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BRIEFING BOOK

ONCOLOGY DRUGS
ADVISORY COMMITTEE MEETING

AVASTIN® (Bevacizumab)

Genentech, Inc.
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25 February 2009

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION
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1. **EXECUTIVE SUMMARY**

Genentech has asked the U.S. Food and Drug Administration (FDA) under its accelerated approval program to consider a supplemental Biologics License Application (sBLA) for Avastin for the treatment of patients with previously treated glioblastoma.

Glioblastoma is devastating to patients and their families, and new treatments are urgently needed. There are no effective FDA-approved systemic therapies or other widely accepted treatments for patients whose disease has relapsed following initial treatment, and virtually no improvements have been made since the 1970s. This sBLA is based on a well-conducted Phase II trial that showed a response rate and response duration of a magnitude that exceeded expectations, a high rate of patients without disease progression at 6 months, and associated decreases in corticosteroid use. Results were markedly better than those reported for available therapies.

An accelerated approval of Avastin in relapsed glioblastoma would provide labeling guidance to physicians and help ensure earlier availability of Avastin to a severely under-served patient population. Results presented in this sBLA meet the criteria required for the accelerated approval:

- Relapsed glioblastoma is a serious, life-threatening disease for which effective therapies are urgently needed.
- The results of the Phase II trial demonstrate a substantial improvement in objective response rate and disease stabilization compared with prior studies in relapsed glioblastoma that used available therapies.
- These results are reasonably likely to predict clinical benefit in patients with previously treated glioblastoma. Results based on independent review and conservative response criteria demonstrate a clinically compelling magnitude of effect.
- Genentech, in collaboration with Roche, will initiate a large, randomized, double-blinded, placebo-controlled, multicenter, global, Phase III trial this year to confirm the clinical benefit of Avastin for the treatment of patients with glioblastoma.
Glioblastoma Is a Serious, Life-Threatening Disease

Glioblastoma is a rapidly progressing and universally fatal cancer that affects approximately 10,000 people per year in the United States (SEER 1973–2005, data on file). The most notable impact on patients is rapid neurologic deterioration, affecting the ability to perform everyday functions, such as eating, walking, and talking. As the tumor invades brain tissue, it can also distort aspects of personality and identity, such as mood, memory, emotion, and intelligence. Median survival in newly diagnosed patients with best available treatments is 14.6 months. Nearly all patients diagnosed with glioblastoma will experience relapse of this aggressive cancer following first-line treatment.

There are no widely accepted systemic therapies (approved or unapproved) for previously treated glioblastoma. Chemotherapies approved in the 1970s (carmustine and lomustine) provide little clinical benefit. Currently, many patients are offered no further therapeutic intervention after first-line treatment. Others may be offered experimental treatments or marginally effective therapies. Historical evidence suggests that even with experimental treatments, the objective tumor response rate is less than 10%, and typically fewer than 20% of patients are progression free at 6 months.

Avastin Provides Substantial Improvement over Currently Available Treatment

Avastin is a humanized monoclonal antibody that inhibits the activity of human vascular endothelial growth factor (VEGF). The rationale for the development of Avastin in glioblastoma is based on the central role VEGF plays in this disease. Glioblastomas express high levels of VEGF and are highly vascularized. Overexpression of VEGF and its receptors is associated with poor prognosis and shorter survival in this disease setting.

The Phase II study AVF3708g enrolled 167 patients with previously treated glioblastoma, the largest Avastin clinical trial to date in this patient population. In this study, single-agent Avastin (85 patients) demonstrated a clinically meaningful objective response rate and duration of response and a 6-month progression-free survival rate that was better than historical controls treated with available therapies.
Key Results from the Phase II Study (Single-Agent Avastin Arm)

- Objective response rate (tumor shrinkage of at least 50%) by independent review was 28.2%, which is substantially increased over rates for available therapies (depicted in the graph below).

- Responses were durable, with median response duration of 5.6 months.

- Six-month progression-free survival was 42.6%, which is approximately double that seen with available therapies.

- Patients who experienced an objective response or stable disease at 6 months were on stable or reduced doses of corticosteroids.

- Median overall survival was 9.3 months, with 38% of patients surviving more than 1 year after initiation of Avastin therapy.

- Findings in this study are supported by results from an independent NCI-sponsored study of 56 patients and by results from the Avastin + irinotecan arm enrolled in Study AVF3708g (82 patients).

Note: Confidence intervals are 97.5% for Study AVF3708g and 95% otherwise.

Avastin was well tolerated, and no new safety signals were observed. The safety profile of Avastin was generally consistent with its established profile described in the AVASTIN® Package Insert and that observed in the estimated 370,000 patients treated to date across multiple tumor types. The incidence of selected adverse events of concern in brain tumors, including central nervous system hemorrhage, seizure, and venous thromboembolic events, was generally consistent with rates based on previous experience with Avastin and/or on historical rates for this patient population. Craniotomy wound-healing complications, including wound dehiscence and cerebrospinal fluid leak, occurred in 2.5% of treated patients.
Objective Response Is Reasonably Likely to Predict Clinical Benefit

In glioblastoma, objective response to therapy is important, as displacement of normal brain due to tumor or mass effect from surrounding edema has severe clinical consequences and can result in disability and death. In 2006, a multi-disciplinary panel of glioblastoma experts, from government research, industry, and medical and academic centers, identified objective response rate and 6-month progression-free survival as important parameters for assessing anti-tumor activity and meaningful clinical impact in this rapidly progressive disease. Accelerated approval in brain cancer has been granted in the past on the basis of objective response rate in a single-arm trial (temozolomide for astrocytoma, 1999).

Genentech is confident in the objective responses demonstrated by Avastin in Study AVF3708g because conservative assessment criteria were used in this study:

- Confirmation of a high-risk glioblastoma population was ensured by the use of central pathology review.
- Response and progression-free survival were determined by independent radiology review, with responses confirmed at least 4 weeks after the initial report.
- Response was determined using the Macdonald criteria (commonly used in brain cancers), which require at least a 50% decrease in tumor size with stable or decreased corticosteroid dose.

On the basis of these criteria, the efficacy of Avastin was demonstrated by a durable objective response rate of clinically compelling magnitude that is reasonably likely to predict clinical benefit. In addition, the doubling of 6-month progression-free survival compared with historical controls, while less definitive, provides further evidence that the response rate observed in this study is reasonably likely to predict clinical benefit.

Commitment to Verify and Describe Clinical Benefit

To confirm the clinical benefit of Avastin in glioblastoma, Genentech, in collaboration with Roche, will initiate a large, randomized, double-blinded, placebo-controlled, multicenter, global, Phase III trial this year. The study, which is under review by the FDA through the Special Protocol Assessment procedure, will evaluate the efficacy and safety of Avastin in combination with radiotherapy and temozolomide for the treatment of patients with newly diagnosed glioblastoma.
2. **INTRODUCTION**

Glioblastoma is a devastating disease affecting approximately 10,000 patients per year in the United States for whom there are no widely accepted, effective systemic therapies (SEER 1973–2005, data on file). This aggressive type of brain cancer is associated with substantial morbidity, often in the form of rapid deterioration of cognitive and psychomotor function, and a 1-year survival rate of approximately 25% following failure of front-line treatment (Lamborn et al. 2008).

**Avastin in Glioblastoma**

Glioblastomas are among the most vascular tumors in the body and as such represent a particularly attractive target for treatment with bevacizumab (Avastin®). Compared with lower-grade anaplastic astrocytoma tumors, glioblastomas express extremely high levels of vascular endothelial growth factor (VEGF), are highly vascularized, and are associated with poor prognosis and shorter survival (Stefanik et al. 2001; Phillips et al. 2006; Kang et al. 2008).

This briefing document summarizes the clinical development program for Avastin in glioblastoma, which built on early promising observations from investigator-conducted studies and confirmed efficacy in relapsed patients in the Phase II setting. The program will culminate in a global Phase III program that seeks to definitively assess the benefit of Avastin in newly diagnosed patients.

**sBLA Submitted on 31 October 2008**

Genentech is seeking accelerated approval for single-agent Avastin for the treatment of patients with relapsed glioblastoma and has asked the U.S. Food and Drug Administration (FDA) to consider a supplemental Biologics License Application (sBLA) based on compelling results for objective response rate from the Phase II study. The contents of the sBLA have been discussed with the FDA and agreed upon. Genentech is requesting expansion of the Avastin label to include the following indication:

Avastin, as a single agent, is indicated for the treatment of patients with previously treated glioblastoma.
Contents of the sBLA in Relapsed Glioblastoma

The application is based on Study AVF3708g, a well-conducted, multicenter, Phase II trial in 167 patients (85 treated with single-agent Avastin) with relapsed glioblastoma that incorporated conservative and uniform tumor assessment by independent radiologic review.

Results from Study AVF3708g are further supported by the independent review of the objective response rate in an NCI-sponsored, Phase II trial of Avastin in 56 patients with relapsed glioblastoma (Study NCI 06-C-0064E).

Justification for Accelerated Approval

Accelerated approval is available for applications fulfilling the following criteria:

- The product treats a serious or life-threatening illness and provides a meaningful therapeutic benefit to patients over existing treatments.¹

- The claim is based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or is based on an effect on a clinical endpoint other than survival or irreversible morbidity.

- The sponsor conducts additional clinical research to further verify and define the clinical benefit.

An accelerated approval would provide labeling guidance to physicians and help ensure earlier availability³ of Avastin for the treatment of patients with relapsed glioblastoma, a severely under-served patient population.

In this briefing document, we will demonstrate that approval of single-agent Avastin for relapsed glioblastoma is justified under the accelerated approval procedure on the basis of the following:

- **Serious or life-threatening illness.** Glioblastoma is a rapidly progressing and universally fatal cancer that is devastating to patients. The most notable complication experienced by patients is the loss of neurologic function and ability to

---

¹ For example, patients unresponsive to or intolerant of available therapy or improved patient response over available therapy (21 CFR §601.40). Available therapy (and the term existing treatments) is defined as treatments that are specified in the approved labeling of regulated products, with only rare exceptions (Guidance for Industry, Available Therapy, CDER & CBER, FDA, July 2004, Clinical Medical).

² On the basis of epidemiologic, therapeutic, pathophysiologic, or other evidence (21 CFR §601.41).

³ Reinventing the Regulation of Cancer Drugs—Accelerated Approval and Expanding Access (March 1996), CBER.
perform everyday functions. There are no widely accepted or effective systemic treatments for patients with relapsed glioblastoma, and many patients with recurrent disease will receive best supportive care measures only. (See Section 3.)

- **Adequate and well-controlled trial.** The Phase II study AVF3708g was a well-conducted, multicenter trial in a defined population and incorporated central pathology, best current knowledge of glioblastoma imaging, and an independent radiologic review based on rigorous, prospectively defined, and systematically applied disease assessment criteria. (See Sections 3.3.3 and 5.1.)

As defined by the FDA (21 CFR §314.126), adequate and well-controlled studies may incorporate the use of a historical control arm in special circumstances. Given the high mortality associated with relapsed glioblastoma and the consistently poor activity of currently available therapies, the efficacy findings in the Avastin arm of the Phase II study were compared with historical controls (large pooled analyses from academic clinical trial networks and a control arm from a recent Phase III multicenter study) that were chosen to have similar patient populations and disease assessment criteria. (See Section 5.3.1.)

- **Meaningful benefit over existing therapies.** Treatment with Avastin in Study AVF3708g resulted in a durable objective response rate of 28.2% based on independent review, with median response duration of 5.6 months. These findings are substantial and compelling when compared with response rates of less than 10% for historical controls receiving available therapies or for the lomustine control arm of a recently reported Phase III study in a nearly identical patient population. The objective response rate finding was confirmed by independent review of the NCI-sponsored study and by responses seen in the Avastin+irinotecan arm of the Phase II trial. Avastin was well tolerated in this population, with a side effect profile that was consistent with product labeling and glioblastoma-specific events described in historical reports. (See Sections 5.2, 5.3, 5.4, and 6.)

- **Effect on a surrogate endpoint reasonably likely to predict clinical benefit.** Glioblastomas are aggressive tumors. As they grow within the enclosed space of the cranium, they distort adjacent brain tissue, causing increased intracranial pressure and structural abnormalities, which result in severe clinical complications, disability, and potentially death. Thus, reduction in tumor volume and associated edema would be expected to provide clinical improvements over and above local tumor effects. In the Phase II study, improvements in objective response rate were supported by the 6-month progression-free survival (PFS) rate of 42.6%, associated reductions in corticosteroid use, and median overall survival of 9.3 months, with 38% of patients surviving more than 1 year from the start of treatment. In addition, objective response by independent review was predictive of overall survival in this study, based on landmark analyses. (See Sections 5.1 and 5.3.)
Additional study to verify clinical benefit. To further study Avastin in glioblastoma, Genentech, in collaboration with F. Hoffmann–La Roche, is initiating a global Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The study is designed to evaluate the efficacy and safety of Avastin when used in combination with radiotherapy and temozolomide, the current standard of care, for the treatment of patients with newly diagnosed glioblastoma. The FDA is reviewing the protocol for this study through the Special Protocol Assessment procedure, and the study is planned to commence in Q2 2009. (See Section 4.2.2 and Appendix A.)
3. RELAPSED GLIOBLASTOMA

3.1 DIAGNOSIS AND DISEASE COURSE

Glioblastoma, also known as Grade IV astrocytoma, is the most common primary brain tumor in adults. Newly diagnosed glioblastoma accounts for approximately 50% of the 18,820 new diagnoses and 12,820 deaths due to primary malignant brain tumors in the United States (Jemal et al. 2006). Glioblastoma also represents the fourth leading cause of cancer-related deaths in individuals younger than 54 years of age (Jemal et al. 2006). Even with the best available therapy, patients with newly diagnosed glioblastoma have a median survival of 14.6 months from the time of diagnosis (Stupp et al. 2005).

Nearly all patients with glioblastoma will experience progression or recurrence of their cancer following primary treatment. The main goal of treatment for relapsed disease is tumor stabilization or shrinkage to help restore or preserve neurologic function and the capacity to perform daily activities, with the ultimate goal of reducing morbidity and prolonging overall survival (Macdonald et al. 2005). Despite available interventions, some of which contribute significant toxicities of their own, recurrent glioblastoma is universally and rapidly fatal, and the preservation of neurologic function remains elusive.

3.2 CLINICAL COMPLICATIONS

Clinical abnormalities are noted in newly diagnosed patients and become increasingly apparent with tumor relapse and progression. Glioblastomas are aggressive tumors, and as they grow within the enclosed space of the cranium, they distort adjacent brain tissue, causing mass effect and increased intracranial pressure (Jaeckle 1997). Patient-reported symptoms are generally related to the site and size of the lesion and vary among individuals (Scheibel et al. 1996). Symptoms related to increased intracranial pressure include headache, nausea, vomiting, personality changes, and slowing of psychomotor function. Seizures are a presenting symptom in 19%–47% of patients with brain tumors and may be difficult to treat (Moots et al. 1995; Pace et al. 1998; Hwang et al. 2004; Hildebrand et al. 2005; Salmaggi et al. 2005; CDER Application Number NDA 21029, Temozolomide).

Additional complications of glioblastoma include intra-tumoral hemorrhage (1.6%–7.8%), craniotomy wound-healing complications (0.5%–13.6%), and venous
thromboembolic disease (4.2%–31.2%) (Wakai et al. 1982; Kondziolka et al. 1987; Brandes et al. 1997; Lieu et al. 1999; Chang et al. 2003; Everaert et al. 2004; Streiff et al. 2004; Hildebrand et al. 2005; Salmaggi et al. 2005; Semrad et al. 2007; Simanek et al. 2007; Attenello et al. 2008; CDER Application Number NDA 21029, Temozolomide; Gliadel® Package Insert). The most catastrophic complication of glioblastoma is brain herniation, secondary to intracranial tumor and associated edema, resulting in severe morbidity or death.

In addition to symptoms caused by encroaching tumor, radiotherapy and chemotherapy affect the frontal-subcortical white matter, causing impairments in cognitive speed, apathy, sustained attention, bilateral fine motor control, memory retrieval, and frontal lobe executive function (e.g., mental flexibility; Meyers and Hess 2003; Meyers and Brown 2006).

On magnetic resonance imaging (MRI) scans, mass effect and increased intracranial pressure are demonstrated by sulcal effacement (swelling of the normal folds of the brain), midline shift (shifting of the brain to one side), ventricular compression (closing of the normal fluid-containing spaces of the brain), and blurred gray–white junction (swelling of the brain resulting in a blurring of clear demarcations of normal structures) (Leeds et al. 2002; Nelson and Chan 2005). Examples of brain imaging in glioblastoma are presented in Appendix B.

**Use of Corticosteroids**

Corticosteroids are used in brain tumor patients with symptomatic peri-tumoral edema to reduce mass effect and lower intracranial pressure; however, their effect on overall survival is at best modest (Schiff and Purow 2008). Dexamethasone is the agent of choice, as it has relatively little mineralocorticoid activity and is associated with a lower risk of infection and cognitive impairment compared with other corticosteroids (Wen et al. 2006). If focal neurologic symptoms are due to peri-tumoral edema, dexamethasone induces improvement within 48 hours (Wen et al. 2006).

Use of high-dose corticosteroids contributes to the overall treatment morbidity in glioblastoma patients, including predisposition to opportunistic infections and other well-recognized complications of chronic corticosteroid administration (Wen et al. 2006). Steroid reduction, or tapering, is initiated in patients with
stabilized disease and occurs over days to weeks, depending on the duration of use. The goal of tapering is to discontinue corticosteroid administration or to achieve or maintain physiologic levels equal to 1 mg/day dexamethasone (Wen et al. 2006). Unfortunately, ineffective treatment options for patients with relapsed disease have prevented major progress in this area.

3.3 DEVELOPMENTS IN THE TREATMENT OF BRAIN CANCER

3.3.1 Historical Perspective

The development of effective new therapies to treat primary brain tumors has been limited by the chemo-resistance of brain tumors and by problems with drug delivery to the central nervous system (CNS). Figure 1 illustrates the important milestones in the brain cancer field since the 1970s, when the first therapeutic agents were approved.

![Figure 1](image)

**Figure 1**
Milestones in the Development of Brain Cancer Therapies over the Last 30 Years

- Radiotherapy
  - Lomustine Approved 1976
  - Carmustine Approved 1977
- Levin Criteria: CT scans
- Macdonald Criteria: MRI+corticosteroids
- First U.S. Commercial MRI
- Carmustine Wafer Approved 1996
- Temozolomide relapsed AA Approved 1999
- Temozolomide first-line GBM Approved 2005
- Workshop on Brain Tumor Clinical Trial Endpoints

AA = anaplastic astrocytoma; CT = computed tomography; GBM = glioblastoma; MRI = magnetic resonance imaging.

* Accelerated approval.

Lomustine and carmustine were approved by the FDA in the 1970s, in the setting of palliative therapy or in combination with established therapy, in both primary and metastatic brain tumors for patients who had already received appropriate surgery and/or radiotherapy. Approval was based on studies using computed tomography (CT) to assess response and progression. Use of these agents is uncommon today and limited primarily by their relative lack of clinical benefit.
In a recently reported Phase III trial in relapsed glioblastoma in which 92 patients in the control arm were assigned to lomustine therapy, the overall response rate reported was 4%, median PFS was 1.64 months, and overall survival was 7.13 months (Fine et al. 2008). These disappointing trial results from a study using contemporary imaging methodology and patient management represent a “modern day” baseline for efficacy for the approved therapies.

Some progress was made in 1996 with the approval of the carmustine wafer (Gliadel®), which is indicated for patients with recurrent glioblastoma as an adjunct to surgery. However, the majority of patients with relapsed disease are not candidates for additional surgery, resulting in a large unmet need for this patient population.

In the late 1970s, Levin et al. proposed response criteria for patients with malignant (i.e., anaplastic) glioma receiving chemotherapy using CT scans, which introduced consistency to clinical studies of brain tumor (Levin et al. 1977). During the 1990s, important advances were made in the technology of disease imaging and in the rigor of disease assessment criteria. Following the introduction of MRI in the 1980s, Macdonald proposed new criteria, built on the World Health Organization (WHO) criteria (percent change in tumor area), that incorporated MRI and controlled for the influence of corticosteroids on brain tumor images (Macdonald et al. 1990).

In summary, while improvements have been made in the treatment of newly diagnosed patients with the approval of temozolomide in combination with radiotherapy in 2005, no further advances for patients with relapsed glioblastoma for whom additional surgery is not indicated have occurred since the late 1970s.
3.3.2 Current Treatment Options for Relapsed Glioblastoma

The current treatment options for patients with relapsed disease are illustrated in Figure 2.

Figure 2
Current Therapeutic Strategies for Relapsed Glioblastoma

- **Surgery**
  - Establish tissue diagnosis, debulk the lesion when feasible; gross total excision is associated with longer survival and improved neurologic function

- **Radiotherapy**
  - Temozolomide

- **Relapsed Glioblastoma**
  - Best Supportive Care
  - Further Surgery
  - Drug Treatment
    - FDA Approved Carmustine Wafer
    - FDA Approved Lomustine Carmustine
    - NCCN Guidelines
      - Platinum-Based Regimens
      - Temozolomide
      - Avastin+Irinotecan

**PCV** = procarbazine + lomustine + vincristine

Surgery may be indicated in a minority of relapsed patients with disease that is symptomatic from mass effect, but it results in only limited prolongation of survival (Keles et al. 2004). Survival may be improved by combining surgery with the carmustine wafer (Gliadel® Package Insert) for this selected group of patients. Radiotherapy for relapsed glioblastoma is controversial, and chemotherapy in these patients is inconsistent and associated with limited clinical benefit (Butowski et al. 2006; Yung et al. 2000).

Two agents approved in the late 1970s for relapsed glioblastoma, lomustine and carmustine, are not widely adopted outside of clinical trials because of their relative lack of clinical benefit. The National Comprehensive Cancer Network (NCCN) Practice Guidelines (NCCN 2008) reflect the consensus of accepted approaches to treatment that are more commonly used in relapsed glioblastoma. Trials studying platinum agents, combined procarbazine + lomustine + vincristine
(PCV), and single-agent temozolomide have reported objective response rates of 14%, 11%, and 5.4%, respectively (see Table 1). The study of platinum-based regimens included some patients with lower-grade tumors, which may not represent expected outcomes in glioblastoma patients, and the PCV regimen is used in a limited fashion owing to poor tolerability. Although temozolomide was approved in the first-line setting, the objective response rate of 5.4% was not sufficient to allow FDA approval in relapsed patients.

On the basis of the NCCN’s review of published data (Vredenburgh et al. 2007; discussed further in Section 4.2.1), the combination of Avastin and irinotecan was added to the NCCN Practice Guidelines in 2008.

<table>
<thead>
<tr>
<th>Agents Listed in the NCCN Practice Guidelines</th>
<th>Response Rate % (95% CI)</th>
<th>Six-Month PFS Rate % (95% CI)</th>
<th>Median Overall Survival Months (95% CI)</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum-based regimens b</td>
<td>14</td>
<td>NR</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>PCV c</td>
<td>11</td>
<td>29</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Temozolomide d</td>
<td>5.4</td>
<td>21 (13, 29)</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Avastin with irinotecan e</td>
<td>57 (39, 74)</td>
<td>46 (32, 66)</td>
<td>9.7 (8.0, 13.8)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; NR = not reported; PFS = progression-free survival.

a Overall survival data reported in weeks were converted to months assuming 4.35 wk/mo.
b Yung et al. 1991. Included both anaplastic astrocytoma and glioblastoma.
c Combination of procarbazine, lomustine, and vincristine; Kappelle et al. 2001.
d CDER Application Number NDA 21029, Temozolomide.
e Vredenburgh et al. 2007.

In summary, there are no widely accepted therapies (approved or unapproved) for patients with relapsed glioblastoma, with the exception of the minority of patients who are candidates for the carmustine wafer as an adjunct to a second surgery. There are considerable data on relatively ineffective treatments for patients with previously treated glioblastoma, with no overtly compelling data to establish a standard therapy. Treatment discussions and decisions resort to physician and patient preference based on experience, treatment administration considerations, and safety profile.
3.3.3 **Brain Tumor Endpoints Workshop**

In an effort to acknowledge the need for new agents to treat brain tumors and to address methodological challenges associated with brain tumor clinical trial design, the FDA co-sponsored a public workshop on brain tumor clinical trial endpoints with the American Association for Cancer Research and the American Society of Clinical Oncology in January 2006. This workshop focused on clinical trial endpoints intended to support the approval of new drugs for brain cancer and sought debate on the analytic validity of the instrument (e.g., imaging or patient-reported outcomes) and on how well individual endpoints reflect clinical benefit. The FDA summarized the regulatory landscape and the requirements for regular and accelerated approval:

- Endpoints supporting regular approval must show clinical benefit. In primary brain cancers, this could be demonstrated by an improvement in overall survival (the gold standard endpoint) or symptom palliation, if assessed by a hypothesis-driven, valid instrument within a randomized, blinded trial.

- Endpoints supporting accelerated approval must be surrogates that are reasonably likely to predict clinical benefit. Objective response rate can be reliably assessed in a single-arm trial. The 1999 accelerated approval of temozolomide for anaplastic astrocytoma was based on a response rate of 22% (12 patients), including five durable complete responses, in a single-arm trial. The magnitude of the response rate is an important consideration in a disease characterized by large inter-reviewer variability.

- Time-to-event endpoints, such as PFS, must be evaluated within randomized studies. A future Oncologic Drugs Advisory Committee (ODAC) could look at whether 6-month PFS is an established surrogate endpoint, or one that is reasonably likely to predict clinical benefit.

The published summary points of the workshop proceedings were as follows:

- Imaging techniques assess or predict progression well, although there are concerns about reproducibility. They assess or predict response less well, except in the case of complete responders or a dramatically high response rate.

- There was a consensus among panel members that 6-month PFS is an endpoint that should be pursued in trials in the near future.

- There was a consensus among panel members that patient-reported outcomes are not yet sufficiently developed to be acceptable in registration trials in primary brain tumors.
Additional discussion topics are summarized below:

- **Imaging Techniques.** MRI is the gold standard for measurement of brain tumors because it allows improved discrimination of anatomic structures, imaging in multiple planes, better resolution, and advanced imaging techniques. MRI should be performed both with and without contrast administration. MRI scans within 2–4 weeks of high-dose radiotherapy present interpretation challenges. The investigational agent’s possible effect on fluid diffusion and the blood–brain barrier may need to be incorporated into the imaging criteria. To ensure the highest degree of confidence, standard imaging protocols should be used and trials should be performed at tertiary care centers or using central review.

- **Objective Response.** The magnitude and duration of response, including any complete responses, are important to convincingly establish a therapeutic effect in a disease with inter-reader variation in the assessment of response. Response rates greater than 20% or 30% are considered likely to be associated with benefit. Responses must be durable and confirmed by a second scan. Patients should be clinically stable or improving, and the patient’s dose of corticosteroids must be stable or decreasing. Supportive improvements in functional or symptomatic status are helpful in demonstrating that the responses are clinically meaningful.

- **Progression-Free Survival.** Six-month PFS is a clinically meaningful endpoint. Two pooled analyses were presented that showed strong correlations between 6-month PFS and overall survival. Clinical progression needs to be taken into account because a patient who is deteriorating clinically but stable radiographically is not deriving benefit. Because freedom from progression is related to prognostic factors, it is preferable to have a control arm when assessing PFS. The magnitude of effect is an important consideration, with a doubling of PFS or an increase from 15% to 40% more compelling and likely to predict benefit.

- **Symptoms and Functional Endpoints.** From a regulatory standpoint, improvement in symptoms would be considered a direct clinical benefit, but these improvements need to be measured with the same rigor as used for other endpoints. Self-reported assessments are subject to bias because only the more highly functioning patients can report them. Concomitant medications, such as anti-seizure medications, can confuse interpretation of patient function. Neurocognitive battery testing has been established in brain metastases, but there is limited experience in primary brain cancer.
4. **BEVACIZUMAB IN GLIOBLASTOMA**

4.1 **SCIENTIFIC RATIONALE**

Targeting tumor vasculature in human cancer as a treatment strategy is based on the observation that tumor growth is dependent on angiogenesis (Folkman 1990, 1995, 1997). Bevacizumab is a recombinant, humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human VEGF. The increased VEGF expression and resulting angiogenic activity in glioblastomas are ideal targets for a directed therapy such as bevacizumab (Stefanik et al. 2001; Kang et al. 2008).

Histologically, glioblastoma is distinguished from lower-grade astrocytomas by the presence of one or both of two pathological features related to angiogenesis: microvascular proliferation and necrosis (Berger et al. 2002; Louis et al. 2007). Compared with lower-grade tumors, glioblastomas express extremely high levels of VEGF (Weindel et al. 1994; Schmidt et al. 1999; Wang et al. 1999; Lamszus et al. 2003; Salmaggi et al. 2003), are more highly vascularized, and are associated with shorter survival. Results of recent molecular profiling studies of glioblastoma tumors indicate that strong expression of VEGF and its receptors identifies a subset of glioblastomas characterized by higher levels of microvascular proliferation and an especially poor prognosis (Freije et al. 2004; Nigro et al. 2005; Phillips et al. 2006). Consistent with the hypothesis that an aggressive pattern of angiogenesis contributes substantially to the dismal prognosis of patients with glioblastoma, quantitative measures of angiogenesis have been shown to correlate with shortened survival in glioma patients (Yao et al. 2005; Bartels et al. 2006).

To directly monitor the effects of anti-VEGF in vivo on growth of a human glioblastoma cell line, the U87 line was tagged with a marker that emits a visible signal (firefly luciferase) and grafted into the brains of mice (Genentech, unpublished studies). In tissue culture, the optical luminescent signal emitted is directly proportional to the number of tumor cells present, and within the grafts, a very good correlation was seen between the optical signal and tumor volumes measured by T2-weighted MRI. Importantly, orthotopic grafts of U87 cells treated with anti-VEGF show parallel effects on suppression of tumor growth as monitored by luminescence and volumetric assessment by T2-weighted MRI. As the
luminescent signal is a direct read-out of tumor burden and is not subject to influences of vascular permeability, these findings indicate an effect of anti-VEGF in slowing tumor growth. This reduction in the rate of tumor growth was accompanied by a survival benefit in the mice receiving anti-VEGF treatment.

A major hurdle to the development of effective therapies for glioblastoma is the difficulty of achieving effective drug delivery. The vasculature of the normal brain is characterized by tight junctions between endothelial cells that effectively preclude the passage of many molecules into the brain. This blood–brain barrier effectively blocks most proteins and many pharmacologic agents from passing from the circulation into the brain. While the blood–brain barrier is anticipated to impede delivery of therapeutic antibodies to normal brain, it is important to recognize that many blood vessels in glioblastoma are both histologically abnormal and “leaky” (de Vries et al. 2005). The leakiness of glioblastoma blood vessels can be demonstrated by the accumulation of systemically delivered MRI contrast agent into the region of brain occupied by the tumor mass. In fact, the appearance of a “contrast-enhancing” lesion surrounded by edema is a radiographic hallmark of glioblastoma. Taken together with experimental demonstrations that VEGF promotes vascular permeability, reports in human glioma of strong correlations between VEGF expression and measures associated with vascular leak (Strugar et al. 1995; Machein et al. 1999; Pope et al. 2008) point to a direct role for VEGF in promoting breakdown of the blood–brain barrier in glioblastoma. These results suggest that within glioblastoma, systemically delivered antibodies, such as bevacizumab, may have the greatest access to regions of the tumor producing high levels of VEGF.

### 4.2 CLINICAL DEVELOPMENT OF AVASTIN IN GLIOBLASTOMA

Avastin is being studied extensively in a comprehensive clinical development program spanning 30 different tumor types in adjuvant and metastatic settings. Avastin has received market approval for the treatment of metastatic colorectal cancer and advanced non-squamous, non–small cell lung cancer, and accelerated approval for metastatic HER2-negative breast cancer (see the AVASTIN® Package Insert; provided in Appendix F).
4.2.1 **Initial Investigations**

Initially, Genentech chose not to study Avastin in primary brain tumors or brain metastases because a patient with brain metastases experienced a CNS hemorrhage in an early Phase I study (Gordon et al. 2001). On the basis of the established efficacy demonstrated by Avastin in solid tumors, neuro-oncology researchers began to investigate the utility of Avastin in gliomas, first in case studies in the community setting and then within a large academic center (see Table 2).

These studies combined Avastin with chemotherapy, since it was postulated that combination therapy would be required for optimal benefit. Irinotecan was chosen because this topoisomerase 1 inhibitor is not inhibited by the resistance enzyme MGMT (high levels of MGMT are associated with resistance to alkylating agents such as lomustine and carmustine) and has excellent penetration through the blood–brain barrier (Vredenburgh et al. 2007). These initial studies showed encouraging results for the combination of Avastin and irinotecan, with response rates of 44% and 57% and median overall survival of 9.7 months in one study.

**Table 2**

Initial Investigator-Conducted Research of Avastin in Relapsed Glioblastoma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Stark-Vance a (n=21)</th>
<th>Vredenburgh b (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin (5 mg/kg q2wk)</td>
<td>Avastin (10 mg/kg q2wk Cohort 1; 15 mg/kg q3wk Cohort 2)</td>
<td></td>
</tr>
<tr>
<td>Irinotecan (125 mg/m² q2wk)</td>
<td>Irinotecan (125/340 mg/m² q2wk–qD1, 8, 22, 29 based on EIAID use)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with glioblastoma</th>
<th>11</th>
<th>Cohort 1: 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with anaplastic astrocytoma</td>
<td>10</td>
<td>Cohort 2: 12</td>
</tr>
</tbody>
</table>

| Objective response rate (95% CI) | 44% | 57% (39%, 74%) |
| Six-month PFS (95% CI) | NR | 46% (32%, 66%) |
| Overall survival (median) | NR | 9.7 months |

CI = confidence interval; D = day; EIAID = enzyme-inducing anti-epileptic drug; NA = not applicable; NR = not reported; PFS = progression-free survival; q = every; wk = week.

a Stark-Vance 2005.
b Vredenburgh et al. 2007.
4.2.2 **Genentech’s Clinical Development Program**

In a setting in which there have been few new agents over the last 30 years, it is prudent to validate the results of small, single-center experiences, in which unintentional and unavoidable bias can lead to over estimation of results, to ensure that larger numbers of patients are not unnecessarily exposed to ineffective investigational agents.

Consequently, to confirm the initial encouraging results for Avastin in relapsed glioblastoma in a more controlled setting, Genentech conducted Study AVF3708g, a larger Phase II, multicenter trial with the following objectives:

- To confirm the encouraging results seen with Avastin + irinotecan in an investigator-sponsored study
- To investigate the single-agent activity of Avastin in an effort to avoid some of the toxicity associated with chemotherapy and delineate a development pathway in newly diagnosed glioblastoma

Table 3 summarizes the key features for this Phase II study.

**Table 3**

Genentech Development Program for Avastin in Glioblastoma

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Design</th>
<th>Population</th>
<th>Treatment Arms</th>
<th>Sample Size</th>
<th>Primary Endpoint</th>
</tr>
</thead>
</table>
| AVF3708g  | Randomized, open-label, non-comparative, multicenter, U.S., Phase II | Previously treated glioblastoma; previously treated with XRT and TMZ | Arm 1: Avastin (10 mg/kg q2wk)  
Arm 2: Avastin (10 mg/kg q2wk) + irinotecan (125/340 mg/m² q2wk based on EIAID use) | 85 (Arm 1)  
82 (Arm 2) | Objective response and PFS-6 by independent radiologic review |
| BO21990/AVF4396g | Randomized, double-blind, placebo-controlled, multicenter, global, Phase III | Newly diagnosed glioblastoma | Avastin/placebo (10 mg/kg q2wk) in combination with XRT and TMZ | 920 planned | Overall and progression-free survival |

EIAED = enzyme-inducing anti-epileptic drug; PFS-6 = progression-free survival at 6 months; q = every; TMZ = temozolomide; wk = week; XRT = radiotherapy.
On the basis of the positive results from Study AVF3708g, Genentech initiated discussions with the Agency regarding the accelerated approval and further development of Avastin in glioblastoma.

During the time period in which Genentech was conducting the Phase II study, the NCI conducted an independent, single-site, Phase II study of Avastin in recurrent glioblastoma (Study NCI 06-C-0064E), which was reported in 2008 (see Appendix C). As part of the discussions on the contents of the sBLA, the FDA requested Genentech to perform an independent radiology review of all patients in this study (see Section 5.3.1 for a summary of results).

To confirm the clinical benefit of Avastin in glioblastoma, a large randomized, double-blind, global, Phase III study will be conducted by Genentech and its international development partner, Roche. As summarized in Table 3, this study will evaluate the efficacy and safety of Avastin when used in combination with radiotherapy and temozolomide for the treatment of patients with newly diagnosed glioblastoma. This study is described in more detail in Appendix A.

4.2.3 Regulatory Interactions

Table 4 summarizes the key regulatory interactions between Genentech and the FDA and the key events pertinent to decisions regarding the clinical development of Avastin in glioblastoma.
Table 4
Key Regulatory Interactions and Major Activities in the Development of Avastin in Glioblastoma

<table>
<thead>
<tr>
<th>Interactions and Activities</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA/AACR/ASCO Workshop on Brain Tumor Clinical Trial Endpoints</td>
<td>20 January 2006</td>
</tr>
<tr>
<td>Avastin Orphan Drug Designation application</td>
<td>28 March 2006</td>
</tr>
<tr>
<td>Special Protocol Assessment (SPA) application for Study AVF3708g</td>
<td>30 March 2006</td>
</tr>
<tr>
<td>FDA denies request for SPA for Study AVF3708g</td>
<td>24 April 2006</td>
</tr>
<tr>
<td>Original Protocol AVF3708g submitted to Avastin IND</td>
<td>1 May 2006</td>
</tr>
<tr>
<td>Orphan Drug Designation approval</td>
<td>26 May 2006</td>
</tr>
<tr>
<td>FDA provides comments on Protocol AVF3708g</td>
<td>25 July 2006</td>
</tr>
<tr>
<td>Genentech submits amendment to Statistical Analysis Plan to clarify corticosteroid use</td>
<td>25 June 2007</td>
</tr>
<tr>
<td>Type B meeting to discuss preliminary results of Study AVF3708g</td>
<td>28 January 2008</td>
</tr>
<tr>
<td>FDA requests Genentech to conduct an independent radiology review of all patients in Study NCI 06-C-0064E</td>
<td></td>
</tr>
<tr>
<td>Genentech submits Independent Radiology Review (IRF) Charters for Studies AVF3708g (amended) and NCI 06-C-0064E to FDA</td>
<td>29 July 2008</td>
</tr>
<tr>
<td>Pre-sBLA meeting to obtain agreement on the contents of the sBLA</td>
<td>23 September 2008</td>
</tr>
<tr>
<td><strong>sBLA submission</strong></td>
<td><strong>31 October 2008</strong></td>
</tr>
<tr>
<td>FDA provides comments on IRF Charters for Studies AVF3708g and NCI 06-C-0064E</td>
<td>31 October 2008</td>
</tr>
<tr>
<td>SPA application for Phase III confirmatory study</td>
<td>13 November 2008</td>
</tr>
<tr>
<td>FDA acknowledges acceptability of sBLA filing and grants priority review</td>
<td>18 December 2008</td>
</tr>
<tr>
<td>60-Day sBLA Safety Update with cutoff date of 15 July 2008</td>
<td>22 December 2008</td>
</tr>
<tr>
<td>FDA provides comments on SPA for the Phase III study</td>
<td>29 December 2009</td>
</tr>
<tr>
<td>Genentech submits response to FDA comments on the IRF Charter</td>
<td>13 January 2009</td>
</tr>
<tr>
<td>Genentech submits responses to the FDA comments on the SPA for the confirmatory Phase III study</td>
<td>30 January 2009</td>
</tr>
</tbody>
</table>
5. RESULTS OF THE PHASE II STUDY AVF3708g

The proposed indication for Avastin for the treatment of patients with previously treated glioblastoma is based on results from the single-agent arm of the Phase II study. Data from the Avastin + irinotecan arm of the same study provide supportive information and have been included in the discussions that follow.

5.1 STUDY OBJECTIVES AND DESIGN

5.1.1 Study Design

Study AVF3708g was an open-label, multicenter, randomized, non-comparative, Phase II trial designed to evaluate the efficacy and safety of Avastin alone and in combination with irinotecan in patients with glioblastoma in first or second relapse. The study schema is shown in Figure 3.

Figure 3
Schema for Study AVF3708g

Avastin: 10 mg/kg IV every 2 weeks
Irinotecan:
- EIAED: 340 mg/m^2 IV over 90 minutes
- Non-EIAED: 125 mg/m^2 IV over 90 minutes

EIAED = enzyme-inducing anti-epileptic drug; IV = intravenously; PS = performance status.

Adults with histologically confirmed glioblastoma in first or second relapse and a Karnofsky performance status of ≥70 were included in the study. Patients were required to have received prior temozolomide and radiotherapy. Detailed eligibility criteria are provided in Appendix E.
Patients in the Avastin arm were allowed to receive Avastin + irinotecan after disease progression as optional post-progression therapy. Patients in the Avastin + irinotecan arm who experienced unmanageable toxicity may have discontinued the toxicity-causing agent and continued the remaining agent.

5.1.2 **Study Objectives**

- The primary objective was to evaluate objective response rate and 6-month PFS by independent review in patients with glioblastoma in first or second relapse treated with either Avastin or Avastin + irinotecan.

- Secondary objectives were to characterize the safety of Avastin in these two regimens and to evaluate the efficacy of these two Avastin-containing regimens as measured by PFS, duration of response, and overall survival.

- Exploratory objectives included analyses of objective response rate and 6-month PFS by investigator assessment, changes in neurocognitive functioning, and objective response rate in patients in the Avastin arm who crossed over to receive Avastin in combination with irinotecan.

5.1.3 **Important Elements of the Study Design**

This study was designed to reduce variability in patient population and tumor assessment criteria, which has been reported in historical glioblastoma trials.

**Central Pathology**

Central pathology review was conducted to ensure a consistent histologic diagnosis of glioblastoma. Patients with lower-grade histologies, and thus a better prognosis, have been inadvertently enrolled in many historical clinical trials that did not conduct central pathology review to establish patient eligibility (Scott et al. 1995).

**Imaging Criteria Using MRI**

MRI scans of contrast-enhancing and non-contrast-enhancing index and non-index lesions using T1-weighted pre- and post-contrast and T2-weighted (fluid-attenuated inversion recovery [FLAIR]) images were performed every 6 weeks. See [Appendix B](#) for radiographic images of glioblastomas.
Independent Radiology Facility
To maintain an objective, blinded, and uniform assessment of radiographic endpoints, an independent review facility (IRF) was used in Study AVF3708g. The IRF provided an independent review of the MRI scans and corticosteroid data to determine tumor response and progression. All scans taken during the planned treatment period were provided to the reviewers at the IRF (RadPharm, Inc.), who were blinded to treatment assignment and the investigators’ assessments of the efficacy outcomes. The IRF Charter, which was reviewed by the FDA, specified imaging requirements (contrast-enhancing and non−contrast-enhancing tumor) for designation of index and non-index lesions and for progression determination, and applied a consistent approach to the incorporation of corticosteroid data.

Response and Progression Criteria
Because of the complexities of imaging brain cancers and the difficulty of confirming responses in a rapidly progressive disease, tumor assessment criteria used in prior studies in glioblastoma have been less uniform compared with those used in solid tumors (e.g., WHO criteria and the Response Evaluation Criteria in Solid Tumors). Assessment criteria in earlier studies may not have required confirmation of responses; assessed only the contrast-enhancing portion of the lesion; not accounted for changes in corticosteroid dosing; used subjective assessment of changes in lesion size (e.g., Levin criteria; Levin et al. 1977); or defined response using a more liberal standard (e.g., 25% reduction).

Tumor assessment criteria in this study were adapted from the WHO criteria for use with MRI scans in brain cancer and incorporated corticosteroid dose and clinical deterioration attributable to progressive tumor burden (Macdonald et al.1990):

- Index lesions are contrast-enhancing lesions with clear borders that are $\geq 10$ mm at baseline. These lesions were measured bi-dimensionally at each scan using the outer diameter of the contrast-enhancing component, and the sum of the product of diameters (SPD) of index lesions was calculated at each visit.

- Non-index lesions are enhancing lesions that are small or with unclear borders, as well as non−contrast-enhancing lesions (such as hyper-intensity on FLAIR sequences) or leptomeningeal disease.
• A complete response required disappearance of all index and non-index lesions; in addition, the patient could not be taking corticosteroids above the physiologic level (i.e., equivalent of 20 mg of hydrocortisone per day) and could have no observed clinical deterioration by investigator assessment.

• A partial response required a $\geq 50\%$ decrease in the SPD of index lesions; in addition, the corticosteroid dose at the time of the MRI scan could be no greater than the maximum dose used in the first 6 weeks after initiation of therapy. The patient could have no observed clinical deterioration by investigator assessment.

• Both complete and partial responses had to be confirmed at a second scan at least 4 weeks later.

• Progressive disease was defined by any of the following: appearance of a new lesion, $\geq 25\%$ increase in the SPD of index lesions compared with the nadir, unequivocal progression of non-index lesions, including non-contrast-enhancing lesions, or clear clinical deterioration by investigator assessment in the absence of radiologic worsening.

5.1.4 **Statistical Methods**

In this non-comparative, randomized study, the primary efficacy endpoints for the Avastin arm and the Avastin + irinotecan arm were compared against the historical rates for patients receiving salvage chemotherapy and irinotecan, respectively:

• For the Avastin arm, the historical objective response rate was assumed to be 5% and 6-month PFS was assumed to be 15% for patients with previously treated glioblastoma receiving salvage chemotherapy. These rates were based on a pooled analysis of 225 patients from eight consecutive Phase II trials at the M.D. Anderson Cancer Center representing the best available treatment at the time the study was designed (Wong et al. 1999).

• For the Avastin + irinotecan arm, the historical objective response rate was assumed to be 10% and 6-month PFS was assumed to be 15% for patients with previously treated glioblastoma receiving irinotecan alone. These rates were based on findings from multiple trials of irinotecan alone (Friedman et al. 1999; Cloughesy et al. 2003; Prados et al. 2006).

For each treatment arm, the objective response rate and 6-month PFS were compared with the assumed historical rates for that arm using a two-sided 0.025 significance level to account for the existence of two primary endpoints. Thus, 97.5\% confidence intervals are reported for the co-primary endpoints and...
95% confidence intervals are reported for secondary endpoints. Because historical control rates were estimated with uncertainty, point estimates and confidence intervals are emphasized in the discussion of the results.

The primary efficacy and safety results were based on a data cutoff date of 15 September 2007, which provided a minimum of 6 months of follow-up data for all patients enrolled in the study. An updated safety database with a cutoff of 15 July 2008 (submitted to the FDA on 22 December 2008) provided more comprehensive follow-up data on significant safety events and overall survival.

5.2 STUDY PATIENTS

5.2.1 Patient Disposition

Between 30 June 2006 and 15 February 2007, 167 patients were randomized into Study AVF3708g at 11 study centers in the United States. Patient disposition is summarized in Table 5. The most common reason for treatment discontinuation in both treatment arms was disease progression. Forty-four patients in the Avastin alone arm crossed over to receive Avastin + irinotecan following disease progression. Eighty-three patients (39 patients in the Avastin arm and 44 patients in the Avastin + irinotecan arm) had died at the time of the data cutoff on September 2007.

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=85)</th>
<th>Avastin+Irinotecan (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized patients</td>
<td>85 (100.0%)</td>
<td>82 (100.0%)</td>
</tr>
<tr>
<td>Treated patients</td>
<td>84 (98.8%)</td>
<td>79 (96.3%)</td>
</tr>
<tr>
<td>Still on planned treatment</td>
<td>22 (25.9%)</td>
<td>20 (24.4%)</td>
</tr>
<tr>
<td>Enrolled in optional post-progression phase a</td>
<td>44 (51.8%)</td>
<td>NA</td>
</tr>
<tr>
<td>Still on post-progression treatment</td>
<td>2 (2.4%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable.

a Includes patients who experienced disease progression and received post-progression treatment of irinotecan in combination with Avastin.
5.2.2 **Patient Characteristics**

Demographic and baseline characteristics were typical of patients with previously treated glioblastoma (see Table 6). All patients had received prior radiotherapy and at least one systemic therapy that included temozolomide. The median time from completion of prior radiotherapy to initiation of Avastin therapy in treated patients was 6.2 months (range: 1.2 to 42 months).

An independent central pathology review of baseline slides confirmed the diagnosis of glioblastoma for 83 patients in the Avastin arm (97.6%) and for all patients in the Avastin+irinotecan arm.

<table>
<thead>
<tr>
<th>Table 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and Baseline Characteristics</td>
</tr>
<tr>
<td>(Randomized Patients)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=85)</th>
<th>Avastin+Irinotecan (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median 54</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Range 23 to 78</td>
<td>23 to 78</td>
<td>23 to 79</td>
</tr>
<tr>
<td>≥65</td>
<td>12.9%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male 68.2%</td>
<td>69.5%</td>
<td></td>
</tr>
<tr>
<td>Female 31.8%</td>
<td>30.5%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White 90.6%</td>
<td>89.0%</td>
<td></td>
</tr>
<tr>
<td>Non-White 9.4%</td>
<td>11.0%</td>
<td></td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90−100</td>
<td>44.7%</td>
<td>37.8%</td>
</tr>
<tr>
<td>70−80</td>
<td>55.3%</td>
<td>62.2%</td>
</tr>
<tr>
<td>Relapse status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 81.2%</td>
<td>80.5%</td>
<td></td>
</tr>
<tr>
<td>Second 18.8%</td>
<td>19.5%</td>
<td></td>
</tr>
<tr>
<td>EIAEDs at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 21.2%</td>
<td>36.6%</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 50.6%</td>
<td>52.4%</td>
<td></td>
</tr>
</tbody>
</table>

EIAEDs = enzyme-inducing anti-epileptic drugs.
5.3 EFFICACY RESULTS

The completeness of scans for independent review in Study AVF3708g was very high and indicative of a well-conducted study. By Week 24, 99.7% of the protocol-specified tumor assessments had been performed by the investigators for the Avastin arm and 99.4% for the Avastin + irinotecan arm. All MRI scans, with the exception of one scan for 1 patient in the Avastin arm (at Week 18), were available for independent review.

5.3.1 Objective Response Rate

Objective response rate in the single-agent Avastin arm provides the primary evidence supporting accelerated approval in this license application. Because responses can be wholly attributed to the effect of the administered agent, there is a precedent for the use of response rate in single-arm studies for the purpose of accelerated approval for tumors with a high unmet medical need (Johnson et al. 2003). In 1999, the FDA granted accelerated approval for temozolomide for the treatment of refractory anaplastic astrocytoma (a Grade III glioma) on the basis of response rate in a single-arm study.

Objective response in Study AVF3708g was defined as a complete or partial response determined on two consecutive assessments at least 4 weeks apart, as determined by independent review.

Response Rate by Independent Review (Primary Analysis)

The objective response rate based in independent review in the Avastin arm was 28.2% (97.5% CI: 18.5%, 40.3%), with median response duration of 5.6 months (95% CI: 3.0, 5.8 months) (see Table 7). This rate was significantly higher (p < 0.0001, exact binomial test) than the assumed historical control rate of 5% for patients in this population receiving salvage chemotherapy. All of the responders were confirmed to have a diagnosis of glioblastoma by the independent central pathology review. The nature of the changes in the different kinds of radiographic images (with and without contrast, FLAIR image) is illustrated for several of the responding patients in Appendix B.

These results are supported by the finding in the Avastin + irinotecan arm, in which the objective response rate based on independent review of 37.8% was also significantly higher (p < 0.0001) than the assumed historical control rate of 10% for
patients receiving irinotecan alone. Response rates in relapsed glioblastoma patients treated with irinotecan monotherapy in historical studies range from 0 to 15%, with the majority of studies reporting response rates below 10% (Vredenburgh et al. 2009).

**Table 7**
Objective Response, as Determined by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=85)</th>
<th>Avastin + Irinotecan (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate by independent review, n %</td>
<td>24 (28.2)</td>
<td>31 (37.8)</td>
</tr>
<tr>
<td>(97.5% CI)</td>
<td>(18.5, 40.3)</td>
<td>(26.5, 50.8)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(19.0, 38.4)</td>
<td>(27.9, 48.3)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>23 (27.1)</td>
<td>29 (35.4)</td>
</tr>
<tr>
<td>p-value a</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>5.6</td>
<td>4.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.0, 5.8)</td>
<td>(4.2, – )</td>
</tr>
<tr>
<td>Range</td>
<td>1.4+ to 11.1+</td>
<td>1.4+ to 9.7+</td>
</tr>
</tbody>
</table>

CI = confidence interval; a dash indicates that the upper limit of the confidence interval could not be obtained; + indicates that the duration was censored.

a Compared with historical control rates.

**Duration of Response**

The response duration is illustrated in Figure 4 for the 24 patients in the Avastin arm who had an objective response based on independent review. The horizontal line depicts the time on study from randomization until disease progression by investigator assessment (vertical bar) or time of database cutoff (right arrow). The period during which the patient was responding by independent review is shown by the bold black line, starting at the date of first response and ending at the date of progression (solid circle) or last non-progression tumor assessment (open circle) by independent review.

Five of the responding patients did not have progression by independent review at the time of database cutoff. In approximately half of the responding patients, the investigator continued the patient on study treatment beyond the time of progression based on independent review. Thirteen of the 24 responding
patients remained on study treatment without investigator-assessed progression at the database cutoff, as indicated by the right arrows in Figure 4.

**Figure 4**

*Duration of Objective Response by Independent Review, Shown Relative to the Start of Avastin Treatment*

IRF = Independent Review Facility; PFS = progression-free survival.

**Response Rate by Investigator Assessment**

In Study AVF3708g, response rates by independent review were lower than investigator-assessed response rates (41.2% in the Avastin arm and 51.2% in the Avastin + irinotecan arm; see Table 8), which is typical of studies with assessment of objective response rate by external independent review (Ford et al. 2009). There was 77.6% agreement between the independent and investigator assessments of objective response in the Avastin arm and 74.4% agreement in the combination arm. The median duration of response, as determined by the investigators, was 8.1 months in the Avastin arm and 8.3 months in the Avastin + irinotecan arm.
Reasons for the difference between investigator and independent assessments described for other studies include such factors as lesions selected for review, differing opinions of individual neuro-radiologists, non-radiographic information, interpretation of response criteria, assessment of non-index disease, perception of new lesions, and bias due to knowledge of treatment assignment (Ford et al. 2009). In the Avastin arm, 4 patients were considered to be responders by independent review but not by investigator assessment, and 15 patients were considered to be responders by investigator assessment but not by independent review.

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Comparison of Objective Response by Independent Review and by Investigator Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avastin (n=85)</td>
</tr>
<tr>
<td>Objective response rate, n (%)</td>
<td>24 (28.2)</td>
</tr>
<tr>
<td>Independent review</td>
<td>35 (41.2)</td>
</tr>
<tr>
<td>Investigator</td>
<td></td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>5.6</td>
</tr>
<tr>
<td>Independent review</td>
<td></td>
</tr>
<tr>
<td>Investigator</td>
<td>8.1</td>
</tr>
</tbody>
</table>

**Change in Corticosteroid Dosing and Clinical Deterioration in Responders**

Consistent with the Macdonald criteria, patients with an objective response based on independent review in Study AVF3708g had to be on stable or reduced doses of corticosteroids. As shown in Appendix D, all patients in the Avastin arm with an objective response based on independent review were on a stable or reduced corticosteroid dose, relative to their baseline dose, at the time of the initial response, and many patients had substantial decreases in their corticosteroid dose during the period of response.

Per the Macdonald criteria, patients with an objective response could not have experienced clinical deterioration, and clinical assessment by investigators was captured in this trial every 6 weeks. No patient had their objective response downgraded as the result of clinical progression.
Subgroup Analyses

Subgroup analyses supported the robustness of the objective response results in the Avastin arm: an objective response rate of ≥20% was observed for various subgroups defined by baseline characteristics and risk factors, with the exception of patients in second relapse and patients with lower-grade histology at initial diagnosis (see Figure 5). Because of the small sample size in many of these subgroups, no definitive conclusions can be drawn. Objective response rates of ≥20% were achieved in all subgroups in the Avastin + irinotecan arm.

**Figure 5**

Study AVF3708g: Objective Response Rate, Based on Independent Review, by Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Avastin</th>
<th></th>
<th>Avastin + Irinotecan</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>Response Rate</td>
<td>95% CI</td>
<td>Total n</td>
</tr>
<tr>
<td>All subjects</td>
<td>85</td>
<td></td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
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<td></td>
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<tr>
<td>&lt; 65</td>
<td>74</td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>&gt;= 65</td>
<td>11</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>24</td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>&gt;= 50</td>
<td>61</td>
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<td>54</td>
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<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Female</td>
<td>27</td>
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<td></td>
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<tr>
<td>Male</td>
<td>58</td>
<td></td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>8</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>White</td>
<td>77</td>
<td></td>
<td></td>
<td>73</td>
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<tr>
<td>Karnofsky performance status</td>
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<td></td>
</tr>
<tr>
<td>90 - 100</td>
<td>38</td>
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<td>31</td>
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<tr>
<td>70 - 90</td>
<td>47</td>
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<td></td>
<td>51</td>
</tr>
<tr>
<td>Relapse status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First relapse</td>
<td>69</td>
<td></td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>Second relapse</td>
<td>16</td>
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<td>16</td>
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<tr>
<td>Baseline EIAED use</td>
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<tr>
<td>Yes</td>
<td>18</td>
<td></td>
<td></td>
<td>30</td>
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<tr>
<td>No</td>
<td>67</td>
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<td></td>
<td>52</td>
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<tr>
<td>Baseline corticosteroid use</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td></td>
<td></td>
<td>43</td>
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<tr>
<td>No</td>
<td>42</td>
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<td>39</td>
</tr>
<tr>
<td>Prior diagnosis of glioma</td>
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<td></td>
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<tr>
<td>GBM</td>
<td>78</td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Extent of initial surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>36</td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Partial resection</td>
<td>42</td>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Cl = confidence interval; EIAED = enzyme-inducing anti-epileptic drug; GBM = glioblastoma.

Note: Exact 95% confidence intervals for objective response rate were computed using the Blyth-Still-Casella method.
Maximum Changes in Tumor Burden

The majority of patients experienced tumor shrinkage at some point during the study. Figure 6 shows the maximum post-baseline change in SPD by response status. A few patients with a maximum decrease greater than 50% were considered not to have an objective response in the primary analysis because either the initial response was not confirmed at least 4 weeks later or the corticosteroid dose was not stable or reduced at the time of response.

**Figure 6**

Maximum Post-Baseline Change in the Sum of the Product of Tumor Diameters by Objective Response Status, as Determined by Independent Review

SPD = sum of the product of diameters.

Note: Patients with non-measurable disease (2 in the Avastin arm and 3 in the Avastin+irinotecan arm) were considered to have missing values in this analysis and are denoted by the absence of vertical lines for the early patient indices.

Confirmation of Objective Response Rate in Study NCI 06-C-0064E

This independently conducted, NCI-sponsored, single-site, Phase II trial evaluated single-agent Avastin for the treatment of patients with previously treated high-grade gliomas (Kreisl et al. 2009; see Appendix C). As part of the discussions with the FDA regarding the submission of Study AVF3708g for accelerated approval, Genentech agreed to conduct a retrospective independent radiology review of objective response in the NCI trial to confirm the findings in
Study AVF3708g. The independent review process and tumor assessment methodology were identical to those used for Study AVF3708g, with the exception that MRI scans were collected every 4 weeks in the NCI-sponsored study (compared with every 6 weeks in Study AVF3708g).

Fifty-six patients with glioblastoma were enrolled in the NCI-sponsored study; all patients had received prior surgery, radiotherapy, and systemic therapy. The median age was 54 years (compared with 54 years in Study AVF3708g), 53.6% of patients were male (compared with 68% in Study AVF3708g), and 98.2% were White (compared with 91% in Study AVF3708g). The Karnofsky performance status was 90–100 for 67.9% of patients, 70–80 for 17.9%, 60 for 7.1%, and missing for 7.1% (compared with 45% with a status of 90–100 and 55% with a status of 70–80 in Study AVF3708g).

Response was assessed using the Macdonald criteria (the same tumor response criteria as used for the independent review of Study AVF3708g). On the basis of these criteria, the NCI-sponsored study demonstrated an objective response rate of a magnitude similar to that shown in Study AVF3708g (see Table 9). Eleven patients achieved an objective response, for an objective response rate of 19.6% (95% CI: 10.9%, 31.3%). All of the objective responses were partial responses, and the median duration of objective response was 3.9 months (95% CI: 2.4, 17.4 months).

Table 9
Objective Response, as Determined by Independent Review in Study NCI 06-C-0064E (Intent-to-Treat Patients)

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate by independent review, n (%)</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(10.9, 31.3)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>Median duration of objective response (months)</td>
<td>3.9</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(2.4, 17.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
An additional 3 patients who achieved two consecutive assessments of partial response were not considered to be confirmed responders by this independent review because the second response was prior to the required 28 days following the initial determination of response (27, 26, and 23 days after initial observed response).

The objective response rate based on investigator assessment in the NCI-sponsored study was 35% (Kreisl et al. 2009; see Appendix C). The difference between the rate based on investigator assessment and that based on independent review was due in part to methodologic differences (locked sequential reads were performed by the independent reviewers but not by the investigator) as well as response criteria differences (confirmation of responses within a 28-day interval was not required by the investigator).

The results of the independent radiologic review for the NCI-sponsored study, a contemporary trial with a similar patient population to Study AVF3708g using identical disease assessment criteria, provide independent support for the efficacy of Avastin for the treatment of patients with relapsed glioblastoma.

**Comparison of Objective Response Rate with Historical Control**

In the absence of an internal comparator arm, the results of Study AVF3708g were reviewed in the context of external historical or contemporary data in order to demonstrate improvement over existing available therapies.

Interpretation of historical data in patients with previously treated glioblastoma is complicated by changes in histologic grading definitions; varied criteria for radiographic techniques and interpretation, including inconsistent application of corticosteroid dosing and neurologic function; and variability in key prognostic factors. Many studies in the literature are small, enroll patients with mixed histology, used less conservative tumor assessment criteria (e.g., CT scans, Levin criteria; Levin et al. 1977), or did not require confirmation of responses or stable corticosteroid dosing in responders.

The best available historical data at the time Study AVF3708g was designed, and which were the basis for the assumed historical control rates for the single-agent Avastin arm, were derived from a pooled analysis of eight Phase II
trials at the M.D. Anderson Cancer Center that enrolled consecutively over the period of 1986 to 1995 (Wong et al. 1999). This analysis included 225 patients with glioblastoma and was the largest combined analysis available at the time, with a pooled objective response rate of 6% and 6-month PFS of 15% (see Table 10).

Following initiation of the Phase II study, two additional pooled analyses of Phase II studies in glioblastoma (Ballman et al. 2007; Lamborn et al. 2008) were published; these are summarized in Table 10. The larger and more recent of these studies, Lamborn 2008 (n=437), reported a pooled objective response rate of 7% and 6-month PFS of 16%, which are very similar to the control rates assumed in the study protocol (5% and 15%).

With continuing advances in patient identification, tumor assessment techniques, prior therapies, and supportive care, it would be advantageous to include a more contemporary study as a comparison group. The publication of the Phase III trial investigating the efficacy of enzastaurin in relapsed glioblastoma by Fine et al. (2008) is perhaps the most pertinent reference, as the study is contemporary with respect to enrollment period, central pathology, prior therapy, and MRI techniques. Additionally, the study included lomustine in the control arm, which provides insight into the clinical efficacy of an agent approved in the 1970s when measured using current standards of technology and methodology. The reported objective response rate was 4.3% in the lomustine arm and 2.9% in the experimental arm, and the study was terminated early because of futility.
Table 10
Historical Control Studies in Patients with Previously Treated Glioblastoma

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Patient Population</th>
<th>Response Rate (95% CI)</th>
<th>Six-Month PFS (95% CI)</th>
<th>Median Overall Survival, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight Phase II trials enrolled in 1986–1995 (Wong et al. 1999)</td>
<td>Recurrent glioblastoma (n=225)</td>
<td>6% (2.9%, 9.1%)</td>
<td>15% (10%, 19%)</td>
<td>5.7 (4.8, 6.4)</td>
</tr>
<tr>
<td>Sixteen mainly Phase II trials by NCCTG enrolled in 1980–2004 (Ballman et al. 2007)</td>
<td>Previously treated glioblastoma (n=345)</td>
<td>NR</td>
<td>9%</td>
<td>5.0 (4.6, 5.4)</td>
</tr>
<tr>
<td>Twelve Phase II NABTC trials with patients treated in 1998–2002 (Lamborn et al. 2008)</td>
<td>Recurrent Grade IV glioma (n=437)</td>
<td>7% (4.6%, 9.4%)</td>
<td>16% (12%, 20%)</td>
<td>6.9 (6.2, 7.6)</td>
</tr>
<tr>
<td>Lomustine control arm from Phase III study of enzastaurin (Fine et al. 2008)</td>
<td>Recurrent, intracranial glioblastoma (n=92)</td>
<td>4.3% (0.2%, 8.4%)</td>
<td>19% (10%, 28%)</td>
<td>7.1 (6.0, 8.8)</td>
</tr>
</tbody>
</table>

CI = confidence interval; NABTC = North America Brain Tumor Coalition; NCCTG = North Central Cancer Treatment Group; NR = not reported; PFS = progression-free survival.

Note: In some cases in which the publication did not report a confidence interval, it was calculated using the normal approximation method.

Patient characteristics (age, sex, Karnofsky performance status, number of prior chemotherapy regimens) were very similar for Study AVF3708g and for the two most recent comparator studies (Lamborn 2008 and Fine 2008), shown in Table 11. Note that the Lamborn pooled analysis included 27% of patients with no prior chemotherapy (likely to be a better prognosis group) and 5% of patients with a Karnofsky performance status of 60 (worse prognosis group); neither of these groups was eligible for Study AVF3708g.
### Table 11
Patient Characteristics in Historical Control Studies and Study AVF3708g

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Ballman 2007 (n=345)</th>
<th>Lamborn 2008 (n=437)</th>
<th>Fine 2008 (n=92)</th>
<th>AVF3708g Avastin (n=85)</th>
<th>AVF3708g Avastin + Irinotecan (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>52</td>
<td>55</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Range</td>
<td>19 to 79</td>
<td>21 to 84</td>
<td>19 to 76</td>
<td>23 to 78</td>
<td>23 to 79</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61%</td>
<td>64%</td>
<td>61%</td>
<td>68%</td>
<td>70%</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>16% * a</td>
<td>40%</td>
<td>50%</td>
<td>45%</td>
<td>38%</td>
</tr>
<tr>
<td>70–80</td>
<td>78% * a</td>
<td>54%</td>
<td>50%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>60</td>
<td>6% * a</td>
<td>5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Line of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior chemotherapy</td>
<td>NR</td>
<td>27%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First relapse</td>
<td>NR</td>
<td>50%</td>
<td>77%</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>Second relapse</td>
<td>NR</td>
<td>23%</td>
<td>23%</td>
<td>19%</td>
<td>20%</td>
</tr>
</tbody>
</table>

KPS = Karnofsky performance status; NR = not reported.

Note: Wong et al. (1999) did not report patient characteristics for the glioblastoma cohort and is not included.

* Converted from ECOG performance status using ECOG 0 = KPS 90–100, ECOG 1 = KPS 70–80, ECOG 2 = KPS 60.

Tumor imaging and assessment criteria in the historical control studies and Study AVF3708g are shown in Table 12. The more recent studies (Lamborn 2008 and Fine 2008) uniformly used MRI for tumor imaging, whereas the older studies used a mix of CT and MRI methods. Tumor assessment frequency ranged from 6 weeks to 12 weeks. None of the historical studies incorporated an external independent radiology review, although two of the publications described independent confirmation of responses. Two of the studies (Lamborn 2008 and Wong 1999) did not require confirmation of response at a second scan. The Fine study used modified Levin criteria, which are based on a more subjective global assessment of the scan rather than the percent change in linear measurements of target lesions (Levin et al. 1977). All studies incorporated change in corticosteroid dose in the assessment criteria.
### Table 12

**Tumor Assessment in Study AVF3708g and Historical Control Studies**

<table>
<thead>
<tr>
<th></th>
<th>Wong 1999</th>
<th>Ballman 2007</th>
<th>Lamborn 2008</th>
<th>Fine 2008</th>
<th>Lapustine</th>
<th>AVF3708g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan type</td>
<td>CT/MRI</td>
<td>CT/MRI</td>
<td>MRI</td>
<td>MRI</td>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>Scan frequency in first year</td>
<td>2 months</td>
<td>2 months</td>
<td>8 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Assessment criteria</td>
<td>Similar to Macdonald</td>
<td>Similar to Macdonald</td>
<td>Macdonald</td>
<td>Modified Levin</td>
<td>Macdonald</td>
<td></td>
</tr>
<tr>
<td>Independent review of responders</td>
<td>NS</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, by IRF</td>
<td>Yes</td>
</tr>
<tr>
<td>Confirmation of response at second scan</td>
<td>NS</td>
<td>NA</td>
<td>No</td>
<td>NS</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CT = computed tomography; IRF = Independent Review Facility; MRI = magnetic resonance imaging; NA = not applicable; NS = not specified.

On the basis of the above review of patient characteristics and tumor assessment criteria, the two more recent studies (Lamborn 2008 and Fine 2008) provide the most contemporary and equivalent patient experience with which to compare the results of Study AVF3708g. Figure 7 compares the objective response rate by both independent review and investigator assessment in Study AVF3708g with the rates reported in three historical studies. The objective response rate seen in Study AVF3708g is substantially increased compared with the rates reported for all of the historical studies.
**Figure 7**  
Comparison of Objective Response Rate in the Avastin Arm with Historical Controls

INV = investigator; IRF = Independent Review Facility.
Note: Confidence intervals are 97.5% for Study AVF3708g by independent review, and 95% otherwise.

**Genentech’s Assessment of the Results for Objective Response Rate**

The objective response rate for Study AVF3708g provides clinically compelling evidence for the effectiveness of Avastin as a single-agent therapy in patients with previously treated glioblastoma. The reported response rate of 28.2% based on independent review was durable, with median duration of 5.6 months, and is substantially better than the rates for other available agents used in this setting. The robustness of the objective response results is further supported by the subgroup analyses and findings in the NCI-sponsored study. A comparison of the durable objective response rate seen in Study AVF3708g with the results from historical studies and a concurrent study enrolling similar patient populations and employing similar study procedures demonstrates an improvement in response rate that is likely to predict clinical benefit in patients with previously treated glioblastoma.
5.3.2 Progression-Free Survival at Six Months

Six-month PFS was defined as the percentage of patients who were alive and progression free at 24 weeks. PFS was defined as the time to disease progression, as determined by independent review using the Macdonald criteria, clear clinical progression in the absence of an MRI determination of progression, or death from any cause. Data for patients who started alternative anti-tumor therapy (including crossover to Avastin + irinotecan for patients in the Avastin alone arm) prior to disease progression were censored at the last tumor assessment date prior to receiving the alternative therapy.

Strong concordance between 6-month PFS and 1-year overall survival has been demonstrated in pooled analyses of Phase II trials of patients with glioblastoma treated with systemic agents, suggesting that 6-month PFS is an informative endpoint (Ballman et al. 2007; Lamborn et al. 2008).

Six-Month Progression-Free Survival by Independent Review and Investigator Assessment

For patients in the Avastin arm, 6-month PFS was 42.6% and 43.6%, based on independent review and investigator assessments, respectively (see Table 13). Median PFS in the Avastin arm was 4.2 months by both independent review and investigator assessment.

Six-month PFS based on independent review was significantly higher ($p < 0.0001$, normal approximation method) than the assumed historical control rate of 15% for patients in this population receiving salvage chemotherapy (Wong et al. 1999).
Table 13
Six-Month and Median Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=85)</th>
<th>Avastin + Irinotecan (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Six-month PFS (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Independent review</td>
<td>42.6</td>
<td>50.3</td>
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<tr>
<td>(97.5% CI)</td>
<td>(29.6, 55.5)</td>
<td>(36.8, 63.9)</td>
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<tr>
<td>(95% CI)</td>
<td>(31.3, 53.9)</td>
<td>(38.5, 62.2)</td>
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<tr>
<td>Investigator assessment</td>
<td>43.6</td>
<td>57.9</td>
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<tr>
<td>(95% CI)</td>
<td>(33.0, 54.3)</td>
<td>(46.6, 69.2)</td>
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<tr>
<td><strong>Median PFS (months)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Independent review</td>
<td>4.2</td>
<td>5.6</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(2.9, 5.8)</td>
<td>(4.4, 6.2)</td>
</tr>
<tr>
<td>Investigator assessment</td>
<td>4.2</td>
<td>6.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.0, 6.9)</td>
<td>(5.0, 8.2)</td>
</tr>
</tbody>
</table>

CI= confidence interval; PFS = progression-free survival.

These results are supported by the findings for the Avastin + irinotecan arm, with 6-month PFS of 50.3% and 57.9%, based on independent review and investigator assessments, respectively. Median PFS in the Avastin + irinotecan arm was 5.6 and 6.8 months, based on independent review and investigator assessments, respectively.

The independent and investigator reviews of PFS in this study produced very similar conclusions. This finding is consistent with a recent report in other solid tumors which concluded that treatment effects calculated using investigator and independent review results are usually consistent in well-conducted trials (Dodd et al. 2008).

**Clinical Deterioration and Change in Corticosteroid Dosing in Patients Who Were Progression Free at Six Months**

The tumor assessment criteria allowed progression to be called by clear clinical deterioration by investigator assessment in the absence of radiologic progression. Although this was allowed, there were no instances in this study in which the patient was considered to have clinical progression by the investigator prior to determination of progression by independent review.
Absence of disease progression over the first 6 months was associated with a reduction in corticosteroid doses in both treatment arms. This can be seen in Figure 8, which plots the median daily corticosteroid dose (solid line) together with the 25% and 75% percentiles (dotted lines) over the first 24 weeks of the study for patients who were progression free, based on independent review, at 6 months and who were receiving corticosteroids at the time of study entry. Given the high rate of complications associated with chronic corticosteroid use, the decrease in daily corticosteroid dosing seen in patients who were progression free at 6 months demonstrates an additional impact of disease stabilization in these patients.

Figure 8
Corticosteroid Dose over the First 24 Weeks for Patients Who Were Receiving Corticosteroids at Baseline or on Study and Who Were Progression Free by Independent Review at Six Months

Note: Corticosteroid doses are expressed in dexamethasone (Decadron®) equivalents, with a physiologic dose corresponding to approximately 0.75 to 1.0 mg per day.
Subgroup Analyses
Six-month PFS of ≥30% was achieved in all patient subgroups in the Avastin arm, with the exception of patients ≥65 years old (18.2%), patients in second relapse (27.8%), and patients with a non-glioblastoma initial diagnosis (0%). However, because of the small sample size in these subgroups (n=11, n=16, and n=7, respectively), no definitive conclusions can be drawn.

Sensitivity Analyses
In this study, 6-month PFS was defined as the percentage of patients who were progression-free at 24 weeks, which coincided with the fourth tumor assessment. We performed a sensitivity analysis to assess whether calculating the endpoint with a cutoff of 26 weeks instead of 24 weeks would give a different conclusion. The conclusions were unchanged for the Avastin arm, with 6-month PFS of 42.6% (97.5% CI: 29.6%, 55.5%) based on the 24-week analysis and 38.2% (97.5% CI: 25.4%, 51.0%) based on the alternative 26-week analysis. A larger difference was observed for the Avastin+irinotecan arm: 6-month PFS by independent review was 50.3% (97.5% CI: 36.8%, 63.9%) based on the 24-week analysis and 41.1% based on the alternative 26-week analysis (97.5% CI: 27.6%, 54.5%).

Comparisons with Historical Controls
In the absence of a randomized control arm, comparison of PFS results with those observed in previous studies in relapsed glioblastoma is complicated by possible differences in patient population, frequency of tumor assessments, tumor assessment criteria, and extent of follow-up. On the basis of discussions at the 2006 Workshop on Brain Tumor Clinical Trial Endpoints, a substantial effect size would be needed in the 6-month PFS endpoint in a single-arm study to mitigate possible differences in population and methodologies across trials. Figure 9 shows comparative results in key studies with similar patient populations and assessment criteria used to establish the assumed historical control for objective response rate in Section 5.3.1. Six-month PFS was 15% for Wong et al. (1999), 9% for Ballman et al. (2007), 16% for Lamborn et al. (2008), and 19% for the lomustine arm in the enzastaurin Phase III study (Fine et al. 2008). The 6-month PFS results seen in Study AVF3708g are approximately double those seen in the comparator studies.
Genentech’s Assessment of Six-Month Progression-Free Survival Results

Brain cancer experts have identified 6-month PFS as an important endpoint for assessing disease stabilization (2006 Workshop on Brain Tumor Clinical Trial Endpoints). Assessment of PFS is ideally done in a randomized study that controls for possible imbalances in prognostic characteristics. Nevertheless, a high 6-month PFS (one that is approximately double the expected rate) is reasonably likely to be clinically meaningful. The 6-month PFS of 42.6% in this study is substantially better than predicted for similar patients treated with other available agents used in this setting (typically 6-month PFS is below 20%). This provides additional evidence that the activity of Avastin shown by the objective response data in this study is reasonably likely to predict clinical benefit.
5.3.3 Overall Survival

As of the data cutoff of 15 September 2007, 39 patients (45.9%) in the Avastin arm and 44 patients (53.7%) in the Avastin + irinotecan arm had died. Median overall survival was 9.3 months (95% CI: 8.2, – months) in the Avastin arm and 8.8 months (95% CI: 7.8, – months) in the Avastin + irinotecan arm.

The updated database, with a data cutoff of 15 July 2008, included 67 deaths (78.8%) in the Avastin arm and 66 deaths (80.5%) in the Avastin + irinotecan arm; all surviving patients had been followed for more than 12 months. The updated survival results are consistent with the results shown above, with median overall survival of 9.3 months (95% CI: 8.2, 11.8 months) in the Avastin arm and 8.9 months (95% CI: 7.9, 11.9 months) in the Avastin + irinotecan arm.

Kaplan–Meier curves for overall survival based on the updated database are shown in Figure 10. In the Avastin arm, 37.6% (95% CI: 27.3, 47.9) of patients were alive for more than 1 year after randomization, with a similar observation in the combination arm (37.8% alive for more than 1 year [95% CI: 27.3%, 48.3%]).

In the absence of a randomized control arm, comparison of these overall survival results with those observed in previous studies in relapsed glioblastoma is complicated by possible differences in patient population, supportive health measures, subsequent therapies, and duration of follow-up.

For studies mentioned in the NCCN Practice Guidelines (see Section 3.3.2), median overall survival was 7.6 months for platinum-containing regimens, 7.6 months for the PCV combination regimen, and 7.6 months for temozolomide, compared with 9.7 months for the combination of Avastin + irinotecan (Vredenburgh et al. 2007).

For key studies used to establish the historical control for objective response rate (see Table 10 and accompanying text), median overall survival was 5.7 months for Wong et al. (1999), 5.0 months for Ballman et al. (2007), 6.9 months for Lamborn et al. (2008), and 7.1 months for the lomustine arm in the enzastaurin Phase III study (Fine et al. 2008). The proportion of patients alive for more than 1 year was 21% for patients receiving salvage chemotherapy in Wong et al. (1999), 14% in Ballman et al. (2007), and 25% (95% CI: 21%, 29%) in Lamborn et al. (2008).
Figure 10
Kaplan–Meier Estimates of Overall Survival Based on Updated Data
(Randomized Patients)

One-year survival 37.6%

Median Overall Survival (95% CI):
9.3 (8.2, 11.8) months

One-year survival 37.8%

Median Overall Survival (95% CI):
8.9 (7.9, 11.9) months

CI = confidence interval.
Association between Objective Response and Overall Survival

A recent presentation showed a statistically significant association between objective response and overall survival in a cohort of 1348 patients with newly diagnosed glioblastoma (Jaeckle et al. 2008). However, in the same report, a second cohort with relapsed glioblastoma (345 patients) did not show a statistically significant association between response and survival, possibly owing to the low number of responders in the relapsed group (7%) and resulting lack of statistical power.

Analyses that examine whether objective response can be an early predictor of overall survival are subject to biases (Anderson et al. 2008). Two important biases are survivorship bias, which arises because a responding patient must be alive and on study long enough to have a confirmed response, and selection bias, in which patients who respond to study treatment may have favorable prognostic characteristics that would predispose them to longer overall survival even without the experimental treatment. These biases can be addressed through the use of landmark analyses and by stratifying or adjusting for baseline prognostic factors (Anderson et al. 2008).

We performed an exploratory analysis of overall survival in responders and non-responders for the two treatment arms pooled in Study AVF3708g. As expected, patient prognostic factors were slightly better in the 55 responders, as assessed by the proportion of patients with a Karnofsky performance status of 90–100 (53% vs. 36% in non-responders) and the proportion of patients in first relapse (87% vs. 78%). To correct for survivorship and selection bias, landmark analyses were conducted to predict residual survival by objective response status by independent review at 9, 18, and 26 weeks into the study (Jaeckle et al. 2008). Cox regression analysis was used, with terms for objective response status at that timepoint, as well as the prognostic factors of age, baseline Karnofsky performance status, first versus second relapse, and treatment arm.

These analyses, as shown in Table 14, demonstrated that objective response status was a statistically significant predictor of residual survival at 9 weeks (hazard ratio of 0.52), 18 weeks (hazard ratio of 0.48), and 26 weeks (hazard ratio of 0.43), indicating that non-responders were approximately twice as likely to die within a given time period compared with responders.
An additional analysis performed for the Avastin arm alone yielded similar hazard ratios, although with wider confidence intervals owing to the lower number of patients and responses. One limitation of the analysis is that the adjustment by baseline characteristics in the Cox model may not have removed all selection bias due to possible imbalances between responders and non-responders in other prognostic factors.

Table 14
Landmark Analyses of Objective Response by Independent Review and Residual Survival (Both Treatment Arms Combined)

<table>
<thead>
<tr>
<th></th>
<th>9 Weeks</th>
<th>18 Weeks</th>
<th>26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Non-Responders</td>
<td>Responders</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>127</td>
<td>46</td>
</tr>
<tr>
<td>Median residual survival (weeks) (^a)</td>
<td>58</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(43, 68)</td>
<td>(27, 36)</td>
<td>(35, 60)</td>
</tr>
<tr>
<td>Hazard ratio (^b)</td>
<td>0.52</td>
<td>0.48</td>
<td>0.43</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.32, 0.85)</td>
<td>(0.31, 0.74)</td>
<td>(0.27, 0.67)</td>
</tr>
<tr>
<td>p-value (^b)</td>
<td>0.0091</td>
<td>0.0010</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

\(\text{CI}=\) confidence interval; a dash indicates that the upper limit of the confidence interval could not be obtained.

\(^a\) Residual survival is defined as the survival duration from the landmark timepoint onward, in patients who were still alive at that timepoint.

\(^b\) Cox proportional hazards model including terms for responder status at the landmark timepoint, age (<65, \(\geq\) 65 years), baseline Karnofsky performance status (70–80, 90–100), first versus second relapse, and treatment arm.

In summary, these exploratory analyses of objective response status and overall survival support the hypothesis that objective response based on independent review was an early predictor for survival in this study.

5.3.4 Neurocognitive Function Tests

To document neurocognitive changes in the single-agent Avastin arm while on study treatment, three domains of neurocognitive function were measured as exploratory endpoints in this study: memory, visuomotor scanning speed (e.g., complex visual scanning with a motor component), and executive function (e.g., mental flexibility). These domains were assessed every 6 weeks by trained test administrators using the Hopkins Verbal Learning Test–Revised.
(HVLT-R; Benedict et al. 1998), the Trail Making Test, Parts A (TMTA) and B (TMTB; Lezak 1995), and the Controlled Oral Word Association test (COWA; Benton and Hamsher 1989).

On the basis of the methodology used in a Phase III trial of patients with brain metastases from solid tumors receiving whole brain radiation with or without motexafin gadolinium (Meyers et al. 2004), neurocognitive decline was defined in the Study Analysis Plan as a worsening of ≥3 standard deviations in the test’s normalized scores relative to a normative distribution (Fromm-Auch and Yeudall 1983; Benton et al. 1994; Benedict et al. 1998). According to this criterion, the majority of patients in the Avastin arm demonstrated stable neurocognitive function while on study treatment: 8%, 10%, and 16% of patients experienced a decline in the three memory tests, 15% experienced a decline in visuomotor scanning speed, and 18% and 0% experienced a decline in the two executive function tests at any time.

Experts in the field of neurocognitive function have advised Genentech that the definition of decline (≥3 standard deviations) pre-specified for this study is large and may be insensitive to clinically meaningful changes in function in relapsed patients. Analyses based on the reliable change index (RCI) methodology may provide a more sensitive assessment. The RCI approach sets a threshold for decline and improvement in neurocognitive function based on raw scores; the method and normative data used to derive the thresholds are well established (Jacobson and Truax 1991; Ruff et al. 1996; Benedict et al. 1998; Dikmen et al. 1999; Levine et al. 2004). Changes from baseline in a given test are required to be confirmed by a change in the same direction at the subsequent visit.

When employing the RCI criteria, the majority of patients in the Avastin arm demonstrated stable neurocognitive function while on study treatment, although a higher percentage of patients experienced a decline owing to the lower threshold for decline: 33%, 33%, and 41% of patients experienced a decline in the three memory tests, 25% experienced a decline in visuomotor scanning speed, and 28% and 6% experienced a decline in the two executive function tests at any time.

Changes in neurocognitive function using the RCI criteria were evaluated for the 24 patients in the Avastin arm with an objective response by independent review
to determine whether these patients had stable or improved neurocognitive function at the time of tumor response. Figure 11 illustrates the change from baseline in neurocognitive function at the first timepoint at which an objective response was observed in these patients. Each cell shows the change in neurocognitive status for a given patient (rows) on each test (columns), with change in neurocognitive function displayed as green (improvement), blue (stable), red (decline), or gray (missing).

As indicated by the blue and green cells, the majority of responders had stable neurocognitive function at the time of objective response assessed by independent review, with occasional improvements noted in some of the tests. Six patients had a decline in one of the tests at the time of objective response. In all cases, the decline was seen on a single test, and in three cases, the patient had a mixed assessment (improvements in some tests and a decline in another test). Seven patients had a missing change from baseline for at least one of the tests owing to a missing test result at baseline or at follow-up.

Although the stability of neurocognitive function in these exploratory analyses and the consistency of effects across the three domains are encouraging, these findings should be interpreted cautiously because of the lack of a control arm and the limited experience with these tests in patients with relapsed glioblastoma.
### Figure 11

**Change in Neurocognitive Function at the Time of Objective Response by Independent Review (RCI Method)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>HVL-T-A (Total Recall)</th>
<th>HVL-T-B (Delayed Recall)</th>
<th>HVL-T-C (Delayed Recognition)</th>
<th>Trail Making Test A</th>
<th>Trail Making Test B</th>
<th>COWA (Controlled Oral Word Association)</th>
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</thead>
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<tr>
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</tr>
<tr>
<td>20459</td>
<td>S</td>
<td>D</td>
<td>S</td>
<td>S</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>20461</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>S</td>
</tr>
</tbody>
</table>

D = decline in function; I = improved function; M = missing valid scores either at baseline or at follow-up test; RCI = reliable change index S = stable function.

Note: Change from baseline to first assessment of objective response by independent review.

**5.3.5 Response Status in Patients Treated with Avastin + Irinotecan following Progression on the Avastin Arm**

Of the 85 patients randomized to the Avastin arm, 44 patients (51.8%) transitioned to the optional post-progression phase and received irinotecan in combination with Avastin. No confirmed objective responses based on investigator assessments were observed during the post-progression phase.
5.3.6 **Efficacy Conclusions**

Study AVF3708g was a well-conducted, Phase II, multicenter clinical trial that demonstrated clinically meaningful activity of single-agent Avastin in patients with previously treated glioblastoma:

- The objective response rate based on independent review was 28.2% (97.5% CI: 18.5%, 40.3%) in the Avastin arm, with a median duration of 5.6 months (95% CI: 3.0, 5.8 months). The objective response rate was confirmed by the results of an independent review of the NCI-sponsored study.

- Six-month PFS based on independent review was 42.6% (97.5% CI: 29.6%, 55.5%) in the Avastin arm, and median PFS was 4.2 months (95% CI: 2.9, 5.8 months).

- Patients in the Avastin arm with an objective response or stable disease at 6 months had stable or reduced doses of corticosteroids.

- Median overall survival was 9.3 months (95% CI: 8.2, 11.8 months) in the Avastin arm, with 38% of patients surviving for more than 1 year.

- Exploratory analyses adjusted for time on study and baseline characteristics found that objective response was a significant predictor of survival in this study.

- The efficacy results from the Avastin + irinotecan arm are supportive of these findings, with an objective response rate based on independent review of 37.8%, median duration of response of 4.3 months, and 6-month PFS of 50.3%.

The objective response rate findings in this study compared with historical controls, together with support from the independent review of the NCI-sponsored study, demonstrate an impact on objective response rate of a magnitude that is likely to predict clinical benefit. In addition, the doubling of 6-month PFS compared with historical controls, though less definitive because of the lack of a concurrent control arm, is of a magnitude that supports the objective response rate demonstrated in this study.

5.4 **SAFETY RESULTS**

The safety profile of Avastin has been well characterized through the clinical development programs for approval and labeling in four indications. Avastin is being studied in more than 450 clinical trials and 30 different tumor types; over 370,000 patients have been treated worldwide.
The most serious adverse events associated with Avastin across all trials have been gastrointestinal perforation, wound-healing complication, hemorrhage, non-gastrointestinal fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, nephrotic syndrome, and congestive heart failure (AVASTIN® Package Insert; provided in Appendix F).

Medical complications associated with glioblastoma are distinct from those encountered in other Avastin indications. These include seizures (range of 19%–47%), intra-tumoral hemorrhage (1.6%–7.8%), craniotomy wound-healing complications (0.5%–13.6%), and venous thromboembolic disease (4.2%–31.2%) (Wakai et al. 1982; Kondziolka et al. 1987; Moots et al. 1995; Brandes et al. 1997; Pace et al. 1998; Lieu et al. 1999; Chang et al. 2003; Hildebrand et al. 2005; Salmaggi et al. 2005; Everaert et al. 2004; Streiff et al. 2004; Semrad et al. 2007 Simanek et al. 2007; Attenello et al. 2008; CDER Application Number NDA 21029, Temozolomide; Gliadel® Package Insert).

In Study AVF3708g, adverse events of any grade were collected from the start of treatment until 30 days after the end of treatment. Patients who at the termination visit had an ongoing Grade 3 or 4 adverse event, serious adverse event, or adverse event leading to discontinuation of Avastin were followed every month until the event resolved, the investigator assessed the event as stable, or the patient was lost to follow-up.

5.4.1 Analysis Population and Extent of Exposure

Eighty-four patients in the Avastin arm and 79 patients in the Avastin+irinotecan arm received at least one dose of study treatment and were evaluable for safety. Analyses of exposure and adverse events were based on treated patients (safety-evaluable population) unless otherwise specified. Only adverse events that occurred on or after the day of first study treatment were included in the safety analyses.

Safety data were summarized separately for the planned treatment period from both treatment arms and the post-progression phase for those patients who received Avastin+irinotecan after disease progression on Avastin, to provide the
complete safety profile in this patient population and to isolate the safety profile of Avastin alone.

The median duration of Avastin treatment in the planned treatment period was 3.7 months (range: 0.0 to 12.9 months) in the Avastin arm and 5.1 months (range: 0.0 to 13.2 months) in the Avastin + irinotecan arm. The median number of Avastin doses received was 9 in the Avastin arm and 12 in the Avastin + irinotecan arm.

The median duration of irinotecan treatment was 4.9 months in the Avastin + irinotecan arm.

Forty-four patients (51.8%) in the Avastin arm received optional treatment with Avastin + irinotecan following disease progression.

5.4.2 Analysis of Adverse Events during the Planned Treatment Period

Overview of Adverse Events

The overall safety results are summarized in Table 15.

Table 15
Study AVF3708g: Overall Safety Results during the Planned Treatment Period (Safety-Evaluable Patients)

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=84)</th>
<th>Avastin + Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>98.8%</td>
<td>100%</td>
</tr>
<tr>
<td>Any Grade ≥3 adverse events</td>
<td>46.4%</td>
<td>65.8%</td>
</tr>
<tr>
<td>Adverse events leading to death</td>
<td>2.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Adverse events leading to treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avastin</td>
<td>4.8%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>NA</td>
<td>17.7%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>26.2%</td>
<td>43.0%</td>
</tr>
</tbody>
</table>

NA = not applicable.
Treatment-Emergent Adverse Events

Adverse events of any grade were reported in 83 patients (98.8%) in the Avastin arm and 79 patients (100%) in the Avastin+irinotecan arm during the planned treatment period. Grade ≥3 adverse events were reported in 39 patients (46.4%) in the Avastin arm and 52 patients (65.8%) in the Avastin+irinotecan arm. Grade ≥3 adverse events that occurred in ≥5% of patients in either treatment arm are summarized in Table 16.

Table 16
Study AVF3708g: Incidence of Grade ≥3 Adverse Events Occurring in ≥5% of Patients in Either Treatment Arm during the Planned Treatment Period (Safety-Evaluable Patients)

<table>
<thead>
<tr>
<th>MedDRA System Organ Class/Preferred Term</th>
<th>Avastin (n=84)</th>
<th>Avastin+Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade ≥3 adverse events</td>
<td>46.4%</td>
<td>65.8%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.2%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphasia</td>
<td>3.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Convulsion</td>
<td>6.0%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Pyramidal tract syndrome</td>
<td>1.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusional state</td>
<td>2.4%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.3%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

MedDRA = Medical Dictionary for Regulatory Activities.
The adverse event rates observed during the optional post-progression phase were consistent with those observed during the planned treatment period. No new safety signals were identified.

Deaths

Among treated patients, 79 patients died during the study or follow-up period prior to the data cutoff of 15 September 2007 (see Table 17).

Table 17
Study AVF3708g: Survival Status
(Safety-Evaluable Patients)

<table>
<thead>
<tr>
<th></th>
<th>Avastin (n=84)</th>
<th>Avastin+Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who died, n (%)</td>
<td>38 (45.2)</td>
<td>41 (51.9)</td>
</tr>
<tr>
<td>Primary cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>35 (41.7)</td>
<td>39 (49.4)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 (2.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.2)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

The reason for death for the five deaths that were not due to progressive disease is listed in Table 18.

Table 18
Reasons for Death Other Than Disease Progression

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Cause of Death</th>
<th>Reason for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>Adverse event</td>
<td>Neutropenia infection(^a)</td>
</tr>
<tr>
<td></td>
<td>Adverse event</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Complication due to elective surgery(^b)</td>
</tr>
<tr>
<td>Avastin+Irinotecan</td>
<td>Adverse event</td>
<td>Convulsion</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Clinical deterioration</td>
</tr>
</tbody>
</table>

\(^a\) This patient had a recent history of methicillin-resistant *Staphylococcus aureus* infection following a craniotomy and developed pneumonitis, Grade 4 neutropenia, and a fatal neutropenic infection approximately 2 weeks after the initial dose of Avastin.

\(^b\) This patient died after a right frontal lobe craniotomy with tumor debulking and placement of an Ommaya reservoir.
Adverse Events Leading to Study Treatment Discontinuation

In the Avastin arm, 4 patients (4.8%) discontinued Avastin because of an adverse event, including one event each of myocardial infarction, neutropenic infection, adenocarcinoma (metastatic mucinous adenocarcinoma; received one dose of Avastin), and serious Grade 1 cerebral hemorrhage.

In the Avastin+irinotecan arm:

- Fourteen patients (17.7%) discontinued Avastin because of an adverse event. Adverse events leading to Avastin discontinuation that occurred in ≥2% of treated patients were fatigue (2.5%) and cerebral hemorrhage (3.8%, 1 of each Grades 1, 2, and 4).

- Fourteen patients (17.7%) discontinued irinotecan because of an adverse event. Adverse events leading to irinotecan discontinuation that occurred in ≥2% of treated patients were fatigue (6.3%) and cerebral hemorrhage (2.5%, 1 of each Grades 2 and 4).

Serious Adverse Events

Among treated patients, 22 patients (26.2%) in the Avastin arm and 34 patients (43.0%) in the Avastin+irinotecan arm experienced a serious adverse event. Serious adverse events reported in ≥2% of treated patients during the planned treatment period are summarized in Table 19.

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Avastin (n=84)</th>
<th>Avastin+Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>26.2%</td>
<td>43.0%</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>1.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Convulsion</td>
<td>6.0%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.0%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

MedDRA = Medical Dictionary for Regulatory Activities.
Adverse Events and Safety Assessments of Special Interest

Adverse events of special interest were selected on the basis of previous Avastin studies, with the inclusion of two additional events of special interest for this disease setting, seizure and cerebral hemorrhage. Each of the selected adverse events of interest is a composite of MedDRA preferred terms reviewed by the Genentech Medical Monitor. The incidences of all grade and Grade ≥3 selected adverse events of special interest are summarized in Table 20.

Table 20
Study AVF3708g: Selected Adverse Events of Interest
(Safety-Evaluable Patients)

<table>
<thead>
<tr>
<th>Selected Adverse Events a</th>
<th>Avastin (n=84)</th>
<th>Avastin + Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>27.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Seizure</td>
<td>17.9%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Wound-healing complications</td>
<td>6.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>4.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>3.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>RPLS</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

RPLS = reversible posterior leukoencephalopathy syndrome.

Each of the selected adverse events of interest is a composite of MedDRA preferred terms reviewed by the Genentech Medical Monitor.

Adverse events of special interest associated with Avastin therapy, including hypertension, proteinuria, thromboembolic (arterial and venous) events, and gastrointestinal perforation, were observed at incidences similar to those reported in Avastin Phase III trials in other tumor types and as described in the AVASTIN® Package Insert (provided in Appendix F).

Adverse events of specific concern to patients with glioblastoma include seizure, wound-healing complications, and cerebral hemorrhage; these are discussed in detail below.
**Wound-Healing Complications.** Avastin impairs wound healing in animal models and has been associated with post-operative wound-healing complications in up to 15% of treated patients with colorectal carcinoma (AVASTIN® Package Insert; provided in Appendix F). In this trial, wounds/wound-healing complications of any grade occurred in 5 patients (6%) in the Avastin arm and 2 patients (2.5%) in the Avastin+irinotecan arm. Wound-healing adverse events related to craniotomy-incision sites (all grades) occurred in 3 patients (3.6%) in the Avastin arm and 1 patient (1.3%) in the Avastin+irinotecan arm. In 2 patients, the wound-healing complication was associated with cerebrospinal fluid leak.

For the 4 patients in both treatment arms who experienced impaired craniotomy wound healing, the time from last surgery to the onset of the on-study wound-healing complication was a median of 158 days (range: 86 to 697 days). All 4 patients required surgical repair for these events.

Craniotomy-related wound-healing complications have been reported at rates of 0.5%–13.6% (Chang et al. 2003; Atteneloo et al. 2008; Gliadel® Package Insert). Data from the Glioma Outcomes Project indicated that patients with Grade 3 or 4 gliomas who underwent a second operation had a peri-operative wound infection rate of 1.1% (Chang et al. 2003). The wound-healing events reported in Study AVF3708g may reflect Avastin’s observed ability to impair wound healing of soft tissue and bone in animal models (Street et al. 2002).

**Cerebral Hemorrhage.** In the early development trials with Avastin, patients with primary or metastatic brain cancers were excluded on the basis of one case of intracerebral hemorrhage that occurred in a Phase I study in a patient with CNS involvement. More recent work in this area, namely in patients with treated brain metastases and those with previously treated glioblastoma, suggests that the rate of CNS hemorrhage is low (AVASTIN® Package Insert; provided in Appendix F). In Study AVF3708g, cerebral hemorrhage occurred in 2 patients (2.4%; both Grade 1 events) in the Avastin arm and 3 patients (3.8%; one Grade 1, one Grade 2, and one Grade 4 event) in the Avastin+irinotecan arm. Two Grade 1 cerebral hemorrhages occurred in patients receiving anticoagulation. The patient in the Avastin+irinotecan arm with a Grade 4 cerebral hemorrhage
had concomitant thrombocytopenia (platelet count of 21,000/µL) and underwent an unspecified surgical procedure for the hemorrhage.

Comparisons of the rate of cerebral hemorrhage with that in the literature are limited by the lack of large series and the inclusion of other pathologic conditions that may predispose a patient to hemorrhage. Rates of CNS hemorrhage reported in the literature for Phase II and observational studies of malignant glioma range from 1.6% to 7.8% (Wakai et al. 1982; Kondziolka et al. 1987; Lieu et al. 1999; Chang et al. 2003).

**Seizure.** Seizures are a presenting symptom in approximately 19%–47% of patients with brain tumors and may be difficult to treat (Moots et al. 1995; Pace et al. 1998; Hwang et al. 2004; Hildebrand et al. 2005; Salmaggi et al. 2005; CDER Application Number NDA 21029, Temozolomide). In Study AVF3708g, 45.9% of patients randomized to the Avastin arm and 56.1% in the Avastin + irinotecan arm had a history of seizure reported at the time of study entry.

To assess the rate of seizure in Avastin-treated patients on study, the seizure category included the following MedDRA preferred terms: complex partial seizures, convulsion, grand mal convulsion, partial seizures, and status epilepticus. Seizures of all grades occurred in 17.9% and 24.1% of the safety-evaluable patients in the Avastin and Avastin + irinotecan arms, respectively.

Comparisons with the published literature are limited by the lack of large series and inclusion of lower-grade gliomas, which are associated with overall seizure rates as high as 85%. In the application for temozolomide, seizure of any grade occurred in 24% of 400 patients with recurrent glioblastoma or anaplastic astrocytoma (CDER Application Number NDA 21029, Temozolomide).

### 5.4.3 Adverse Events Based on the Updated Database

Additional safety data were collected between 15 September 2007 and 15 July 2008 to provide an additional 10-month of safety data. No new safety concerns related to Avastin or Avastin + irinotecan were identified. On the basis of the updated safety data,

- Three additional Grade ≥3 adverse events were observed at a frequency of ≥5% during the planned treatment period: muscular weakness (6%) and hemiparesis (6%) in the Avastin arm, and headache (6.3%) in the Avastin + irinotecan arm.
• One additional death attributed to an adverse event (pulmonary embolism) was reported.

• The incidences of selected adverse events remained stable and continued to be comparable to the rates seen in other tumor types and in other Phase III studies of patients treated with Avastin.

5.4.4 Safety Conclusions

In the setting of a Phase II trial without a non-Avastin control arm, full delineation of the safety profile is incomplete. However, the safety profile of Avastin in Study AVF3708g was consistent with that established in combination with chemotherapy in other tumor types and in other Phase III studies, and/or that associated with the underlying disease process, glioblastoma. No new safety concerns were noted.

• Among patients in the Avastin arm, 39 patients (46.4%) experienced a Grade ≥3 adverse event, the most common of which were hypertension (8.3%) and convulsion (6.0%). Among patients in the Avastin + irinotecan arm, 52 patients (65.8%) experienced a Grade ≥3 adverse event, the most common of which were convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%).

• Adverse events led to discontinuation of Avastin for 4 patients (4.8%) in the Avastin arm and 14 patients (17.7%) in the Avastin + irinotecan arm; adverse events led to irinotecan discontinuation in 14 patients (17.7%) in the Avastin + irinotecan arm.

• Adverse events of special interest associated with Avastin therapy, including hypertension, proteinuria, thromboembolic (arterial and venous) events, and gastrointestinal perforation, were observed at incidences similar to those found in Phase III trials in other tumor types.

• Wounds/wound-healing complications of all grades occurred in 5 patients (6%) in the Avastin arm and 2 patients (2.5%) in the Avastin + irinotecan arm. Wound-healing adverse events related to craniotomy-incision sites (all grades) occurred in 3 patients (3.6%) in the Avastin arm and in 1 patient (1.3%) in the Avastin + irinotecan arm.

• Cerebral hemorrhage occurred in 2 patients (2.4%; two Grade 1 events) in the Avastin arm and 3 patients (3.8%; one Grade 1, one Grade 2, and one Grade 4 event) in the Avastin + irinotecan arm.

• Seizures of all grades were observed in this study (17.9% in the Avastin arm and 24.1% in the Avastin + irinotecan arm).

• Safety results based on the updated database, which provided an additional 10 months of safety data, were consistent with the primary safety analysis. No new safety concerns were identified based on the updated database.
6. **BENEFIT–RISK ASSESSMENT**

Glioblastoma is a rapidly progressive and uniformly fatal disease affecting approximately 10,000 patients per year in the United States. No widely accepted or effective systemic therapy exists for patients with relapsed glioblastoma, and many patients do not receive further treatment beyond front-line therapy because of co-morbidities and limited treatment options. Available treatments in this setting are minimally effective, with objective response rates typically less than 10% and 6-month PFS typically less than 20%.

The data presented in this document are based on a randomized, non-comparative, Phase II study in 167 patients that was designed to confirm the activity of Avastin observed in earlier investigator-sponsored studies, either as a single agent or in combination with irinotecan. Although the design of this Phase II study (moderate sample size and absence of a non-Avastin control arm) was not sufficient to establish definitive clinical benefit, the strong results in the study led to an agreement with the FDA for submission of an application under the accelerated approval procedure. Data from the independent review of objective response rate in the 56-patient NCI-sponsored study provided additional support.

**Benefit**

In the single-agent Avastin arm of the Phase II trial (85 patients), treatment was associated with an objective response rate of 28.2%; responses were durable, with a median duration of response of 5.6 months. Patients were on stable or reduced corticosteroid doses at the time of response and had stable neurologic status.

Confidence in the objective responses seen with Avastin is supported by the study conduct and tumor assessment criteria in Study AVF3708g:

- Response and PFS were determined by independent centralized radiology review based on an FDA-reviewed charter; this process ensured an objective, blinded, and uniform assessment of radiographic endpoints.
- Response was determined using conservative criteria that required shrinkage of tumors by at least 50%, with stable or decreased corticosteroid dosing, absence of clinical progression, and confirmation of response at a second scan at least 4 weeks after the initial documentation of response.
• Both contrast-enhancing and non-contrast-enhancing lesions were included in tumor assessments to ensure that all disease was assessed. Radiologic progression could be declared based on an increase in non-contrast-enhancing lesions.

• Compliance with the protocol-specified tumor assessments was high and indicative of a well-conducted study. By Week 24, over 99% of the protocol-specified tumor assessments had been performed by the investigators, and all but one MRI scan were available for independent review.

• Central pathology was employed to ensure enrollment of a high-risk glioblastoma population. Two of 167 patients in the study were not confirmed to have glioblastoma (both were in the single-agent Avastin arm and neither was a responder by independent review).

• Landmark analyses of residual survival by objective response status found that objective response by independent review was a statistically significant predictor of survival in this study.

The response rate was substantially higher than that reported for historical controls with similar patient characteristics receiving available therapies and was consistent across patient subgroups. The objective responses seen with single-agent Avastin were confirmed by an independent NCI-sponsored study conducted in a similar relapsed population over the same time period. Responses in the NCI-sponsored study were based on independent radiologic review using the same criteria as for Study AVF3708g.

The objective response rate was supported by 6-month PFS of 42.6%, an important measure of disease stabilization in glioblastoma. Decreases in corticosteroid doses in patients with tumor shrinkage or stable disease at 6 months are also supportive and demonstrate a meaningful impact for patients. Median overall survival was 9.3 months in the Avastin arm, with 38% of patients surviving more than 1 year.

The efficacy results in the Avastin + irinotecan arm of the Phase II study support the results in the Avastin alone arm. Although the contribution of Avastin cannot be definitively isolated in the Avastin + irinotecan arm because of the lack of an irinotecan-alone concurrent control, the increase in objective response rate in this study is in line with the expected efficacy of irinotecan therapy. Response rates in relapsed glioblastoma patients treated with irinotecan monotherapy in
historical studies range from 0 to 15%, with the majority of studies reporting response rates below 10% (Vredenburgh et al. 2009).

Risk
A total of 163 patients were treated with Avastin in this Phase II study, which is the largest safety experience to date for Avastin in relapsed glioblastoma. Nevertheless, the single-arm design and short duration of therapy limit the ability to fully define the safety of Avastin in this disease, necessitating a review of the safety of Avastin in other tumor types and prior studies of other therapies in glioblastoma for perspective.

The safety profile seen in Study AVF3708g was generally consistent with the safety and toxicities observed since Avastin’s initial approval more than 5 years ago for metastatic colorectal cancer (AVASTIN® Package Insert; provided in Appendix F). Treatment-related adverse events were predictable on the basis of prior experience and led to discontinuation of Avastin in fewer than 5% of patients in the single-agent arm.

For clinical complications expected in glioblastoma, the single-arm design of Study AVF3708g makes it difficult to distinguish between drug toxicity and disease co-morbidity. In this study, wound-healing complications and CNS hemorrhage were observed, but were infrequent.

Craniotomy wound-healing complications, including wound dehiscence and cerebrospinal fluid leak, occurred in 2.5% of treated patients (4 of the 163 treated patients). Confounding factors for wound-healing complications included concomitant corticosteroid use, previous radiotherapy, and timing of Avastin initiation relative to surgical resection.

Cerebral hemorrhage occurred in 2 patients (2.4%; both Grade 1 events) in the Avastin arm and in 3 patients (3.8%; one Grade 1, one Grade 2, and one Grade 4 event) in the Avastin+irinotecan arm. This is similar to the rates of CNS hemorrhage reported in the literature for Phase II and observational studies of malignant glioma (range from 1.6% to 7.8%), although the literature are limited by small sample sizes and inclusion of other pathologic conditions that may predispose a patient to hemorrhage.
Seizures of all grades occurred in 17.9% and 24.1% of the patients in the Avastin and Avastin + irinotecan arms of Study AVF3708g, respectively. In this study, 45.9% and 56.1% of patients in the Avastin and Avastin + irinotecan arm, respectively, had a history of seizure at baseline. These rates are similar to those reported in the literature. Seizures are a presenting symptom in approximately 19%–47% of patients with brain tumors. In the application for temozolomide, seizures of any grade occurred in 24% of 400 patients with recurrent glioblastoma or anaplastic astrocytoma.

The large safety experience in the randomized, 920-patient, Phase III confirmatory study will be important to better characterize the toxicity profile of Avastin in this disease setting and to further investigate potential events such as wound-healing complications and CNS hemorrhage when Avastin is administered in closer proximity to the original surgery and radiotherapy.

Overall, the safety profile of Avastin observed in this study was predictable on the basis of the existing knowledge of Avastin toxicity and was favorable compared with other systemic therapies administered in this setting. This may make Avastin an option for patients with relapsed glioblastoma who are not candidates for chemotherapy because of co-morbidity or low performance status.

**Benefit–Risk Summary**

Treatment with single-agent Avastin led to a high rate of durable response, assessed using conservative criteria, which is reasonably likely to predict clinical benefit. In this disease, objective response to therapy is important, as displacement of normal brain due to tumor or mass effect from surrounding edema has severe clinical consequences and can result in disability and death. All secondary endpoints and analyses were supportive of the objective response rate. Patients with objective responses or stable disease at 6 months had associated decreases in corticosteroid doses, which could reduce the risk of steroid-related complications, such as mood swings, high blood pressure, diabetes, infections, adrenal insufficiency, and Cushing’s syndrome. Finally, 38% of patients were alive for more than 1 year, and landmark analyses demonstrated a statistically significant association between objective response and residual survival in this study.
Overall, the objective responses achieved by patients treated with single-agent Avastin, weighed against the predictable toxicity profile of Avastin, were encouraging. The observed Avastin safety profile compared well against other systemic therapies commonly used in this clinical setting. In all, these observations support a favorable benefit–risk profile for single-agent Avastin as a treatment for patients with relapsed glioblastoma.
7. **OVERALL CONCLUSIONS**

Genentech is seeking accelerated approval of Avastin for the treatment of patients with previously treated glioblastoma on the basis of results from Study AVF3708g. Accelerated approval would provide labeling guidance to physicians and ensure earlier availability of Avastin to a severely under-served patient population. The company will soon initiate a global, Phase III study to further evaluate Avastin in glioblastoma, with results expected in 2014.

Recurrent or progressive glioblastoma is devastating to patients and their families. The neurologic damage associated with returning tumors may impact a patient’s cognition, psychomotor functioning, personality, and emotions. There are no effective FDA-approved systemic therapies for patients with previously treated glioblastoma, and there have been virtually no improvements since the 1970s, with the exception of the carmustine wafer in the small proportion of patients for whom a second surgery is indicated.

The majority of patients with glioblastoma will develop recurrent or progressive disease after first-line treatment. Of these, many will be offered no further active therapy and will receive only best supportive care. The remainder will be offered experimental treatment or therapies that are minimally effective, with objective response rates typically less than 10% and 6-month PFS typically less than 20%.

In this context, the efficacy and safety findings from Study AVF3708g represent improvements over historical controls that are likely to predict clinical benefit in an aggressive disease for which there are currently few options. The totality of the data available on Avastin in this setting, the high quality with which Study AVF3708g was conducted, and Genentech’s commitment to continued clinical study of Avastin in this disease support accelerated approval of single-agent Avastin for the treatment of patients with previously treated glioblastoma.
8. REFERENCES


Gliadel® (polifeprosan 20 with carmustine implant) Package Insert, MGI Pharma, Inc.


SEER (Surveillance Epidemiology and End Results), National Cancer Institute. Available at: http://seer.cancer.gov.


APPENDIX A
Overview of Glioblastoma Commitment Study

Study BO21990/AVF4396g is a global, Phase III, randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy and safety of Avastin used in combination with radiotherapy and temozolomide for the treatment of patients with newly diagnosed glioblastoma. The study schema is shown in Figure 1.

This study will evaluate the addition of Avastin to the regimen of temozolomide and radiotherapy studied in the 573-patient EORTC/NCIC Phase III trial (Stupp et al. 2005), which established a benefit in overall survival compared with radiotherapy alone and led to the approval of temozolomide in newly diagnosed glioblastoma (15 March 2005), resulting in the wide adoption of this regimen.

The primary objective of this study is to evaluate the superiority of the experimental regimen as assessed by the co-primary endpoints of overall survival and progression-free survival (PFS). Secondary objectives include comparison by treatment arm of 1- and 2-year survival rates, overall safety profile, and health-related quality of life (EORTC QLQ C-30, BN-20).

The study population includes adults with newly diagnosed glioblastoma (histologically confirmed with surgical resection or biopsy) who have not been previously treated with chemotherapy, immunotherapy, or radiotherapy. Therapy will be initiated 4–7 weeks following the last surgical procedure.

Assessment of tumor progression or response will be based on the Macdonald criteria (Macdonald et al. 1990), incorporating radiographic, neurologic, and corticosteroid dosing criteria. The adaptations take into account assessment of contrast-enhancing target lesions and non–contrast-enhancing non-target lesions and scenarios more frequently encountered in patients with newly diagnosed glioblastoma (pseudo-progression [Taal et al. 2008] and patients with no measurable disease who will have a no-change category).

This study is targeting enrollment of the first patient in Q2 2009. The last patient is expected to be enrolled 3.5 years after the start of enrollment, and final results should be available approximately 5 years after the start of enrollment.
Figure 1
Schema of Confirmatory Study BO21990/AVF4396g

Newly diagnosed glioblastoma following debulking surgery or biopsy

920 patients randomized, stratified by RPA class and country

Radiotherapy for 6 weeks
TMZ qd
Placebo 10 mg/kg q2wk

Radiotherapy for 6 weeks
TMZ qd
Avastin 10 mg/kg q2wk

Treatment Break (4 weeks)

TMZ 5/28
Placebo 10 mg/kg q2wk

Placebo 15 mg/kg q3wk until PD

Avastin 15 mg/kg q3wk until PD

Treatment Starts
4–7 weeks post-surgery

Concurrent Phase
6 weeks

Maintenance Phase (six cycles)
24 weeks

Monotherapy Phase

PD = progressive disease; RPA = recursive partitioning analysis; RT = radiotherapy; TMZ = temozolomide.

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Radiographic Characteristics of Glioblastoma

Glioblastomas are typically very heterogeneous and highly infiltrative tumors with ill-defined margins. They are best visualized with magnetic resonance imaging (MRI), in which they appear heterogeneous in signal intensity on different sequences as well as before and after injection of intravenous gadolinium contrast material (see Scans 1–3).

Glioblastomas are aggressive tumors, and as they grow within the enclosed space of the cranium, they distort adjacent brain tissue. As a result, patients with glioblastoma experience clinical symptoms due to mass effect and increased intracranial pressure. While focal symptoms and neurologic deficits depend on location and extent of the tumor, general symptoms associated with increased intracranial pressure can include headache, nausea, vomiting, altered level of consciousness, breathing irregularities, and herniation (a usually deadly side effect following displacement of brain tissue outside the skull).

Signs of mass effect on MRI scans include sulcal effacement (swelling of the normal folds of the brain), midline shift (shifting of the brain to one side), ventricular compression (closing of the normal fluid-containing spaces of the brain), and blurred gray–white junction (swelling of the brain resulting in a blurring of clear demarcations of normal structures).

Scans 1–3 highlight the basic MRI characteristics of glioblastoma. These scans are for a patient with glioblastoma who enrolled in Study AVF3708g after having progressed on standard conventional therapies (chemotherapy and radiotherapy).
Scan 1 is a T1-weighted image of a left fronto-temporal glioblastoma before contrast administration. The turquoise arrows denote tumor tissue, which appears somewhat darker than the surrounding brain tissue; the brown arrow denotes the remnants of a surgical procedure (in other patients, such dark regions can also reflect dead/necrotic tumor tissue).

Scan 2 is a T1-weighted image of the same patient following contrast administration. While some portion of the tumor remains non-enhancing (turquoise arrow), a substantial portion of the tumor appears bright (red arrow). This contrast-enhancing portion represents regions where the tumor has disrupted the blood–brain barrier (a protective physiologic barrier that prevents certain substances from entering the brain tissue) and is considered the most aggressive part of the tumor.

Scan 3 is a FLAIR (fluid-attenuated inversion recovery) image. The bright signal (purple arrows) reflects the extent of the overall anatomic abnormality and represents, beyond the contrast-enhancing component, a mixture of tumor cell infiltration and peri-tumoral edema.

Example Cases

MRI examples of such anatomical changes are depicted for a series of patients at baseline, at 6 weeks into treatment with Avastin, and at the time of the last declared partial response (a term that describes a measurable reduction in the volume of contrast enhancement of at least 50%).
**Patient 20026.** The MRI scans for Patient 20026 show contrast-enhancing tumor (red arrows) on T1-weighted post-contrast images surrounding the remnants of a surgical cavity (brown arrows), and extensive bright signal on axial FLAIR image (purple arrow). The tumor caused a mass effect with midline shift (pink arrow) and compression of the anterior horn of the left ventricle (blue arrow). This patient experienced a response to therapy. Following treatment with Avastin, there was a marked decrease in tumor size on both T1-weighted post-contrast images and FLAIR images. These changes were accompanied by significant improvements in ventricular compression and midline shift and were persistent at 36 weeks.
Patient 20062. The MRI scans for Patient 20062 show a ring contrast-enhancing glioblastoma (red arrows) with central necrosis (orange arrows), surrounding extensive tumor infiltration, and peri-tumoral edema (purple arrow), which caused midline shift (pink arrow) and ventricular compression (blue arrow). This patient experienced a response to therapy. Following treatment with Avastin, there was a marked decrease in tumor size, as evidenced by a significant reduction in the extent of contrast enhancement and FLAIR abnormality, accompanied by resolution of midline shift and ventricular compression. These improvements persisted at 30 weeks.
Patient 20459. The MRI scans for Patient 20459 show multiple foci of contrast-enhancing tumor (red arrows), some of which exhibit central necrosis (orange arrows), within the extent of bright signal abnormality on FLAIR images (purple arrows). This patient experienced a response to therapy. Following treatment with Avastin, all contrast-enhancing foci of the tumor as well as the extent of peri-tumoral edema/infiltration decreased significantly at 6 weeks. These improvements persisted at 30 weeks.
Patient 20118. The MRI scans for Patient 20118 show contrast-enhancing tumor (red arrows) surrounding the prior surgical cavity (brown arrows) and high signal intensity on FLAIR images (purple arrow). The resulting midline shift (pink arrows), ventricular compression (blue arrow), and blurred gray–white junction (green arrows) are evident. This patient experienced a response to therapy. Following treatment with Avastin, there was a decrease in contrast-enhancing tumor size and extent of edema/infiltration, with accompanying improvements in midline shift and gray–white junction, and resolution of ventricular compression. These improvements persisted at 24 weeks.
Patient 20154. The MRI scans for Patient 20154 show a nodular contrast-enhancing rim (red arrows) surrounding the prior resection cavity (brown arrows), with extensive bright signal on FLAIR images (purple arrow). The resulting sulcal effacement (yellow arrows) and a slight midline shift (pink arrows) are evident. This patient experienced a response to therapy. Following treatment with Avastin, there was a reduction in the nodular contrast-enhancing components, a significant reduction in FLAIR signal intensity, and associated neuroradiographic improvement, with separation of sulci and resolution of midline shift. These improvements persisted at 24 weeks.
**Patient 20305.** The MRI scans for Patient 20305 show a multifocal contrast-enhancing glioblastoma with lesions in the right occipital (left red arrow) and left temporal (right red arrow) lobes and moderate FLAIR signal intensity (purple arrows). This patient experienced a response to therapy. Following treatment with Avastin, there was a significant reduction in the contrast-enhancing volume of both lesions and surrounding FLAIR abnormality. These improvements persisted at 24 weeks.
APPENDIX C
Manuscript by Kreisl and Co-Workers


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APPENDIX D
Corticosteroid Profiles for Patients in the Avastin Arm with an Objective Response by Independent Review

For the assessment of objective response, the baseline corticosteroid dose was defined to be the maximum daily dose between the start of the study and the first MRI assessment at 6 weeks. Eight patients who had an objective response were not receiving corticosteroids at baseline and did not receive corticosteroids at any point during the study.
APPENDIX D (cont’d)
Corticosteroid Profiles for Patients in the Avastin Arm with an Objective Response by Independent Review

Patient 20119

Patient 20062

Patient 20107

Patient 20026

Patient 20118

Patient 20009
APPENDIX D (cont’d)
Corticosteroid Profiles for Patients in the Avastin Arm with an Objective Response by Independent Review

Patient 20203

Patient 20409

Patient 20402

Patient 20305
APPENDIX E  
Key Design Features of Study AVF3708g

TITLE
A Phase II, Multicenter, Randomized, Non-Comparative Clinical Trial to Evaluate the Efficacy and Safety of Bevacizumab Alone or in Combination with Irinotecan for Treatment of Glioblastoma Multiforme in First or Second Relapse

OUTCOME MEASURES

Primary Outcome Measures
The primary efficacy outcome measures for this study were 6-month progression-free survival (PFS) and objective response rate, as determined by the Independent Review Facility (IRF) using the modified World Health Organization (WHO) Response Evaluation Criteria.

Secondary Outcome Measures
• Safety outcome measures such as the incidence, nature, relatedness, and severity of adverse events and serious adverse events graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 3.0
• PFS, as determined by the IRF
• Duration of objective response, as determined by the IRF
• Overall survival

ELIGIBILITY

Inclusion Criteria
• Signed Informed Consent Form
• Age ≥ 18 years
• Histologically confirmed glioblastoma multiforme (GBM) in first or second relapse
  A pathology report constituted adequate documentation of histology for study inclusion. Patients with an initial diagnosis of a lower-grade glioma were eligible if a subsequent biopsy determined GBM. The amount of prior systemic therapy for this population was, nevertheless, restricted to two regimens, with one including temozolomide.
• Radiographic demonstration of disease progression following prior therapy
• Bi-dimensionally measurable disease with a minimum measurement of 1 cm (10 mm) in one diameter on MRI performed within 14 days prior to first treatment
  Baseline MRIs for patients who underwent salvage surgery after first or second relapse had to be obtained ≥4 weeks after the procedure.
  If receiving corticosteroids, patients had to be on a stable or decreasing dose of corticosteroids for ≥5 days prior to baseline MRI.
• An interval of ≥4 weeks since prior surgical resection
• Prior standard radiotherapy for GBM
• Prior chemotherapy: first-relapse patients
  All first-relapse patients must have received temozolomide.
• Prior chemotherapy: second-relapse patients
  All second-relapse patients must have received temozolomide either for first-line treatment or for treatment after first relapse.
APPENDIX E (cont'd)
Key Design Features of Study AVF3708g

- Recovery from the effects of prior therapy, including the following:
  - Four weeks from cytotoxic agents (except 6 weeks from nitrosoureas, 3 weeks from procarbazine, 2 weeks from vincristine)
  - Four weeks from any investigational agent
  - One week from non-cytotoxic agents
  - Eight weeks from radiotherapy to minimize the potential for MRI changes related to radiation necrosis that might have been misdiagnosed as progression of disease, or 4 weeks if a new lesion, relative to the pre-radiation MRI, developed that was outside the primary radiation field
- Prior therapy with Gamma Knife® or other focal high-dose radiation was allowed, but the patient must have had subsequent histologic documentation of recurrence, unless the recurrence was a new lesion outside the irradiated field.
- Karnofsky performance status $\geq 70$
- Life expectancy $>12$ weeks
- Use of an effective means of contraception in males and in females of childbearing potential
- Ability to comply with study and follow-up procedures

Exclusion Criteria
Disease and Treatment History
- Prior treatment with irinotecan, bevacizumab, or another VEGF or VEGFR-targeted agent
- Prior treatment with prolifeprospan 20 with carmustine wafer
- Prior intracerebral agents
- Need for urgent palliative intervention for primary disease (e.g., impending herniation)
- Evidence of recent hemorrhage on baseline MRI of the brain with the following exceptions:
  - Presence of hemosiderin
  - Resolving hemorrhagic changes related to surgery
  - Presence of punctate hemorrhage in the tumor
- Received more than two treatment regimens for Grade III and/or Grade IV glioma

Bevacizumab Exclusion Criteria
- Blood pressure of $>150$ mmHg systolic and $>100$ mmHg diastolic
- History of hypertensive encephalopathy
- New York Heart Association Grade II or greater congestive heart failure
- History of myocardial infarction or unstable angina within 6 months prior to Day 0
- History of stroke or transient ischemic attack within 6 months prior to study enrollment
- Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or recent peripheral arterial thrombosis within 6 months prior to Day 0
- Evidence of bleeding diathesis or coagulopathy
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to Day 0
APPENDIX E (cont’d)
Key Design Features of Study AVF3708g

- History of intracerebral abscess within 6 months prior to Day 0
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 0, anticipation of need for major surgical procedure during the course of the study
- Minor surgical procedures (excluding placement of a vascular access device), stereotactic biopsy, fine needle aspirations, or core biopsies within 7 days prior to Day 0
- Serious non-healing wound, ulcer, or bone fracture
- Pregnancy (positive pregnancy test) or lactation
- Known hypersensitivity to any component of bevacizumab

General Exclusion Criteria
- History of any other malignancy within 5 years (except non-melanoma skin cancer or carcinoma in situ of the cervix)
- Pregnant or nursing females
- Unstable systemic disease, including active infection, uncontrolled hypertension, or serious cardiac arrhythmia requiring medication
- Patients unable to undergo an MRI with contrast
- Screening clinical laboratory values:
  - Absolute neutrophil count < 1500/µL
  - Platelet count < 100,000/µL
  - Total bilirubin > 1.6 mg/dL
  - AST/ALT ≥ 2.5 × the ULN
  - Creatinine > 1.2 × the ULN
  - Urine protein/creatinine ratio ≥ 1.0
  - INR > 1.5 and aPTT > 1.5 × the ULN (except for patients receiving anticoagulation therapy) in the absence of therapeutic intent to anticoagulate the patient. Therapeutic anticoagulation was permitted.

STUDY TREATMENT

Bevacizumab
The dose of bevacizumab used in this study was 10 mg/kg IV administered every other week until disease progression or up to 4 years or unacceptable toxicity. The dose was based on the patient’s weight at screening and remained the same throughout the study.

Irinotecan
- For patients on EIAEDs, the starting dose of irinotecan was 340 mg/m² IV over 90 minutes every other week, until disease progression or up to 4 years or unacceptable toxicity.
- For patients not on EIAEDs, the starting dose of irinotecan was 125 mg/m² IV over 90 minutes every other week, until disease progression or up to 4 years or unacceptable toxicity.

A cycle was defined as 6 weeks of therapy, with planned drug administration every other week.

U.S. BL125085/169: Bevacizumab—Genentech, Inc.
3/Briefing Book
1.14.1.2 Final Labeling Text

Avastin®
(Bevacizumab)

For Intravenous Use

WARNINGS

Gastrointestinal Perforations

Avastin administration can result in the development of gastrointestinal perforation, in some instances resulting in fatality. Gastrointestinal perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with Avastin (i.e., was not correlated to duration of exposure). The incidence of gastrointestinal perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients with colorectal cancer and in patients with non-small cell lung cancer (NSCLC) receiving Avastin was 2.4% and 0.9%, respectively. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Gastrointestinal perforation should be included in the differential diagnosis of patients presenting with abdominal pain on Avastin. Avastin therapy should be permanently discontinued in patients with gastrointestinal perforation. (See WARNINGS: Gastrointestinal Perforations and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Wound Healing Complications

Avastin administration can result in the development of wound dehiscence, in some instances resulting in fatality. Avastin therapy should be permanently discontinued in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of Avastin and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined. (See WARNINGS: Wound Healing Complications and DOSAGE AND ADMINISTRATION: Dose Modifications.)
Hemorrhage

Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and Avastin. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% in patients with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis (≥1/2 tsp of red blood) should not receive Avastin. (See WARNINGS: Hemorrhage, ADVERSE REACTIONS: Hemorrhage, and DOSAGE AND ADMINISTRATION: Dose Modifications.)

DESCRIPTION

Avastin® (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use 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.
CLINICAL PHARMACOLOGY

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.

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 weekly, every 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

The clearance of Bevacizumab varied by body weight, by gender, and by tumor burden. After correcting for body weight, males had a higher Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger $V_c$ (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher Bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In a randomized study of 813 patients (Study 1), 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. The relationship between Bevacizumab exposure and clinical outcomes has not been explored.
**Special Populations**
Analyses of demographic data suggest that no dose adjustments are necessary for age or sex.

*Patients with renal impairment.* No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with renal impairment.

*Patients with hepatic dysfunction.* No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with hepatic impairment.

**CLINICAL STUDIES**

**Avastin® In Metastatic Colorectal Cancer (mCRC)**
The safety and efficacy of Avastin in the treatment of patients with metastatic carcinoma of the colon or rectum were studied in three randomized, controlled clinical trials in combination with intravenous 5-fluorouracil–based chemotherapy. The activity of Avastin in patients with metastatic colorectal cancer that progressed on or after receiving both irinotecan based- and oxaliplatin based-chemotherapy regimens was evaluated in an open-access trial in combination with intravenous 5-fluorouracil-based chemotherapy.

**Avastin in Combination with Bolus-IFL**
Study 1 was a randomized, double-blind, active-controlled clinical trial evaluating Avastin as first-line treatment of metastatic carcinoma of the colon or rectum. Patients were randomized to bolus-IFL (irinotecan 125 mg/m² IV, 5-fluorouracil 500 mg/m² IV, and leucovorin 20 mg/m² IV given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL regimen was deemed acceptable.
Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients. Results are presented in Table 1 and Figure 1.

**Table 1**
Study 1 Efficacy Results

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<th>IFL+Placebo</th>
<th>IFL+ Avastin 5 mg/kg q 2 wks</th>
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<td>Number of Patients</td>
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<td>Overall Survival</td>
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*p < 0.001 by stratified logrank test.

*p < 0.01 by χ² test.
The clinical benefit of Avastin, as measured by survival in the two principal arms, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

Among the 110 patients enrolled in Arm 3, median overall survival was 18.3 months, median progression-free survival was 8.8 months, overall response rate was 39%, and median duration of response was 8.5 months.

**Avastin in Combination with 5-FU/LV Chemotherapy**

Study 2 was a randomized, active-controlled clinical trial testing Avastin in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Patients were randomized to receive 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for 6 weeks every 8 weeks) or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) or 5-FU/LV plus Avastin (10 mg/kg every 2 weeks). The primary endpoints of the trial were objective response rate and progression-free survival. Results are presented in Table 2.
Table 2
Study 2 Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>5-FU/LV</th>
<th>5-FU/LV+Avastin 5 mg/kg</th>
<th>5-FU/LV+Avastin 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>36</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>13.6</td>
<td>17.7</td>
<td>15.2</td>
</tr>
<tr>
<td>Progression-free Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>5.2</td>
<td>9.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (percent)</td>
<td>17</td>
<td>40</td>
<td>24</td>
</tr>
</tbody>
</table>

Progression-free survival was significantly longer in patients receiving 5-FU/LV plus Avastin at 5 mg/kg when compared to those not receiving Avastin. However, overall survival and overall response rate were not significantly different. Outcomes for patients receiving 5-FU/LV plus Avastin at 10 mg/kg were not significantly different than for patients who did not receive Avastin.

Avastin in Combination with 5-FU/LV and Oxaliplatin Chemotherapy

Study 3 was an open-label, randomized, 3-arm, active-controlled, multicenter clinical trial evaluating Avastin alone, Avastin in combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4 alone in the second-line treatment of metastatic carcinoma of the colon or rectum. Patients were previously treated with irinotecan and 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and leucovorin 200 mg/m² concurrently IV, then 5-FU 400 mg/m² IV bolus followed by 600 mg/m² continuously IV; Day 2: leucovorin 200 mg/m² IV, then 5-FU 400 mg/m² IV bolus followed by 600 mg/m² continuously IV; repeated every 2 weeks), FOLFOX4 plus Avastin, or Avastin monotherapy. Avastin was administered at a dose of 10 mg/kg every 2 weeks and for patients in
the FOLFOX4 plus Avastin arm, prior to the FOLFOX4 chemotherapy on Day 1.

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, and 49% had an ECOG performance status of 0. Twenty-six percent had received prior radiation therapy, and 80% received prior adjuvant chemotherapy. Ninety-nine percent received prior irinotecan, with or without 5-FU for metastatic colorectal cancer, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

The Avastin monotherapy arm of Study 3 was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee (DMC), based on evidence of decreased survival in the Avastin alone arm as compared to the FOLFOX4 alone arm. In the two remaining study arms, overall survival (OS) was significantly longer in patients receiving Avastin in combination with FOLFOX4 as compared to those receiving FOLFOX4 alone (median OS 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63, 0.89], p=0.001 stratified log rank test). In addition, patients treated with Avastin in combination with FOLFOX4 were reported to have significantly longer progression-free survival and a higher overall response rate based on investigator assessment. The clinical benefit of Avastin, as measured by survival, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs) and gender.

**Avastin in Third-Line Metastatic Colorectal Cancer**

Study 4 was an open access, multicenter, single arm study that evaluated the activity of Avastin in combination with bolus or infusional 5-FU/LV in 339 patients with metastatic colorectal cancer with disease progression following both irinotecan- and oxaliplatin-containing chemotherapy regimens. The majority (73%) of patients received concurrent 5-FU/LV according to a bolus regimen.
There was one objective partial response in the first 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

**Avastin® In Unresectable Non-Squamous, Non-Small Cell Lung Cancer (NSCLC)**

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 (Study 5, n=878), supported by a randomized, dose ranging, active controlled Phase 2 study (Study 6, n=98).

In Study 5, chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous NSCLC were randomized (1:1) to receive six cycles of paclitaxel 200 mg/m² and carboplatin AUC = 6.0, both by IV infusion on day 1 (PC) or PC in combination with Avastin at a dose of 15 mg/kg by IV infusion on day 1 (PC plus Avastin). After completion or upon discontinuation of chemotherapy, patients in the PC plus Avastin arm continued to receive Avastin alone until disease progression or until unacceptable toxicity. Cycles were repeated every 21 days. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥1/2 tsp of red blood), or unstable angina and those receiving therapeutic anticoagulation were excluded. The main outcome measure of the study was duration of survival.

Among the 878 patients randomized to the two treatment arms, the median age was 63, 46% were female, 43% were ≥ age 65, and 28% had ≥5% weight loss at study entry. Eleven percent had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease. The survival curves are presented in Figure 2. Overall survival was statistically significantly higher among patients receiving PC plus Avastin compared with those receiving PC alone; median OS
was 12.3 mos vs. 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p-value 0.013, stratified log-rank test). Based on investigator assessment which was not independently verified, patients were reported to have longer progression-free survival with Avastin in combination with PC compared to PC alone.

Figure 2
Duration of Survival in Study 5

In an exploratory analyses across patient subgroups, the impact of Avastin on overall survival was less robust in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age ≥ 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)].

Avastin in Metastatic Breast Cancer
The efficacy and safety of Avastin as first-line treatment of patients with metastatic breast cancer was studied in a single, open-label, randomized, multicenter study (Study 7, N=722). The efficacy and safety of Avastin as second- and third-line treatment of patients with metastatic breast cancer was studied in a single open-label randomized study (Study 8, N=462).
**Study 7**

In Study 7, patients who had not received chemotherapy for locally recurrent or metastatic breast cancer were randomized (1:1) to receive paclitaxel (90 mg/m² IV once weekly for 3 out of 4 weeks) alone or in combination with Avastin (10 mg/kg IV infusion every 2 weeks). Patients were treated until disease progression or unacceptable toxicity. In situations where paclitaxel was discontinued or held, treatment with Avastin alone could be continued until disease progression. Patients with breast cancer overexpressing HER2 were not eligible unless they had received prior therapy with Herceptin®. Prior hormonal therapy for the treatment of metastatic disease was allowed, as was prior adjuvant chemo or hormonal therapy. Adjuvant taxane therapy, if received, must have been completed 12 or more months prior to study entry. Patients with central nervous system metastasis were excluded. The main outcome measure of the study was progression-free survival (PFS), as assessed by an independent review facility (IRF). Secondary outcome measures were overall survival and objective response rate.

Of the 722 patients randomized to the two treatment arms, the median age was 55 years (range 27 - 85), 76% were white, 55.3% were postmenopausal, and 64% were ER and/or PR positive. The patient characteristics were similar across the treatment arms. Thirty-six percent had received prior hormonal therapy for advanced disease, and 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior anthracycline use. Efficacy results are summarized in Table 3.
Table 3
Avastin Efficacy Results from Study 7

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Avastin + Paclitaxel (n=368)</th>
<th>Paclitaxel Alone (n=354)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free Survival</td>
<td>11.3 (10.5, 13.3)</td>
<td>5.8 (5.4, 8.2)</td>
<td>&lt;0.0001</td>
<td>0.48 (0.39, 0.61)</td>
</tr>
<tr>
<td>Overall Survival [median, months (95% CI)]</td>
<td>26.5 (23.7, 29.2)</td>
<td>24.8 (21.4, 27.4)</td>
<td>0.14</td>
<td>0.87 (0.72, 1.05)</td>
</tr>
<tr>
<td>Partial Response Rate^1 (PR)</td>
<td>48.9%^2</td>
<td>22.2%</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
</tbody>
</table>

^1 Includes only patients with measurable disease.
^2 The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant improvement in overall survival. Partial response rates in patients with measurable disease were higher with Avastin plus paclitaxel. No complete responses were observed.

Thirty-four percent of the patients had incomplete follow-up for disease progression, therefore, an exploratory analysis was performed providing a hazard ratio of 0.57.

Study 8
In Study 8, patients who had received prior anthracycline and taxane therapy in the adjuvant setting or for their metastatic breast cancer were randomized (1:1) to receive capecitabine alone or in combination with Avastin. The study enrolled 462 patients. The median age was 51 years (range 29 – 78), 80.5% were white, and 50% were ER and 40% were PR positive. The patient characteristics were similar across the treatment arms. The study failed to demonstrate a statistically significant effect on PFS or overall survival. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm (log-rank p-value = 0.86, hazard ratio 0.98). The median overall survival was 14.5 months in the capecitabine arm and
15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

INDICATIONS AND USAGE
Avastin®, in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

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

Avastin®, in combination with paclitaxel is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer.

The effectiveness of Avastin in metastatic breast cancer is based on an improvement in progression free survival. Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Avastin in breast cancer. (See CLINICAL STUDIES.)

CONTRAINDICATIONS
None.

WARNINGS
Gastrointestinal Perforations (See DOSAGE AND ADMINISTRATION: Dose Modifications)
Gastrointestinal perforation complicated by intra-abdominal abscesses or fistula formation and in some instances with fatal outcome, occurs at an increased incidence in patients receiving Avastin as compared to controls. In Studies 1, 2, and 3, the incidence of gastrointestinal
perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess) in patients receiving Avastin was 2.4%. These episodes occurred with or without intra-abdominal abscesses and at various time points during treatment. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and emesis.

In post-marketing clinical studies and reports, gastrointestinal perforation, fistula formation in the gastrointestinal tract (e.g., gastrointestinal, enterocutaneous, esophageal, duodenal, rectal), and/or intra-abdominal abscess occurred in patients receiving Avastin for colorectal and for other types of cancer. The overall incidence in clinical studies was 1%, but may be higher in some cancer settings. Of the reported events, approximately 30% were fatal. Patients with gastrointestinal perforation, regardless of underlying cancer, typically present with abdominal pain, nausea and fever. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most events occurring within the first 50 days.

Permanently discontinue Avastin in patients with gastrointestinal perforation (gastrointestinal perforation, fistula formation, and/or intra-abdominal abscess).

Non-Gastrointestinal Fistula Formation (See DOSAGE AND ADMINISTRATION: Dose Modifications)

Non-gastrointestinal fistula formation has been reported in patients treated with Avastin in controlled clinical studies (with an incidence of < 0.3%) and in post-marketing experience, in some cases with fatal outcome. Fistula formation involving the following areas of the body other than the gastrointestinal tract have been reported: tracheo-esophageal, bronchopleural, biliary, vagina and bladder. Events were reported throughout treatment with Avastin, with most events occurring within the first 6 months.
Permanently discontinue Avastin in patients with fistula formation involving an internal organ.

**Wound Healing Complications (See DOSAGE AND ADMINISTRATION: Dose Modifications)**

Avastin impairs wound healing in animal models. In clinical studies of Avastin, patients were not allowed to receive Avastin until at least 28 days had elapsed following surgery. In clinical studies of Avastin in combination with chemotherapy, there were 6 instances of dehiscence among 788 patients (0.8%).

The appropriate interval between discontinuation of Avastin and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined. In Study 1, 39 patients who received bolus-IFL plus Avastin underwent surgery following Avastin therapy; of these patients, six (15%) had wound healing/bleeding complications. In the same study, 25 patients in the bolus-IFL arm underwent surgery; of these patients, one of 25 (4%) had wound healing/bleeding complications. The longest interval between last dose of study drug and dehiscence was 56 days; this occurred in a patient on the bolus-IFL plus Avastin arm.

The interval between termination of Avastin and subsequent elective surgery should take into consideration the calculated half-life of Avastin (approximately 20 days).

Discontinue Avastin in patients with wound healing complications requiring medical intervention.

**Hemorrhage (See DOSAGE AND ADMINISTRATION: Dose Modifications)**

Two distinct patterns of bleeding have occurred in patients receiving Avastin. The first is minor hemorrhage, most commonly NCI-CTC Grade 1 epistaxis. The second is serious, and in some cases fatal, hemorrhagic events.
In Study 6, four of 13 (31%) Avastin-treated patients with squamous cell histology and two of 53 (4%) Avastin-treated patients with histology other than squamous cell, experienced serious or fatal pulmonary hemorrhage as compared to none of the 32 (0%) patients receiving chemotherapy alone. Of the patients experiencing pulmonary hemorrhage requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during Avastin therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical intervention for the PC plus Avastin arm was 2.3% (10 of 427) compared to 0.5% (2 of 441) for the PC alone arm. There were seven deaths due to pulmonary hemorrhage reported by investigators in the PC plus Avastin arm as compared to one in the PC alone arm. Generally, these serious hemorrhagic events presented as major or massive hemoptysis without an antecedent history of minor hemoptysis during Avastin therapy. Do not administer Avastin to patients with recent history of hemoptysis of \( \geq \frac{1}{2} \) tsp of red blood. Other serious bleeding events occurring in patients receiving Avastin across all indications include gastrointestinal hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. Some of these events were fatal. (See ADVERSE REACTIONS: Hemorrhage.)

Interim data from two ongoing clinical studies in patients with non-small cell lung cancer, in which patients with CNS metastases had completed either radiation and/or surgery more than 4 weeks prior to the start of Avastin and were evaluated on study with CNS imaging, documented symptomatic Grade 2 CNS hemorrhage in one of 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06% – 5.93%). Discontinue Avastin in patients with serious hemorrhage (i.e., requiring medical intervention) and initiate aggressive medical management. (See ADVERSE REACTIONS: Hemorrhage.)
Arterial Thromboembolic Events (see DOSAGE AND ADMINISTRATION: Dose Modifications and PRECAUTIONS: Geriatric Use)

Arterial thromboembolic events (ATE) occurred at a higher incidence in patients receiving Avastin in combination with chemotherapy as compared to those receiving chemotherapy alone. ATE included cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and a variety of other ATE. These events were fatal in some instances.

In a pooled analysis of randomized, controlled clinical trials involving 1745 patients, the incidence of ATE was 4.4% among patients treated with Avastin in combination with chemotherapy and 1.9% among patients receiving chemotherapy alone. Fatal outcomes for these events occurred in 7 of 963 patients (0.7%) who were treated with Avastin in combination with chemotherapy, compared to 3 of 782 patients (0.4%) who were treated with chemotherapy alone. The incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients receiving Avastin compared to chemotherapy alone. The relative risk of ATE was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).

(See PRECAUTIONS: Geriatric Use.)

The safety of resumption of Avastin therapy after resolution of an ATE has not been studied. Permanently discontinue Avastin in patients who experience a severe ATE during treatment. (See DOSAGE AND ADMINISTRATION: Dose Modifications and PRECAUTIONS: Geriatric Use.)

Hypertension (See DOSAGE AND ADMINISTRATION: Dose Modifications)

The incidence of severe hypertension was increased in patients receiving Avastin as compared to controls. Across clinical studies the incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8-18%. 
Medication classes used for management of patients with NCI-CTC Grade 3 hypertension receiving Avastin included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. Development or worsening of hypertension can require hospitalization or require discontinuation of Avastin in up to 1.7% of patients. Hypertension can persist after discontinuation of Avastin. Complications can include hypertensive encephalopathy (in some cases fatal) and CNS hemorrhage.

In the post-marketing experience, acute increases in blood pressure associated with initial or subsequent infusions of Avastin have been reported (see PRECAUTIONS: Infusion Reactions). Some cases were serious and associated with clinical sequelae.

Permanently discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management. (See DOSAGE AND ADMINISTRATION: Dose Modifications.)

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (See DOSAGE AND ADMINISTRATION: Dose Modifications)**

RPLS has been reported in clinical studies (with an incidence of <0.1%) and in post-marketing experience. RPLS 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, but is not necessary for diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of Avastin.

In patients developing RPLS, discontinue Avastin and initiate treatment of hypertension, if present. Symptoms usually resolve or improve within days, although some patients have experienced
ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known.

**Neutropenia and Infection (See PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS: Neutropenia and Infection)**

Increased rates of severe neutropenia, febrile neutropenia, and infection with severe neutropenia (including some fatalities) have been observed in patients treated with myelosuppressive chemotherapy plus Avastin. (See PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS: Neutropenia and Infection.)

**Proteinuria (See DOSAGE AND ADMINISTRATION: Dose Modifications)**

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to control. In Studies 1, 3 and 5 the incidence of NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours, ranged up to 3.0% in Avastin-treated patients.

Nephrotic syndrome occurred in seven of 1459 (0.5%) patients receiving Avastin in clinical studies. One patient died and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of Avastin. No patient had normalization of urinary protein levels (by 24-hour urine) following discontinuation of Avastin.

The highest incidence of proteinuria was observed in a dose-ranging, placebo-controlled, randomized study of Avastin in patients with metastatic renal cell carcinoma, an indication for which Avastin is not approved. 24-hour urine collections were obtained in approximately half the patients enrolled. Among patients in whom 24-hour urine collections were obtained, four of 19 (21%) patients receiving Avastin at 10 mg/kg every two weeks, two of 14 (14%) patients receiving Avastin at 3 mg/kg every two weeks, and none of the 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

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In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Discontinue Avastin in patients with nephrotic syndrome. The safety of continued Avastin treatment in patients with moderate to severe proteinuria has not been evaluated. In most clinical studies, Avastin was interrupted for ≥2 grams of proteinuria/24 hours and resumed when proteinuria was <2 gm/24 hours. Patients with moderate to severe proteinuria based on 24-hour collections should be monitored regularly until improvement and/or resolution is observed. (See DOSAGE AND ADMINISTRATION: Dose Modifications.)

**Congestive Heart Failure**

NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients receiving Avastin in clinical studies. In Study 7, the rate of congestive heart failure (defined as NCI-CTC Grade 3 and 4) in the Avastin plus paclitaxel arm was 2.2% versus 0.3% in the control arm. Among patients receiving anthracyclines, the rate of CHF was 3.8% for Avastin treated patients and 0.6% for patients receiving paclitaxel alone. Congestive heart failure occurred in six of 44 (14%) patients with relapsed acute leukemia (an unlabelled indication) receiving Avastin and concurrent anthracyclines in a single arm study.

The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

**PRECAUTIONS**

**General**

Use Avastin with caution in patients with known hypersensitivity to Avastin or any component of this drug product.
Infusion Reactions

In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%) and severe reactions occurred in 0.2% of patients. Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate information on rechallenge is not available. Avastin infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Avastin after experiencing a severe infusion reaction.

Surgery

Avastin therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of Avastin. Because of the potential for impaired wound healing, Avastin should be suspended prior to elective surgery. The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days (see CLINICAL PHARMACOLOGY: Pharmacokinetics) and the interval chosen should take into consideration the half-life of the drug. (See WARNINGS: Gastrointestinal Perforations and Wound Healing Complications.)

Cardiovascular Disease

Patients were excluded from participation in Avastin clinical trials if, in the previous year, they had experienced clinically significant cardiovascular disease. In an exploratory analysis pooling the data from five randomized, placebo-controlled, clinical trials conducted in patients without a recent history of clinically significant cardiovascular
disease, the overall incidence of arterial thromboembolic events, the incidence of fatal arterial thromboembolic events, and the incidence of cardiovascular thromboembolic events were increased in patients receiving Avastin plus chemotherapy as compared to chemotherapy alone.

**Laboratory Tests**

Blood pressure monitoring should be conducted every two to three weeks during treatment with Avastin. Patients who develop hypertension on Avastin may require blood pressure monitoring at more frequent intervals. Patients with Avastin-induced or -exacerbated hypertension who discontinue Avastin should continue to have their blood pressure monitored at regular intervals.

Patients receiving Avastin should be monitored for the development or worsening of proteinuria with serial urinalyses. Patients with a 2+ or greater urine dipstick reading should undergo further assessment, e.g., a 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

**Drug Interactions**

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In Study 6, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a greater paclitaxel exposure at Day 63 than at Day 0.
**Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenicity data are available for Avastin in animals or humans.

Avastin may impair fertility. Dose-related decreases in ovarian and uterine weights, endometrial proliferation, number of menstrual cycles, and arrested follicular development or absent corpora lutea were observed in female cynomolgus monkeys treated with 10 or 50 mg/kg of Avastin for 13 or 26 weeks. Following a 4- or 12-week recovery period, which examined only the high–dose group, trends suggestive of reversibility were noted in the two females for each regimen that were assigned to recover. 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, but uterine weight decreases were still notable, corpora lutea were absent in 1 out of 2 animals, and the number of menstrual cycles remained reduced (67%).

**Pregnancy Category C**

Avastin has been shown to be teratogenic in rabbits when administered in doses that approximate the human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested.

Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Avastin is likely to result in adverse effects on pregnancy. There are no adequate and well-controlled studies in pregnant women. Avastin should be used during pregnancy or in any woman not employing adequate contraception only if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk.
of Avastin to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving Avastin, she should be apprised of the potential hazard to the fetus and/or the potential risk of loss of pregnancy. Patients who discontinue Avastin should also be counseled concerning the prolonged exposure following discontinuation of therapy (half-life of approximately 20 days) and the possible effects of Avastin on fetal development.

**Nursing Mothers**

It is not known whether Avastin is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown. Women should be advised to discontinue nursing during treatment with Avastin and for a prolonged period following the use of Avastin, taking into account the half-life of the product, approximately 20 days [range 11–50 days]. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics**.)

**Pediatric Use**

The safety and effectiveness of Avastin in pediatric patients has not been studied. However, physeal dysplasia was observed in juvenile cynomolgus monkeys with open growth plates treated for four weeks with doses that were less than the recommended human dose based on mg/kg and exposure. The incidence and severity of physeal dysplasia were dose-related and were at least partially reversible upon cessation of treatment.

**Geriatric Use**

In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL plus Avastin; 109 5-FU/LV plus Avastin), while NCI-CTC Grade 1 and 2 adverse events were collected in a subset of 309 patients. There were insufficient numbers of patients 65 years and older in the subset in which NCI-CTC Grade 1-4 adverse events were collected to determine whether the overall adverse event profile was
different in the elderly as compared to younger patients. Among the 392 patients receiving bolus-IFL plus Avastin, 126 were at least 65 years of age. Severe adverse events that occurred at a higher incidence (≥2%) in the elderly when compared to those less than 65 years were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 3, patients age 65 and older receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 5 patients age 65 and older receiving carboplatin, paclitaxel, and AVASTIN had a greater relative risk for proteinuria as compared to younger patients.

In Study 7, there were insufficient numbers of patients ≥65 years old to determine whether the overall adverse event profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients age 65 or older and 1127 patients less than 65 years of age. 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 arterial thromboembolic events incidence was greater in patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See WARNINGS: Arterial Thromboembolic Events.)

ADVERSE REACTIONS
The most serious adverse reactions in patients receiving Avastin were:

- Gastrointestinal Perforations (see WARNINGS)
- Non-Gastrointestinal Fistula Formation (see WARNINGS)
- Wound Healing Complications (see WARNINGS)
- Hemorrhage (see WARNINGS)
- Arterial Thromboembolic Events (see WARNINGS)
- Hypertensive Crises (see WARNINGS: Hypertension)
- Reversible Posterior Leukoencephalopathy Syndrome (see WARNINGS)
- Neutropenia and Infection (see WARNINGS)
- Nephrotic Syndrome (see WARNINGS: Proteinuria)
- Congestive Heart Failure (see WARNINGS)

Adverse Reactions in Clinical Trials
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Avastin in 1529 patients, including 665 receiving Avastin for at least 6 months and 199 receiving Avastin for at least one year. Avastin was studied
primarily in placebo- and active-controlled trials (n = 501, and n = 1028, respectively).

**Gastrointestinal Perforation**
The incidence of gastrointestinal perforation across all studies ranged from 0–3.7%. The incidence of gastrointestinal perforation, in some cases fatal, in patients with mCRC receiving Avastin alone or in combination with chemotherapy was 2.4% compared to 0.3% in patients receiving only chemotherapy. The incidence of gastrointestinal perforation in NSCLC patients receiving Avastin was 0.9% compared to 0% in patients receiving only chemotherapy. (See **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

**Non-Gastrointestinal Fistula Formation**
(See **WARNINGS: Non-Gastrointestinal Fistula Formation**, **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

**Wound Healing Complications**
The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone. In the same study, the incidence of wound dehiscence was also higher in the Avastin-treated patients (1% vs. 0.5%).

**Hemorrhage**
Severe or fatal hemorrhages, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in Avastin-treated patients compared to patients treated with chemotherapy alone.
NCI-CTC Grade 3–5 hemorrhagic events occurred in 4.7% of NSCLC patients and 5.2% of mCRC patients receiving Avastin compared to 1.1% and 0.7% for the control groups respectively. (See WARNINGS: Hemorrhage.)

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. These events were generally mild in severity (NCI-CTC Grade 1) and resolved without medical intervention. Additional mild to moderate hemorrhagic events reported more frequently in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). (See WARNINGS: Hemorrhage and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Arterial Thromboembolic Events
The incidence of arterial thromboembolic events was increased in NSCLC patients receiving PC plus Avastin (3.0%) compared with patients receiving PC alone (1.4%). Five events were fatal in the PC plus Avastin arm, compared with 1 event in the PC alone arm. This increased risk is consistent with that observed in patients with mCRC. (See WARNINGS: Arterial Thromboembolic Events, DOSAGE AND ADMINISTRATION: Dose Modifications, and PRECAUTIONS: Geriatric Use.)

Venous Thromboembolic Events
The incidence of NCI-CTC Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. In addition, in patients with mCRC the risk of developing a second subsequent thromboembolic event in patients receiving Avastin and chemotherapy is increased compared to patients receiving
chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following NCI-CTC Grade 3 and 4 venous thromboembolic events was higher in patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

**Hypertension**

Fatal CNS hemorrhage complicating Avastin induced hypertension can occur.

In Study 1, the incidences of hypertension and of severe hypertension were increased in patients with mCRC receiving Avastin compared to those receiving chemotherapy alone (see Table 4).
Table 4
Incidence of Hypertension and Severe Hypertension in Study 1

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 IFL + Placebo (n = 394)</th>
<th>Arm 2 IFL + Avastin (n = 392)</th>
<th>Arm 3 5-FU/LV + Avastin (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension(^a) (&gt;150/100 mmHg)</td>
<td>43%</td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td>Severe Hypertension(^a) (&gt;200/110 mmHg)</td>
<td>2%</td>
<td>7%</td>
<td>10%</td>
</tr>
</tbody>
</table>

\(^a\) This includes patients with either a systolic or diastolic reading greater than the cutoff value on one or more occasions.

Among patients with severe hypertension in the Avastin arms, slightly over half the patients (51%) had a diastolic reading greater than 110 mmHg associated with a systolic reading less than 200 mmHg.

Similar results were seen in patients receiving Avastin alone or in combination with FOLFOX4 or carboplatin and paclitaxel.

(See WARNINGS: Hypertension and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Neutropenia and Infection
An increased incidence of neutropenia has been reported in patients receiving Avastin and chemotherapy compared to chemotherapy alone. In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was increased in patients with mCRC receiving IFL+Avastin (21%) compared to patients receiving IFL alone (14%). In Study 5, the incidence of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC receiving PC plus Avastin (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in the PC plus Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment the incidence of
serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

Proteinuria
(See WARNINGS: Proteinuria, DOSAGE AND ADMINISTRATION: Dose Modifications, and PRECAUTIONS: Geriatric Use.)

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

Metastatic Carcinoma of the Colon and Rectum
The data in Tables 5 and 6 were obtained in Study 1. All NCI-CTC Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2 adverse events (hypertension, proteinuria, thromboembolic events) were reported for the overall study population. The median age was 60, 60% were male, 79% were Caucasian, 78% had a colon primary
lesion, 56% had extra-abdominal disease, 29% had prior adjuvant or neoadjuvant chemotherapy, and 57% had ECOG performance status of 0. The median duration of exposure to Avastin was 8 months in Arm 2 and 7 months in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events, which occurred at a higher incidence (≥2%) in patients receiving bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 5.

Table 5
NCI-CTC Grade 3 and 4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥2%) Avastin vs. Control)

<table>
<thead>
<tr>
<th>NCI-CTC Grade 3–4 Events</th>
<th>Arm 1 IFL+Placebo (n=396)</th>
<th>Arm 2 IFL+Avastin (n=392)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>28 (7%)</td>
<td>38 (10%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>20 (5%)</td>
<td>32 (8%)</td>
</tr>
<tr>
<td>Pain</td>
<td>21 (5%)</td>
<td>30 (8%)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (2%)</td>
<td>46 (12%)</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>19 (5%)</td>
<td>34 (9%)</td>
</tr>
<tr>
<td>Intra-Abdominal Thrombosis</td>
<td>5 (1%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (1%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>99 (25%)</td>
<td>133 (34%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (2%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td><strong>Hemic/Lymphatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>122 (31%)</td>
<td>145 (37%)</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>41 (14%)</td>
<td>58 (21%)</td>
</tr>
</tbody>
</table>

* Central laboratories were collected on Days 1 and 21 of each cycle. Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

NCI-CTC Grade 1–4 adverse events which occurred at a higher incidence (≥5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm, are presented in Table 6.
Table 6
NCI-CTC Grade 1–4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥5%) in IFL+Avastin vs. IFL)

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 IFL+Placebo (n=98)</th>
<th>Arm 2 IFL+ Avastin (n=102)</th>
<th>Arm 3 5-FU/LV+Avastin (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>54 (55%)</td>
<td>62 (61%)</td>
<td>67 (62%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>54 (55%)</td>
<td>62 (61%)</td>
<td>55 (50%)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (19%)</td>
<td>27 (26%)</td>
<td>30 (26%)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (14%)</td>
<td>23 (23%)</td>
<td>37 (34%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (7%)</td>
<td>15 (15%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>3 (3%)</td>
<td>9 (9%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>46 (47%)</td>
<td>53 (52%)</td>
<td>51 (47%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29 (30%)</td>
<td>44 (43%)</td>
<td>38 (35%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>28 (29%)</td>
<td>41 (40%)</td>
<td>32 (29%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (18%)</td>
<td>33 (32%)</td>
<td>33 (30%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>15 (15%)</td>
<td>25 (24%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td>GI Hemorrhage</td>
<td>6 (6%)</td>
<td>25 (24%)</td>
<td>21 (19%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>10 (10%)</td>
<td>15 (15%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2 (2%)</td>
<td>7 (7%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Hemic/Lymphatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>20 (20%)</td>
<td>27 (26%)</td>
<td>21 (19%)</td>
</tr>
</tbody>
</table>
Table 6 (cont’d)
NCI-CTC Grade 1–4 Adverse Events in Study 1
(Occurring at Higher Incidence (≥5%) in IFL+Avastin vs. IFL)

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 IFL+Placebo (n = 98)</th>
<th>Arm 2 IFL+ Avastin (n = 102)</th>
<th>Arm 3 5-FU/LV + Avastin (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>38 (39%)</td>
<td>48 (47%)</td>
<td>44 (40%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>10 (10%)</td>
<td>36 (35%)</td>
<td>35 (32%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (15%)</td>
<td>26 (26%)</td>
<td>27 (25%)</td>
</tr>
<tr>
<td>Voice Alteration</td>
<td>2 (2%)</td>
<td>9 (9%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Skin/Appendages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>25 (26%)</td>
<td>33 (32%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Skin Ulcer</td>
<td>1 (1%)</td>
<td>6 (6%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste Disorder</td>
<td>9 (9%)</td>
<td>14 (14%)</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>24 (24%)</td>
<td>37 (36%)</td>
<td>39 (36%)</td>
</tr>
</tbody>
</table>

The data in Table 7 were obtained in Study 3. Only NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were reported. The median age was a 61 years, 40% were female, 87% were Caucasian, 99% received prior chemotherapy for metastatic colorectal cancer, 26% had received prior radiation therapy, and the 49% had an ECOG performance status of 0. Selected NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events which occurred at a higher incidence in patients receiving FOLFOX4 plus Avastin as compared to those who received FOLFOX4 alone, are presented in Table 7. These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 3.
Table 7
NCI-CTC Grade 3–5 Non-Hematologic and Grade 4–5 Hematologic Adverse Events in Study 3
(Occurring at Higher Incidence (≥2%) with Avastin+FOLFOX4 vs. FOLFOX4)

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4 (n=285)</th>
<th>FOLFOX4+ Avastin (n=287)</th>
<th>Avastin (n=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one event</td>
<td>171 (60%)</td>
<td>219 (76%)</td>
<td>87 (37%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (13%)</td>
<td>51 (18%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (5%)</td>
<td>35 (12%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (4%)</td>
<td>32 (11%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>14 (5%)</td>
<td>29 (10%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Ileus</td>
<td>4 (1%)</td>
<td>10 (4%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy–sensory</td>
<td>26 (9%)</td>
<td>48 (17%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Neurologic–other</td>
<td>8 (3%)</td>
<td>15 (5%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (13%)</td>
<td>56 (19%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (5%)</td>
<td>24 (8%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0%)</td>
<td>8 (3%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Cardiovascular (general)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (2%)</td>
<td>26 (9%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2 (1%)</td>
<td>15 (5%)</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

Non-Squamous, Non-Small Cell Lung Cancer
The data in Table 8 were obtained in Study 5. Only NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events were reported. The median age was 63, 46% were female, no patients had received prior chemotherapy, 76% had Stage IV disease, 12% had Stage IIIB disease with malignant pleural effusion, 11% had recurrent disease, and 40% had an ECOG performance status of 0. The median duration of exposure to Avastin was 4.9 months.
NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a $\geq 2\%$ higher incidence in patients receiving PC plus Avastin as compared with PC alone are presented in Table 8.
Table 8
NCI-CTC Grade 3–5 Non-Hematologic and Grade 4 and 5 Hematologic Adverse Events in Study 5
(Occurring at a ≥2% Higher Incidence in Avastin-Treated Patients Compared with Control)

<table>
<thead>
<tr>
<th>NCI-CTC Category Term a</th>
<th>PC (n = 441)</th>
<th>PC + Avastin (n = 427)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>286 (65%)</td>
<td>334 (78%)</td>
</tr>
<tr>
<td>Blood/bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>76 (17%)</td>
<td>113 (27%)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>57 (13%)</td>
<td>67 (16%)</td>
</tr>
<tr>
<td>Cardiovascular (general)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (0.7%)</td>
<td>33 (8%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thrombus/embolism</td>
<td>14 (3%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Infection/febrile neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>12 (3%)</td>
<td>30 (7%)</td>
</tr>
<tr>
<td>Infection with NCI-CTC Grade 3 or 4 neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8 (2%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Pulmonary/upper respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis/pulmonary infiltrates</td>
<td>11 (3%)</td>
<td>21 (5%)</td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5 (1%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (0.5%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Renal/genitourinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0 (0%)</td>
<td>13 (3%)</td>
</tr>
</tbody>
</table>

a Events were reported and graded according to NCI-CTC, Version 2.0. Per protocol, investigators were required to report NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic events.

Metastatic Breast Cancer
The data in Table 9 were obtained in Study 7. Only NCI-CTC Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse
events were reported. The median age was 55 years (range 27 - 85); 76% were white; 36% had received prior hormonal therapy for advanced disease, and 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior anthracyclines use. The median duration of exposure was 9 months with Avastin plus paclitaxel and 5 months for patients receiving paclitaxel alone.

Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events that occurred at a higher incidence (≥2%) in patients receiving paclitaxel plus Avastin compared with paclitaxel alone, are presented in Table 9.
Table 9
NCI-CTC Grade 3–5 Non-Hematologic and Grade 4 and 5 Hematologic Adverse Events in Study 7 (Occurring at Higher Incidence (≥2%) in Paclitaxel + Avastin vs. Paclitaxel alone)

<table>
<thead>
<tr>
<th>NCI-CTC Terminology</th>
<th>Paclitaxel (n = 348)</th>
<th>Paclitaxel + Avastin (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one event</td>
<td>176 (50.6%)</td>
<td>258 (71.1%)</td>
</tr>
<tr>
<td>Neuropathy—sensory</td>
<td>61 (17.5%)</td>
<td>88 (24.2%)</td>
</tr>
<tr>
<td>Cerebrovascular ischemia</td>
<td>0 (0%)</td>
<td>9 (2.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (1.4%)</td>
<td>58 (16.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (0.6%)</td>
<td>13 (3.6%)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>6 (1.7%)</td>
<td>14 (3.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (1.4%)</td>
<td>15 (4.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (2.3%)</td>
<td>20 (5.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (1.4%)</td>
<td>17 (4.7%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (0.9%)</td>
<td>12 (3.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (5.2%)</td>
<td>39 (10.7%)</td>
</tr>
<tr>
<td>Infection w/o neutropenia</td>
<td>16 (4.6%)</td>
<td>33 (9.1%)</td>
</tr>
<tr>
<td>Infection w/ unknown ANC</td>
<td>1 (0.3%)</td>
<td>11 (3.0%)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>11 (3.2%)</td>
<td>21 (5.8%)</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>1 (0.3%)</td>
<td>9 (2.5%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0 (0.0%)</td>
<td>11 (3.0%)</td>
</tr>
</tbody>
</table>

Sensory neuropathy, hypertension, and fatigue were reported at a ≥5% higher absolute incidence in the paclitaxel + Avastin arm compared with the paclitaxel alone arm.

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal pain/weakness/hypotension (2).
Other Adverse Events

The following adverse events occurred either in Avastin clinical studies or post-marketing experience:

Body as a Whole: polyserositis
Cardiovascular: pulmonary hypertension
Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration
Hemic and lymphatic: pancytopenia
Respiratory: nasal septum perforation, dysphonia
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

DOSAGE AND ADMINISTRATION

Do not initiate Avastin until at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of Avastin.

Metastatic Carcinoma of the Colon or Rectum

Avastin, used in combination with intravenous 5-FU-based chemotherapy, is administered as an intravenous infusion (5 mg/kg or 10 mg/kg) every 14 days.

The recommended dose of Avastin, when used in combination with bolus-IFL, is 5 mg/kg.

The recommended dose of Avastin, when used in combination with FOLFOX4, is 10 mg/kg.
Non-Squamous, Non-Small Cell Lung Cancer
The recommended dose of Avastin is 15 mg/kg, as an IV infusion every 3 weeks.

Metastatic Breast Cancer
The recommended dose of Avastin is 10 mg/kg, as an IV infusion every 14 days.

Dose Modifications
There are no recommended dose reductions for the use of Avastin. If needed, Avastin should be either discontinued or temporarily suspended as described below.

Avastin should be permanently discontinued in patients who develop gastrointestinal perforation (gastrointestinal perforation, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ, wound dehiscence requiring medical intervention, serious bleeding, a severe arterial thromboembolic event, nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy. In patients developing RPLS, discontinue Avastin and initiate treatment of hypertension, if present. (See WARNINGS: Reversible Posterior Leukoencephalopathy Syndrome.)

Temporary suspension of Avastin is recommended in patients with evidence of moderate to severe proteinuria pending further evaluation and in patients with severe hypertension that is not controlled with medical management. The risk of continuation or temporary suspension of Avastin in patients with moderate to severe proteinuria is unknown.

Avastin should be suspended at least several weeks prior to elective surgery. (See WARNINGS: Gastrointestinal Perforation and Wound Healing Complications and PRECAUTIONS: Surgery.)
Avastin should not be resumed until the surgical incision is fully healed.

**Preparation for Administration**

Avastin should be diluted for infusion by a healthcare professional using aseptic technique. Withdraw the necessary amount of Avastin to obtain the required dose and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Diluted Avastin solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for up to 8 hours. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

**Avastin infusions should not be administered or mixed with dextrose solutions.**

**Administration**

**DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial Avastin dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

**Stability and Storage**

Avastin vials must be refrigerated at 2–8°C (36–46°F). Avastin vials should be protected from light. Store in the original carton until time of use. **DO NOT FREEZE. DO NOT SHAKE.**
HOW SUPPLIED
Avastin is supplied as 4 mL and 16 mL of a sterile solution in single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial, respectively.

Single unit 100 mg carton: Contains one 4 mL vial of Avastin (25 mg/mL). NDC 50242-060-01

Single unit 400 mg carton: Contains one 16 mL vial of Avastin (25 mg/mL). NDC 50242-061-01

REFERENCES