

10 Questions About the Use of Bevacizumab in the Management of Recurrent Malignant Gliomas

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1 What is bevacizumab?

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a monoclonal antibody that targets the vascular endothelial growth factor (VEGF), a predominant ligand for the VEGF receptors Flt-1 and KDR.¹ The binding of VEGF to its receptors promotes endothelial cell proliferation as well as angiogenesis—a process required for tumor growth beyond 0.125 mm, which involves the formation of new blood vessels from existing vasculature. The rationale for targeting angiogenesis in brain tumors is based on the highly vascularized nature of malignant gliomas and the increased expression of angiogenic mediators, including VEGF, within brain tumors relative to nonmalignant tissue.^{2–5} Several mechanisms of action have been proposed for antiangiogenic therapies, including the inhibition of tumor-associated neoangiogenesis, a direct effect on VEGFR-expressing tumor cells, potential injury to glioma stem cells by disruption of the microvascular stem cell niche, and the normalization of the tumor-associated vasculature, which leads to improved drug delivery.^{6,7}

2 What are the indications for the use of bevacizumab that are approved by the US Food and Drug Administration (FDA)?

After demonstrating significant improvements in progression-free survival (PFS) and overall survival (OS), bevacizumab, in combination with intravenous (IV) 5-fluorouracil-based chemotherapy, was initially approved by the FDA in 2004 for the first-line treatment of patients with metastatic colorectal cancer (mCRC).⁸ Bevacizumab was subsequently approved in combination with standard chemotherapy for the treatment of advanced non-small-cell lung cancer, metastatic breast cancer, and previously treated mCRC because of its ability to improve PFS and/or OS outcomes in these tumor types. In May 2009, the FDA-granted accelerated approval of bevacizumab as a single agent for the treatment of glioblastoma that has progressed following prior therapy.¹ The accelerated approval was based on an improvement in objective response rate reported in 2 studies—an open-label, multicenter, randomized, noncomparative phase 2 trial, BRAIN, that evaluated bevacizumab with and without irinotecan (Camptosar; Pfizer, New York, NY), a topoisomerase I inhibitor, in 167 patients with glioblastoma at first or second relapse,⁹ and the single-arm, single-institution NCI 06-C-0064E trial that evaluated bevacizumab monotherapy in 56 patients with glioblastoma that had progressed following treatment with temozolomide and radiation therapy.¹⁰

3 How is bevacizumab administered?

Consistent with the half-life of bevacizumab (approximately 20 days), as well as regimens used in other tumor types, most studies in patients with recurrent malignant gliomas have evaluated bevacizumab on a schedule of 10 mg/kg IV every 2 weeks or 15 mg/kg every 3 weeks in combination with irinotecan. Recent studies in the treatment of brain tumors have also evaluated bevacizumab as a single agent administered at 10 mg/kg every 2 weeks. Bevacizumab therapy is continued until disease progression, intolerable toxicity, or patient/physician decision to discontinue treatment. Dose modifications of bevacizumab are not required, even when

administered to patients taking enzyme-inducing epileptic drugs.

At first administration, bevacizumab is given by IV infusion over 90 minutes, following the delivery of chemotherapy. In subsequent cycles, infusions can be shortened to 30 to 60 minutes, as tolerated.^{1,11} Bevacizumab is administered without premedication or prechemotherapy hydration.

4 What is the clinical efficacy of bevacizumab in recurrent glioblastoma and anaplastic glioma?

Malignant glioma is associated with a poor prognosis, with almost all cases recurring after initial therapy and with no clearly established standard of care for recurrent disease. Historical phase 2 trials of a variety of chemotherapeutics have reported response rates between 5% and 6% and 6-month PFS (PFS-6) rates between 9% and 28% in patients with previously treated glioblastomas.^{12–14} Patients with recurrent anaplastic gliomas have shown better outcomes in historical trials, with response rates of approximately 35% and PFS-6 rates of between 17% and 47%.^{12,14,15}

In the largest clinical trial⁹ to evaluate bevacizumab in patients with recurrent glioblastomas to date, 38% (31 of 82) of patients treated with bevacizumab and irinotecan responded to therapy, and the PFS-6 rate was 50% (Table 1). In retrospective analyses and additional phase 2 studies, response rates with combination therapy have ranged between 38% and 62%, and PFS-6 rates have ranged between 30% and 46% in patients with recurrent glioblastomas, representing a significant improvement compared with historical outcomes in this patient population.^{16–19} Similar data regarding response and survival are also observed in patients with recurrent glioblastoma treated with single-agent bevacizumab (Table 1).^{9,10,21} Bevacizumab-containing regimens in patients with recurrent anaplastic gliomas also appear to achieve favorable outcomes relative to those with historical regimens, with response rates ranging between 34% and 68% and PFS-6 rates ranging between 32% and 68% (see Table 1).^{20–24} The clinical benefits demonstrated in these studies, have established the use of bevacizumab-containing regimens as an active treatment option for recurrent



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TABLE 1. Outcomes With Bevacizumab-Containing Therapy in Recurrent Glioblastoma and Anaplastic Glioma

Author	Tumor Type	Regimen	Radiographic Response			Progression-Free Survival		
			CR	PR	SD	Median	6 mo	12 mo
Key studies in glioblastoma								
Stark-Vance ¹⁶	Glioblastoma (n = 11), other HGG (n = 10)	BV + irinotecan	5%	38%	52%	NA	NA	NA
Pope et al ¹⁷	Glioblastoma (n = 10), AG (n = 4)	BV + irinotecan or etoposide	0%	50%	21%	NA	NA	NA
Vredenburgh et al ¹⁸	Glioblastoma (n = 23), AG (n = 9)	BV + irinotecan	3%	59%	34%	NA	Overall: 38%; glioblastoma: 30%	NA
Vredenburgh et al ¹⁹	Glioblastoma (N = 35)	BV + irinotecan		57%	24%	24 wk	46%	20%
Cloughesy et al ⁹	Glioblastoma (N = 167)	BV alone (n = 85); BV + irinotecan (n = 82)	BV alone: 28%; BV + irinotecan: 38%		NA	NA	BV alone: 35.1%; BV + irinotecan: 50.2%	NA
Kreisl et al ¹⁰	Glioblastoma (N = 48)	BV + irinotecan	71% by Levin criteria; 35% by MacDonald criteria		NA	16 wk	29%	NA
Norden et al ²⁰	Glioblastoma (N = 33)	BV + CT	NA	NA	NA	NA	42%	NA
Chamberlain and Johnston ²¹	Glioblastoma (N = 50)	BV	42%	42%	NA	NA	42%	22%
Key studies in anaplastic glioma								
Norden et al ²⁰	AG (N = 21)	BV + CT		34%	59%	24 wk	32%	NA
Desjardins et al ²²	AG (N = 33)	BV + irinotecan	9%	52%	33%	35 wk	55%	39%
Chamberlain and Johnston ²³	AA (N = 25)	BV	0%	64%	8%	29 wk	60%	16%
Chamberlain and Johnston ²⁴	AO (N = 22)	BV	0%	68%	5%	28 wk	68%	25%

AA, anaplastic astrocytoma; AG, anaplastic glioma; AO, anaplastic oligodendroglioma; BV, bevacizumab; CR, complete response; CT, chemotherapy; HGG, high-grade glioma; NA, not available; PR, partial response; SD, stable disease.

glioblastoma²⁵; the data regarding the use of bevacizumab-based treatment in recurrent anaplastic glioma are still emerging, but early results in this patient population are promising.

5 Which agents should be used with bevacizumab to maximize clinical benefit?

Bevacizumab was first evaluated in combination with irinotecan for the treatment of previously treated malignant gliomas on the basis of its activity with irinotecan-containing regimens in patients with mCRC.¹⁶ The encouraging response rate (43%) seen in this initial retrospective study in glioma prompted the use of bevacizumab with irinotecan in later phase 2 studies in patients with malignant gliomas.^{9,17-19,22} Several small studies have combined bevacizumab with other chemotherapeutic agents, including carboplatin, carmustine, etoposide, and temozolomide,^{17,20} and a recently published

study demonstrated that bevacizumab with hypofractionated stereotactic irradiation is active in patients with recurrent malignant gliomas.²⁶ Although it appears that bevacizumab-based therapy improves response and PFS-6 rates relative to historical outcomes in patients with recurrent glioma,²⁷ the relative contribution of chemotherapeutic agents to the activity of bevacizumab has yet to be determined. In a recent phase 2 study that evaluated the efficacy of single-agent bevacizumab followed by combination therapy with bevacizumab and irinotecan upon tumor progression in recurrent glioblastoma, the authors concluded that it is “unclear whether irinotecan adds significant antiglioma activity to bevacizumab” when considering the results of their study and the results of the randomized, noncomparative phase 2 study evaluating the safety and efficacy of bevacizumab with and without irinotecan.¹⁰ The ideal partner for bevacizumab has yet to be defined, in part because of the inherent complexity of cross-trial assessments and the lack of trials

directly comparing bevacizumab-containing regimens. This unanswered question highlights the need for prospective, randomized trials to establish the regimen that achieves maximum clinical benefit in patients with recurrent malignant gliomas.

6 Is bevacizumab effective as a monotherapy?

As mentioned previously, several recent studies have evaluated the safety and efficacy of single-agent bevacizumab in recurrent glioblastoma, and data from these studies have supported the accelerated approval by the FDA for single-agent bevacizumab in this setting.¹ In the randomized, noncomparative phase 2 BRAIN study,⁹ bevacizumab monotherapy achieved a response rate of 28% (24 of 85), PFS-6 rate of 43%, and median OS of 9.2 months (Table 1). Responses, based on both World Health Organization radiographic criteria and stable or decreasing corticosteroid use, were seen in

25.9% (95% confidence intervals, 17.0%–36.1%) of patients.¹ Although the randomized design was not intended to compare outcomes between the treatment arms, the response and PFS-6 rates with single-agent bevacizumab were lower than those observed with bevacizumab plus irinotecan (38% and 50%, respectively, but with overlapping confidence intervals), and the median OS was similar (9.2 vs. 8.7 months) between the treatment arms.

In the single-arm NCI 06-C-0064E study,¹⁰ which evaluated the efficacy of single-agent bevacizumab in patients with previously treated glioblastoma, the response rate, PFS-6 rate, and median PFS with single-agent bevacizumab were 35%, 29%, and 16 weeks, respectively (Table 1). When the response assessment criteria in this study were restricted to include both World Health Organization radiographic criteria and stable or decreasing corticosteroid use, the objective response rate was 19.6% (11/56; 95% confidence interval, 10.9%–31.3%).¹ In a retrospective study of 50 patients with recurrent glioblastoma treated with single-agent bevacizumab, the response rate was 42%, the PFS-6 rate was 42%, and the median OS was 8.5 months.²¹ In all of these studies, the authors concluded that single-agent bevacizumab has significant biologic and anti-glioma activity in patients with recurrent glioblastoma. The activity of bevacizumab monotherapy has also been demonstrated in recurrent anaplastic glioma. In 2 retrospective studies^{23,24} with single-agent bevacizumab, response rates were 64% and 68%, PFS-6 rates were 60% and 68%, and median PFS durations were 28 to 29 weeks (Table 1). Potential benefits of using single-agent bevacizumab may include the minimization of toxicity and preferable pharmacoeconomics.

7 What is the side effect profile of bevacizumab in patients with malignant gliomas?

Bevacizumab-containing regimens are generally well tolerated in patients with malignant gliomas, with the most common side effects being low-grade bleeding, hypertension, impaired wound healing, and proteinuria^{1,9,18,19} similar to adverse events seen in other solid cancers treated with bevacizumab. Serious side effects, such as bleeding events, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS), and more severe wound-healing complications, have been reported less frequently. Life-threatening intracranial hemorrhages have occurred in only a small percentage ($\leq 3\%$) of patients treated with bevacizumab^{9,16,18–20}; this incidence is relatively

low and appears to be within the expected range for spontaneous events in this patient population (approximately 2%–3%).^{28,29} Reported rates of thromboembolism in studies evaluating bevacizumab-based therapy in recurrent glioblastoma have ranged from 7.4% to 11%.^{9,19} A confounding factor in interpreting these rates is that patients with recurrent glioblastomas are already at a significant risk of thromboembolic events—an epidemiologic analysis reported a 7.5% incidence of thromboembolism in 9489 patients with malignant gliomas.³⁰ Occasional instances of gastrointestinal perforation and RPLS (each $< 1\%$ incidence) have also been reported with bevacizumab.^{9,31,32} Following reoperation for recurrent glioblastoma and subsequent treatment with bevacizumab-containing treatment, dehiscence at the site of the craniotomy or at the site of the vascular access device may also occur,³³ although the exact incidence is not known.

It is recommended that bevacizumab be discontinued in patients who develop specific severe adverse events (ie, intracranial hemorrhage, bowel perforation, wound dehiscence),³³ and temporary suspension of bevacizumab is recommended in patients with evidence of moderate to severe proteinuria and in patients with severe hypertension that is not controllable with medication.¹ It is of note that the rate of serious treatment-related adverse events appears to be lower when bevacizumab is used as a single agent than when it is used in combination with chemotherapy. In the randomized, noncomparative phase 2 trial of bevacizumab with or without irinotecan, the rate of grade ≥ 3 adverse events was 46% in patients with recurrent glioblastomas treated with bevacizumab monotherapy relative to 66% in patients treated with bevacizumab combined with irinotecan.⁹ Overall, clinical experience suggests that bevacizumab-containing therapy is associated with manageable, class-specific toxicity, and severe bevacizumab-related adverse events are observed in a minority of patients with malignant gliomas.

8 Can bevacizumab treatment alleviate the need for chronic corticosteroid use?

The use of bevacizumab has been shown to decrease both tumoral and peritumoral edema in patients with malignant gliomas, thereby reducing the requirement for chronic corticosteroid use. Several studies have reported that corticosteroid reductions were feasible in 33% to 59% of patients with malignant gliomas following bevacizumab treatment,^{9,10,18,20} and 2 trials have reported average corticosteroid dose reductions of 72% and 59%,^{10,34} respectively. It appears that a considerable proportion of patients

undergoing bevacizumab treatment are able to dramatically reduce their corticosteroid doses, and that this effect of bevacizumab can be rapid. In a study of patients with malignant brain tumors, the number of tumor and peritumoral edema events was reduced as early as 18 days after the start of bevacizumab-based therapy.¹⁷ The ability of bevacizumab-based therapy to reduce corticosteroid dosage may be an important benefit because chronic corticosteroid use in patients with malignant gliomas is associated with significant morbidity and numerous side effects, including a Cushingoid pattern of weight gain; induction of hyperglycemia, skin fragility, and bleeding; myopathy; lymphopenia; infection; and thromboembolism.^{35–37}

9 What are the appropriate treatment options for disease that progresses on antiangiogenic therapy?

Patients with malignant gliomas who experience tumor progression after antiangiogenic treatment have limited treatment options. In a retrospective analysis of 55 patients with malignant gliomas, those patients with disease that progressed after treatment with a bevacizumab-containing chemotherapeutic regimen responded poorly to a second bevacizumab and chemotherapy combination. In fact, no radiographic responses were observed after the regimen switch, and only 9% of patients (2 of 23) had prolonged PFS.²⁰ In a prospective study of 48 patients with heavily pretreated recurrent glioblastomas treated with bevacizumab monotherapy, 19 patients went on to receive bevacizumab plus irinotecan upon disease progression. None of the 19 patients, however, had radiographic responses to postprogression therapy, and the median PFS was 30 days in this cohort.¹⁰ In a retrospective study of 50 patients with recurrent glioblastoma treated with single-agent bevacizumab (the majority at second relapse), response to an alternative cytotoxic therapy in the subset of patients with an initial response to bevacizumab (42%; $n = 21$) was similarly meager, with a median OS of 2.0 months and a survival range of 1.0 to 5.5 months.²¹

One explanation for the lack of response after bevacizumab treatment is that antiangiogenic therapy only treats 1 of several tumor compartments—the angiogenic-dependent contrast-enhancing component—and does not target the highly infiltrative angiogenic-independent compartments. Consequently, at the time of tumor progression, the tumor phenotype has been altered and may resemble gliomatosis cerebri. Although it is currently unclear what the appropriate options are for patients with disease that progresses following antiangiogenic treat-

ment, novel therapies that target glioma infiltration, migration, and interaction with the extracellular matrix may provide new strategies for treating the angiogenic-independent compartments and the emerging phenotype seen in patients failing bevacizumab after an initial response.

10 Has the optimal role of bevacizumab therapy in the management of patients with brain tumors been defined?

Although the accumulating evidence suggests that bevacizumab has a safe risk/benefit ratio in patients with recurrent disease, there are still a number of unanswered questions pertaining to the optimal use of bevacizumab in patients with malignant gliomas. First, no direct comparisons regarding the ideal treatment schedule or dosing of bevacizumab have been performed in this patient population. It is not apparent whether bevacizumab should be administered weekly, biweekly, or every 3 weeks, and dose-response studies of bevacizumab have not been conducted in patients with malignant gliomas to date. Second, there are no clear guidelines for evaluating neuroradiographic response or progression, and it is debatable as to what constitutes the best response criteria for bevacizumab-based therapy.¹⁰ Third, there are indications that bevacizumab should be evaluated in other treatment settings. For example, although small studies have suggested that bevacizumab may be beneficial in patients with radiation-induced necrosis,^{34,38,39} larger studies are needed to further define the role of bevacizumab in this context. In addition, the use of bevacizumab in noncontrast-enhancing gliomas—a component of many glioblastomas and low-grade gliomas and to a lesser extent of anaplastic gliomas—is likely to be ineffective and will require alternative nonantiangiogenic-based therapies. Additionally, the role of bevacizumab in the treatment of other recurrent primary brain tumors such as meningioma, medulloblastoma, and ependymoma is uncertain, and warrants investigation. Also unknown is the potential role of bevacizumab in managing symptomatic patients with suspected pseudoprogression following concurrent temozolomide and radiation for newly diagnosed glioblastoma, as well as its role in patients with inoperable, newly diagnosed glioblastomas complicated by large corticosteroid-dependent tumor masses. Both of these potential indications reflect a secondary benefit of bevacizumab therapy to markedly improve peritumoral edema, leading to reductions in or discontinuance of chronic corticosteroid use.

A final question regarding the optimal use of bevacizumab is whether bevacizumab

should be used beyond the recurrent setting. Several clinical studies being conducted at UCLA and New York University have reported preliminary data on the use of bevacizumab with chemoradiation in newly diagnosed high-grade gliomas in the frontline setting,^{40,41} and additional investigations are also being conducted at Duke University and the University of Chicago to assess the value of bevacizumab treatment in this setting.^{42,43} Importantly, 2 large phase 3 trials in the United States (sponsored by the Radiation Therapy Oncology Group) and Europe (sponsored by the European Organization for Research and Treatment of Cancer) are opening this year to evaluate bevacizumab-containing regimens for patients with newly diagnosed glioblastomas. A key consideration for the medical oncologist is whether bevacizumab, which is arguably the best salvage treatment for recurrent contrast-enhancing malignant glioma, should be used in the frontline setting or whether it should be reserved for use upon disease progression. These questions will need to be resolved by the results of ongoing and future studies to more clearly define the optimal use of bevacizumab in the management of malignant gliomas.

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AQ1—Please provide pull quote for this manuscript, if necessary.

AQ2—Please note that the reference “Chamberlain and Johnston, In press” cited in Table 1 and in the text, has been listed in the reference list as Ref. 21 and the references have been renumbered accordingly.
