MRI scans were retrospectively collected and were available to IRF for response assessment in all patients except for one scan for one patient in the bevacizumab arm.

### **Efficacy Results**

Objective response results per Genentech are shown in Table 4. The objective response rate was reported to be 28.2% in the bevacizumab alone arm (1 CR, 23 PR) and 37.8% in the bevacizumab plus CPT-11 arm (2 CR, 29 PR). Median duration of response was 5.6 months and 4.3 months respectively.

**Table 4. Applicant’s Objective Response Rate and Median Duration of Response per IRF**

	<b>Bevacizumab N=85</b>	<b>Bevacizumab + Irinotecan N=82</b>
<b>Objective Response n (%)</b>	<b>24 (28.2%)</b>	<b>31 (37.8%)</b>
CR	1	2
PR	23	29
97.5% CI	[18.5%, 40.3%]	[26.5%, 50.8%]
p value (historical control) <sup>a</sup>	<0.0001	0.0001
<b>Median Duration of Response (95% CI)</b>	<b>5.6 months</b> [3.0, 5.8]	<b>4.3 months</b> [4.2, -]
# progression	19	16

<sup>a</sup> ORR of Bevacizumab arm vs. 5% ORR with salvage chemotherapy; ORR of Bevacizumab arm+CPT-11 vs. 10% ORR with irinotecan alone

#### **FDA’s Assessment of Objective Tumor Response**

Genentech submitted radiographic images for all patients deemed as responders by an Independent Review Facility (IRF) to the FDA for review. A neuroradiologist, Special Government Employee (SGE) was assigned to assess the quality of the radiographic images and to confirm the objective responses.

Tumor measurements by investigator and the independent review facility (IRF) were included in the submission and reviewed.

The objective response rate determined by the FDA was 25.9% (22/85). Twenty-two patients achieved partial remission, with median duration of response 4.2 months (95% CI 3.0, 5.7).

The response rates and duration of response by the investigators and Genentech are also shown in Table 5. The FDA’s review did not confirm response as claimed by Genentech for two patients (ID 20064 and ID 20017).

**Table 5. Objective Response and Median Duration of Response per FDA Bevacizumab Arm**

	<b>Bevacizumab N = 85 (%)</b>		
	<b>Investigator</b>	<b>Genentech</b>	<b>FDA</b>
<b>Objective Response</b>	35 (41.2)	24 (28.2)	22 (25.9)
CR/PR	2/33	1/23	0/22
97.5% CI	[30.6, 52.3]	[18.5, 40.3]	[15.9, 37.8]
<b>Median Duration of Response (95% CI)</b>	<b>8.1 months</b> (5.6, -)	<b>5.6 months</b> (3.0, 5.8)	<b>4.2 months</b> (3.0, 5.7)

### Independent Review Concordance/Discordance Rate

The known histology of pseudopalisading necrosis of GBM, in addition to the effects of prior surgery and radiation therapy, result in an irregular configuration and makes tumor size difficult to measure by MRI scan. The FDA reviewers examined the rate of concordance/discordance between the neuroradiologists assigned to read the MRI films.

The IRF assessment procedure consisted of two radiologists (R1 and R2) assigned to read all MRI films for each patient. Readings were performed independently and the readers were blinded to the investigator's response assessment. If readings were discordant, a third radiologist (R3) performed adjudication of radiology results. An oncologist reviewed all pertinent corticosteroid information.

**Table 6. Concordance/Discordance between IRF Readers**

	<b>Bevacizumab # scans = 308</b>	<b>Bevacizumab + Irinotecan #scans = 339</b>
R1 agrees with R2	163 (52.9%)	188 (55.5%)
Discordance between R1 and R2	145 (47.1%)	151 (44.5%)
R3 (adjudicator) did not agree with R1 and R2	44 (14.3%)	37 (10.9%)

A total of 308 scans from patients enrolled in the bevacizumab alone arm were collected and submitted to the IRF for review. R1 agreed with R2 in  $\approx 50\%$  of the time and adjudication by a 3<sup>rd</sup> radiologist was required. R3 did not agree with either R1 or R2 in 14% of the scans. Findings from the bevacizumab/irinotecan arm are also shown (Table 6).

The degree of discordance underscores the difficulties in accurately assessing response or progression in GBM.

## Six- Months Progression Free Survival

Sponsor's 6-month PFS results are shown in the following table.

**Table 7. Six-Month PFS by IRF per Genentech**

	<b>Bevacizumab N=85</b>	<b>Bevacizumab + Irinotecan N=82</b>
Patients with PFS event up to 6 months	44 (51.8%)	35 (42.7%)
Disease progression	38 (44.7%)	31 (37.8%)
Death	6 (7.1%)	4 (4.9%)
Event free at 6 months (97.5% C.I.)	42.6% (29.6%, 55.5%)	50.3% (36.8%, 63.9%)

Median follow up time: 3 months (25%, 75%) = (1.5, 6.9)

The median progression free survival times were 4.2 months (95% CI 2.9, 5.8) and 5.6 months (95% CI 4.4, 6.2) for bevacizumab and bevacizumab plus irinotecan, respectively.

Genentech claims that 6-month PFS is significantly higher ( $p < 0.0001$ ) than the assumed historical control rate of 15% for patients receiving salvage chemotherapy for GBM.

As previously stated, given that there is no comparator for the bevacizumab plus irinotecan arm, the FDA's focus is on the bevacizumab alone arm. FDA findings for 6-month PFS in the bevacizumab alone arm is shown in Table 8.

**Table 8. Six-month Progression Free Survival Rate- Bevacizumab Arm**

	<b>Bevacizumab Arm N = 85 (%)</b>		
	<b>Investigator</b>	<b>Genentech</b>	<b>FDA</b>
Patients with PFS event (up to 6 months)			
Disease progression	47 (55.3)	44 (51.8)	50 (58.8)
Death	41 (48.2)	38 (44.7)	42 (49.4)
	6 (7.1)	6 (7.1)	8 (9.2)
Event free at 6 months (97.5% C.I.)	<b>43.6%</b> (33.0%, 54.3%)	<b>42.6%</b> (29.6%, 55.5%)	<b>36.0%</b> (24.0%, 48.0%)

The 6-month PFS rate in bevacizumab-treated arm, per FDA, is 36.0% (97.5% CI 24.0%, 48.0%). The six-month PFS rates were 43.6 % per Genentech and 42.6% per the investigator. Note that the FDA analysis had 6 more PFS events as compared with the Genentech's analysis. The difference of the number of events between the Genentech's

and the FDA's analysis is that Genentech used a 5.52 month cut-point in the computation, while FDA used 6 month cut-point (refer to comment 1 below). In addition FDA did not censor patients who had events that occurred more than 42 days post last treatment date (refer to comment 2 below).

*Comment 1:* The sponsor-performed analysis for the 6-month PFS rate based on the SAP specified analysis except that they used a 5.52 month cut-point (calculated by stating that 24 weeks is equal to 168 days divided by 30.3475 days per month, which equals 5.52 months) instead of 6 months for determination of the 6-month PFS rate.

Six-month PFS rates estimate based on 6-month or 5.52 months is different on this study. Three more PFS events are identified when the cutoff time point of 6 months is used instead of 5.52 months. The 6-month PFS rate is 43% using 5.52 months cutoff date as compared to 38% using the exact 6 months cutoff date.

*Comment 2:* As noted above, the applicant incorporated a censoring rule, i.e. patients who had progression or died more than 42 days post the last treatment date will be censored at the last MRC assessment date prior to the last treatment date plus 42. The sponsor explained that the reason for incorporating this censoring rule was to apply uniform time period for follow-up for all patients based on frequency of tumor assessment.

The FDA does not find the applicant's explanation for censoring patients who had progression or died more than 42 days post the last treatment date compelling. The majority of patients who had the progression events or deaths after the last treatment date +42 days also received non-protocol anti-cancer therapy (NPT), so these patients would be censored at the last tumor assessment date prior to the NPT date regardless of whether this censoring rule is in place or not. After excluding the applicant's censoring rule, the FDA reviewer identified three more events and the 6-month PFS event rate became 36% (97.25% CI=[24%, 48%]).

## **Baseline Characteristics of Responders**

The following table summarizes the distribution of the baseline characteristics among the responders. Please note that many subgroups had very few patients.

Thirteen patients were on corticosteroids at baseline; as part of responder criteria, all responders had decreases in steroid dose requirements at the time of radiographic response.

**Table 9. Baseline Characteristics for Responders**

<b>Baseline Characteristics</b>		<b>N = 22 (%)</b>
Age	<65 years	19 (86.4)
	≥65 years	3 (13.6)
Sex	Female	11 (50)
	Male	11 (50)
Race	White	19 (86.4)
	Non-white	3 (13.6)
KPS	70-80	10 (45.5)
	90-100	12 (54.5)
Relapse	First	20 (90.9)
	Second	2 (9.1)
Corticosteroid at baseline	Yes	13 (59.0)
	No	9 (41.0)

**Post-Progression Phase:**

Forty four patients (52%) on the bevacizumab alone arm were entered in the post-progression phase and received bevacizumab plus irinotecan after progression. According to Genentech, no objective responses were observed.

**Exploratory Analysis - Neurocognitive Function**

Neurocognitive function was assessed using standardized psychometric instrument. Three domains of neurocognitive function were assessed using the following 6 tests: the Hopkins Verbal Learning Test (HVLT) for immediate recall, delayed recall, and recognition (i.e. Part A, B, C, respectively); Trail Making Test A for visual-motor scanning function; Trail Making Test B and the Controlled Oral Word Association (COWA) for two executive function tests. Tests were to be performed at baseline

FDA does not consider the time to neurocognitive progression specified in the statistical analysis plan (defined using change from baseline in the normalized scores of 3 standard deviation) as an appropriate method to analyze the neurocognitive function data, so does Genentech. Genentech provided a post-hoc analysis based on Reliable Change Index to identify percentages of patients who had improved or declined. FDA does not consider these instruments fully validated. The validity of the proposed cutoff point based on Reliable Change Index is unclear. Since the study did not include a comparator arm and the concern about the validity of the instruments, any attempt to quantify the results of the neurocognitive function is considered exploratory in nature.

FDA did attempt to analyze the data submitted for responders. The percentage of patients missing data for these six instruments among the responders at week 24 or earlier ranged from 0% - 32%. Based on the data from the responders, no firm conclusion can be drawn from the data provided. FDA noted a slightly decrease in delayed recognition scores (HVL T part C), however, it is unclear if the decrement is due to reliability of the instrument or a true drop in score.

## Safety Results

The safety population consists of 84 patients in the bevacizumab arm and 79 in the bevacizumab/irinotecan arm who received any amount of bevacizumab or irinotecan (total 163 patients). Adverse events were coded according to MedDRA and graded using NCI CTCAE v3.0.

The overall incidence of adverse events is shown in Table 11. A total of 98.8% of patients experienced an AE. Serious AEs occurred in 26.2 % of patients in the bevacizumab arm. Overall, the incidence of serious AEs and AEs leading to Avastin discontinuation was higher in the bevacizumab plus irinotecan arm.

**Table 11. Overall Incidence of Adverse Events**

	<b>Bevacizumab N=84 (%)</b>	<b>Bevacizumab + Irinotecan N=79 (%)</b>
<b>Any AE</b>	83 (98.8)	79 (100.0)
<b>SAE</b>	22 (26.2)	34 (43.0)
<b>Grade 3-4 AE</b>	39 (46.4)	52 (65.8)
<b>D/C Avastin due to AE</b>	4 (4.8)	14 (17.7)
<b>Adverse event/other</b>	3 (3.6)	2 (2.6)

### Adverse Events Leading to Discontinuation of Bevacizumab

A total of 18 patients discontinued bevacizumab due to adverse events occurring on study (11%, 18/163). Causes include wound healing complications (2), cerebral hemorrhage (3), fatigue (2), seizure (2), myocardial infarction (1), RPLS (1), infection (1), gastrointestinal perforation (1) and others.

## Common Adverse Events

Common AEs occurring in more than 15% of the patients during the planned treatment period are shown in the following table. The most common AEs occurring in patients who received bevacizumab alone were fatigue (45.2%), headache (38.1%) and hypertension (29.8%). Fatigue, gastrointestinal events (nausea, vomiting, constipation and abdominal pain) and neutropenia occurred at a higher frequency in the bevacizumab plus irinotecan arm. Epistaxis, a known bevacizumab associated event occurred in approximately 20% of the patients in both arms.

**Table 12. Common Adverse Events Occurring in > 15% Incidence**

<b>Adverse Event</b>	<b>Bevacizumab % (N=84)</b>	<b>Bev + Irinotecan % (N=79)</b>
Overall	98.8	100.0
Fatigue	45.2	75.9
Headache	36.9	32.9
Hypertension	29.8	21.5
Epistaxis	19.0	22.8
Diarrhea	21.4	74.7
Nausea	15.5	67.1
Vomiting	6.0	36.7
Constipation	14.3	40.5
Abdominal pain	3.6	29.1
Lymphopenia	7.1	16.5
Neutropenia	2.4	15.2
Hyperglycemia	16.7	13.9
Peripheral edema	13.1	17.7
Convulsion	15.5	19.0
Aphasia	13.1	17.7
Confusion	14.3	21.5

The incidence of Grade 3-4 Adverse Events occurring at > 5% incidence on study is shown in Table 13. Overall, more grade 3-4 AEs were reported in the bevacizumab plus irinotecan arm. The most common grade 3-4 AEs reported in the bevacizumab alone arm were convulsion, fatigue, and hypertension.

**Table 13. Safety: grade 3-4 AEs > 5 % incidence**

<b>AE</b>	<b>Bevacizumab N=84 (%)</b>	<b>Bevacizumab + Irinotecan N=79 (%)</b>
Any Grade $\geq$ 3 AE	39 (46.4)	52 (65.8)
Convulsion	5 (6.0)	11 (13.9)
Fatigue	3 (3.6)	7 (8.9)
HTN	7 (8.3)	1 (1.3)
DVT	2 (2.4)	5 (6.3)
Neutropenia	1 (1.2)	7 (8.9)
Diarrhea	1 (1.2)	4 (5.1)
Pneumonia	1 (1.2)	4 (5.1)

**Significant Adverse Events Known to be Associated with Bevacizumab**

The overall incidence of adverse events and of grade 3-4 events known to be associated with bevacizumab occurring on study are shown below. Table 14 includes all AEs known to be associated with bevacizumab from both treatment arms as well as AEs that occurred during the post-progression phase.

Bleeding/hemorrhage occurred in 39.9 % of the patients, with 3/67  $\geq$  grade 3 in severity. Grade 1-2 epistaxis was the most common bleeding event (25.8%). One patient enrolled in the bevacizumab plus irinotecan arm experienced grade 5 retroperitoneal hemorrhage. Hypertension occurred in 31.9% of the patients with 4.9 %  $\geq$  grade 3. Venous thromboembolic event was reported in 8.0 % of the patients, with DVT and pulmonary emboli as the most common causes. The incidence of arterial thromboembolic events, wound healing complications, proteinuria, gastrointestinal perforation and RPLS (reversible posterior leukoencephalopathy syndrome) are also shown in Table 14.

**Table 14. Known Bevacizumab Related Adverse Events on Study**

AEs known to be associated With Bevacizumab	Safety Population N = 163 (%)	
	Any AE	Grade 3-5
<b>Bleeding/Hemorrhage</b>	65 (39.9)	3* (1.8)
Epistaxis	42 (25.8)	-
CNS hemorrhage	8 (4.9)	2 (1.2)
<b>Hypertension</b>	52 (31.9)	8 (4.9)
<b>Venous thromboembolic events</b>	13 (8.0)	12 ^ (7.4)
<b>Arterial thromboembolism events</b>	10 (6.1)	5 (3.1)
<b>Wound-healing complications</b>	9 (5.5)	4 (2.5)
<b>Proteinuria</b>	6 (3.7)	1 (0.6)
<b>Gastrointestinal perforation</b>	3 (1.8)	3 (1.8)
<b>RPLS</b>	1 (0.6)	0 (0.0)
<b>Infection/Neutropenic infection</b> N = 84 (bevacizumab alone)	46 (54.8)	8& (9.5)

\* One grade 5, retroperitoneal hemorrhage

^ One grade 5, pulmonary emboli

& One grade 5, neutropenic infection

*Comment:* The incidence of events known to be associated with bevacizumab does not appear to be significantly increased in GBM patients based on this trial, which lacks an internal control. Events of special concern in this population are CNS hemorrhage, wound-healing complications and venous thromboembolism. Because these events are also inherent to patients with GBM and associated prior surgery/radiation therapy, the attribution of these AEs to either bevacizumab or primary disease or both can not be determined with certainty.

### Deaths on Study

At the time of the data cut-off, 45.2% of the patients in the bevacizumab arm and 51.9% in the bevacizumab plus irinotecan arm had died. Death was attributed to disease progression in 41.7 % of the patients in the bevacizumab arm and 48.1 % in the irinotecan containing arm. There were 2 deaths possibly or probably related to bevacizumab: retroperitoneal hemorrhage (bevacizumab plus irinotecan arm, ID 20164)

and neutropenic infection (bevacizumab arm, ID 20153). Other fatal AEs were: pulmonary emboli (1), complication due to tumor debulking surgery (1), convulsion (1) and clinical deterioration (1).

## **NCI 06-C-0064E**

Study NCI 06-C-0064E is a single-arm, single-center trial of bevacizumab for patients with recurrent high-grade gliomas. The study was conducted at NCI, Bethesda, MD by Dr. Howard Fine.<sup>7</sup>

### **Study Design**

Eligible patients with histologically confirmed intracranial malignant glioma and evidence of tumor progression by MRI after radiotherapy were eligible for study. There was no limit regarding prior systemic chemotherapies. Eligible patients were entered in to two cohorts: glioblastoma cohort (high grade GBM or gliosarcoma) and anaplastic astrocytoma cohort.

The study objectives were to determine the anti-tumor activity of bevacizumab in patients with recurrent high-grade gliomas as determined by PFS and to obtain safety information.

Treatment consisted of bevacizumab 10 mg/kg by IV infusion every 2 weeks on a 4-week cycle. Treatment continued until progressive disease or significant toxicity.

Safety information was coded according to NCI CTC V3.0

### **Summary Results**

Per agreement with Genentech, objective tumor response and duration of response from the glioblastoma cohort, as determined by independent radiologic review would provide support for the activity of bevacizumab. Data from the anaplastic astrocytoma cohort was not required.

The MRI scans and clinical data of the patients enrolled in the glioblastoma cohort were provided by the NCI to Genentech for retrospective review and submission.

### **Patient characteristics**

From January 2006 to September 2007, 56 patients were enrolled in the glioblastoma cohort. One patient was discontinued from study before receiving treatment. At the time of data cut-off, 54 patients had discontinued study: 41 (75%) due to disease progression, 11 (19.6%) due to adverse event, and 2 due to patient request to discontinue.

Of the 56 patients, 98% were Caucasian, 54% male. Median age was 54 years old (range 21 - 69). Sixty eight percent of the patients had KPS 90 -100. All patients had received prior surgery, radiation therapy, and temozolomide or other systemic therapy.

### **Efficacy - Objective Response**

The objective response, as determined by the IRF review was 19.6% (11/56, 95% CI 10.9, 31.3). No complete responses were observed.

Median duration of response was 3.9 months (95% CI 2.4, 17.4 mos)

MRI scan and IRF tumor measurements forms were reviewed by the FDA. FDA agrees with Genentech's findings.

### **Safety**

The incidence of grade 3-4 adverse events that occurred in  $\geq 5\%$  of the patients were: lymphopenia (25.5%), hypophosphatemia (10.9%), seizure (7.3%) and thromboembolism (9.1%).

The following  $\geq$  Grade 3 adverse events known to be related to bevacizumab were reported by the investigator: thrombosis/thrombus/embolism 12.7% (N=7), hypertension 3.6% (N=2), and 1 event (1.8%) each of arterial thromboembolic event, gastrointestinal perforation and wound healing complication.

Eighty percent of the patients had died at the time of data cut-off (June 3, 2008), with 77% of the patients dead due to disease progression. One patient died of pulmonary emboli and cerebral vascular accident and a second patient had venous thromboembolic event, followed by sudden death.

## DISCUSSION

Genentech Inc. seeks accelerated approval for Avastin® (bevacizumab), as a single agent for the treatment of patients with previously treated GBM based on a 25.9% and 19.6% objective response rate in two historically-controlled, single-arm or non-comparative studies. No complete responses were observed. Median durations of response were 4.2 months and 3.9 months, respectively.

In the AVF3708g trial, serious AEs were reported in 26.2% of the subjects in the bevacizumab arm. The most common bevacizumab associated toxicities were: bleeding/hemorrhage (41.1%), hypertension (32.5%) and venous/arterial thromboembolic event (14.0 %). Other serious AEs known to be associated with bevacizumab were also reported: wound-healing complications (6.1%), proteinuria (3.6%) and gastrointestinal perforation (1.8%). There were 2 deaths possibly related to bevacizumab: retroperitoneal hemorrhage and neutropenic infection. CNS hemorrhage, an AE of special concern in this population was reported in 8 patients (4.9%), with 2 (1.2%) being  $\geq$  grade 3. Overall, the incidence of events known to be associated with bevacizumab does not appear to be significantly increased in GBM patients based on this externally controlled trial.

Important issues to be taken into consideration for this application are:

### 1. Objective response as endpoint to support approval of GBM

Objective response has not been used as the basis for accelerated approval for GBM. It is unclear whether the response rate and duration of response seen in this application are of sufficient magnitude to serve as surrogate for clinical benefit for the purpose of accelerated approval in refractory glioblastoma.

GBM are morphologically heterogeneous tumors with varying amounts of edema and necrosis. Due to the diffuse nature of the tumor histology, the anatomical measurement of the enhancing tumors on MRI has several problems<sup>3</sup> and its value as a surrogate endpoint for survival in patients with GBM is unclear.

Objective response as an endpoint to support temozolomide approval for GBM, based on a 5% response rate, was previously discussed at the ODAC meeting of January 12, 1999<sup>4</sup>. Given the issues with accuracy of measuring tumor size in order to determine responses in patients with recurrent glioma, ODAC concluded that “objective response was not an adequate surrogate for clinical benefit for the purpose of accelerated approval of a drug in this population”. ODAC did state however, that “objective response could be an adequate surrogate for clinical benefit under the proper parameters. The response must be well-defined and of sufficient magnitude to overcome the noise level resulting from other variables. Both baseline and follow up quality of life data should be included for all responders”.

This issue of response as an approval endpoint was further discussed at a Public Workshop on Clinical Trial End Points in Primary Brain Tumors on January 2006<sup>5</sup>.

There was agreement among the discussants that a response rate of sufficient magnitude (e.g. greater than 30%) was likely to be associated with clinical benefit as the magnitude of response rate would outweigh the uncertainties associated with interpreting MRI scans.

## **2. Relevance of MRI response criteria in GBM, in the setting of VEGF inhibition by bevacizumab**

The validity of objective response as an endpoint to support approval for GBM is further complicated by the questionable relevance of standard MRI response criteria in the setting of VEGF inhibition. Bevacizumab neutralize VEGF-induced vascular permeability, which stabilizes the blood-brain barrier, leading to decrease in extravasation of fluid into brain parenchyma, resulting in an improvement in edema. This translates into a decrease in gadolinium enhancement in the MRI scan, which should not be taken as anti-tumor effect.

Retrospective studies of MRI in patients with high grade gliomas treated with bevacizumab and chemotherapy have shown striking reduction in edema and response in necrotic appearing areas, whereas solid areas of tumor continued to grow<sup>6</sup>. Profound reductions in enhancement on MRI scans have been observed as soon as 24 hours after the first dose of bevacizumab.<sup>7</sup> Bevacizumab has also shown to reduce radiation necrosis by decreasing capillary leakage and the associated brain edema, with decrease in corticosteroid requirement.<sup>8</sup> These findings indicate that imaging changes seen in recurrent GBM following bevacizumab therapy is distinct from that of other treatments.<sup>9</sup>

It is unclear whether the radiographic improvement accompanied by decrease requirement in steroids reported in this application is the result of an anti-tumor effect of bevacizumab or represents radiographic improvement due to improvement in tumor necrosis and tumor associated brain edema.

ODAC advice is requested.

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