

REVIEW

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Bevacizumab for the Treatment of Recurrent Glioblastoma

Marc C. Chamberlain

Departments of Neurology and Neurological Surgery, University of Washington, Seattle, WA, USA.
Corresponding author email: chambemc@uw.edu

Abstract: Despite advances in upfront therapy, the prognosis in the great majority of patients with glioblastoma (GBM) is poor as almost all recur and result in disease-related death. Glioblastoma are highly vascularized cancers with elevated expression levels of vascular endothelial growth factor (VEGF), the dominant mediator of angiogenesis. A compelling biologic rationale, a need for improved therapy, and positive results from studies of bevacizumab in other cancers led to the evaluation of bevacizumab in the treatment of recurrent GBM. Bevacizumab, a humanized monoclonal antibody that targets VEGF, has been shown to improve patient outcomes in combination with chemotherapy (most commonly irinotecan) in recurrent GBM, and on the basis of positive results in two prospective phase 2 studies, bevacizumab was granted accelerated approval by the US Food and Drug Administration (FDA) as a single agent in recurrent GBM. Bevacizumab therapy is associated with manageable, class-specific toxicity as severe treatment-related adverse events are observed in only a minority of patients. With the goal of addressing questions and controversies regarding the optimal use of bevacizumab, the objective of this review is to provide a summary of the clinical efficacy and safety data of bevacizumab in patients with recurrent GBM, the practical issues surrounding the administration of bevacizumab, and ongoing investigations of bevacizumab in managing GBM.

Keywords: antiangiogenesis, bevacizumab, glioblastoma, vascular endothelial growth factor

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Introduction

Glioblastoma (GBM) is the most lethal subtype of glioma (classified as a World Health Organization Grade 4 infiltrative glioma) and is associated with a median survival of approximately 18 months.¹ Responses to treatment are seen in less than 10% of patients with recurrent GBM, and the median progression-free survival (PFS) is estimated at 9–10 weeks for patients with recurrent GBM.⁴ In 2005, a randomized phase 3 trial demonstrated that the addition of temozolomide (TMZ) to adjuvant radiation therapy followed by 6-months of post-radiotherapy TMZ was associated with an improvement in the median survival of patients with newly diagnosed GBM, from 12.1 months to 14.6 months.^{1,3} While this treatment regimen is now the standard of therapy for GBM, there is still no clearly established standard of care for recurrent GBM albeit both carmustine implants ie, Gliadel (requiring a reoperation for insertion) and bevacizumab have been demonstrated in clinical trials to provide benefit and at least in the United States are approved for this indication.

Essentially all GBM recur after initial therapy, and the majority of patients do not survive beyond 1 year after diagnosis of recurrent disease (1-year survivorship is approximately 20%–25%).^{4,6,7} In historical phase 2 trials utilizing a variety of biologic and chemotherapy-based therapies in patients with recurrent GBM, response rates were 5%–9%, and 6-month PFS (PFS-6) rates ranged between 9% and 28% (median 15%).^{4–7}

Because re-operation and re-radiation are treatment options for only a minority of patients, the majority of patients with recurrent GBM are offered chemotherapy (investigational or best available) at the time of progression. Data from several clinical trials including three prospective studies have established antiangiogenic therapy with the humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody bevacizumab (Avastin®; Genentech, South San Francisco, CA), with or without cytotoxic chemotherapy, as an active treatment option for patients with recurrent GBM who have failed previous TMZ and radiation therapy,⁸ leading to the recent US Food and Drug Administration (FDA) approval of single-agent bevacizumab in previously treated GBM.⁹ This review will provide an overview of the role of angiogenesis in GBM, the development

of bevacizumab treatment for recurrent GBM, the clinical efficacy and safety data of bevacizumab in this cancer setting, insights into bevacizumab administration, and a projection on future use of bevacizumab in the treatment of GBM.

Angiogenesis and Glioblastoma

Angiogenesis is the process by which new blood vessels form from existing vasculature by endothelial cell migration and proliferation. While angiogenesis is a natural physiologic process (ie, in placental growth, wound healing and menses), it is also required for tumor growth beyond 0.125 mm owing to the limits of oxygen and nutrient diffusion.¹⁰ Antiangiogenic strategies are effective in the treatment of cancer, in part, because of the accessibility and genetic stability of endothelial cells (recognizing this is controversial with the recent understanding of tumor cell integration into the tumor vasculature), the fact that angiogenesis is largely absent in healthy adults allowing for therapeutic selectivity, and the residence of cancer stem cells in the (potentially targeted) microvascular niche.¹¹

Glioblastoma is one of the most vascularized cancers,¹² and many preclinical studies use GBM as a tumor model of angiogenesis.¹³ VEGF is an important regulator of angiogenesis that is highly expressed within brain tumors;¹⁴ in GBM, the highest levels of VEGF expression are seen in areas of necrosis and relative hypoxia and regions of endothelial proliferation.^{15,16} The degree of both vasculature density and VEGF expression is correlated with the grade and biologic aggressiveness of gliomas (highest in GBM), as well as with clinical outcomes.^{17–20}

The antiangiogenic agents that were first evaluated in GBM included the oral inhibitors thalidomide, lenalidomide (an analog of thalidomide), and carboxyamidotriazole, as well as the copper-chelating drug penicillamine. The results with these first-generation antiangiogenic therapies, however, were disappointing showing no additional clinical benefit compared to the standard of care (nitrosourea-based chemotherapy), weak inhibition of VEGF-mediated angiogenesis, and a lack of survival benefit.^{21–25} As a consequence more recent investigations have focused on newer, more potent angiogenic inhibitors such as bevacizumab.



Bevacizumab Use in Glioblastoma

The addition of bevacizumab to standard chemotherapy was initially shown to produce significant clinical benefit (PFS or overall survival [OS]) in patients with metastatic colorectal cancer, advanced non-small cell lung cancer, and metastatic breast cancer.^{26–29} These early trials excluded patients with untreated central nervous system (CNS) metastases due to concern for treatment-related intracranial hemorrhage. However the clinical activity in other solid tumors and the need for improved therapy in patients with recurrent GBM resulted in the conduct of a small pilot study using a drug regimen similar to that used for colorectal cancer demonstrating considerable activity (43% objective response rate) and apparent safety with the combination of bevacizumab and irinotecan (Camptosar). As well, a recent meta-analysis reported that patients with CNS metastases treated with bevacizumab had low rates of tumor-associated CNS hemorrhage consistent with historical rates in this patient population, providing further evidence of the safety of bevacizumab in treating brain cancers.^{30,31} Bevacizumab was first evaluated in recurrent high-grade gliomas including GBM in combination with irinotecan, a topoisomerase I inhibitor, owing to its activity with irinotecan-containing regimens in patients with metastatic colorectal cancer.²⁶ These encouraging results prompted the investigation of bevacizumab with irinotecan in subsequent prospective phase 2 studies.^{32–37} Several mechanisms of action have been suggested for the anti-GBM effect of bevacizumab, including direct inhibition of tumor-associated angiogenesis, a direct anti-GBM effect on VEGF receptor-expressing GBM cells, disruption of the glioma stem cell microvascular niche, and improved vascular function or normalization.^{13,39,42,44} The glioma stem cell microvascular niche may represent an important target of antiangiogenic agents, because the resident glioma stem cells are a population of CD133+, nestin+, self-renewing, multipotent GBM-initiating cells that are relatively radio- and chemoresistant.^{38,39}

Efficacy of Bevacizumab

Combination therapy for recurrent glioblastoma

At present, the available data for efficacy of bevacizumab in GBM is derived from several Phase 2 and multiple retrospective studies (Table 1). In the first

completed, prospectively designed, single institution, phase 2 trial of bevacizumab and irinotecan for recurrent GBM, 20 of 35 (57%) patients had at least a partial response (PR), and the PFS-6 rate was 46% (95% confidence interval [CI], 32%–66%).³³ The multicenter, randomized, non-comparative phase 2 BRAIN study (Genentech sponsored) evaluating bevacizumab with or without irinotecan in recurrent TMZ-experienced GBM reported an investigator determined response rate of 38% (31/82) with combination therapy, with a median duration of response of 4.3 months.³⁴ The combination of bevacizumab and irinotecan was associated with a PFS-6 rate of 50% and a median OS of 8.7 months (95% CI, 7.8–10.9 months).³⁴ In retrospective analyses and additional phase 2 studies, investigator determined response rates with bevacizumab-based combination therapy have ranged between 19% and 62%, and PFS-6 rates have ranged between 30% and 46% in patients with recurrent GBM, representing an apparent and significant improvement compared with historical outcomes.^{31,32,37,46,47} An apparent improvement (50%) in median OS (ranging from 31 weeks to 42 weeks) has also been observed with bevacizumab-based regimens relative to historical controls.^{33,34,46,47} In a recent pilot study, the combination of bevacizumab and concurrent radiotherapy (re-radiation) was shown to be active and well tolerated in recurrent malignant glioma.⁴⁸ In this study, patients with recurrent GBM (n = 20) were treated with bevacizumab and hypofractionated stereotactic radiotherapy (HSFRT) with an overall response rate of 50%, PFS-6 of 65%, and median OS of 12.5 months. These results suggested (as has in vitro laboratory data) a possible clinical synergy of radiotherapy and bevacizumab and further suggested potential negative consequences of re-radiation ie, radiation necrosis may be mitigated by concurrent administration of bevacizumab.

Single agent bevacizumab therapy for recurrent glioblastoma

In addition to its activity when combined with irinotecan, bevacizumab has also been shown to increase response and PFS when administered as a single agent in patients with recurrent GBM (Table 1).^{9,34,36} In the phase 2 BRAIN study of patients with GBM who relapsed after TMZ and radiation treatment, the objective response rate with



Table 1. Outcomes with bevacizumab-containing therapy in recurrent glioblastoma and anaplastic glioma.

Author	Tumor type	Regimen	Radiographic response			Progression-free survival			Overall survival Median ^a , months
			CR	PR	SD	Median ^a , months	6 months	12 months	
Key studies in recurrent GB									
Bevacizumab + chemotherapy									
Stark-Vance ³¹	GB (n = 11), other HGG (n = 10)	BV + irinotecan	5%	38%	52%	NA	NA	NA	NA
Pope ⁴⁵	GB (n = 10), AG (n = 4)	BV + irinotecan or etoposide	0%	50%	21%	NA	NA	NA	NA
Vredenburgh ³²	GB (n = 23), AG (n = 9)	BV + irinotecan	3%	59%	34%	Overall: 38%; GB: 30%	NA	NA	GB: 9.23
Vredenburgh ³³	GB (N = 35)	BV + irinotecan	57%		24%	46%	20%		9.7
Friedman ³⁴	GB (N = 167)	BV alone (n = 85); BV + irinotecan (n = 82)	BV + irinotecan: 38%		NA	BV + irinotecan: 50.2%	NA		BV + irinotecan: 8.7
Norden ⁴⁶	GB (N = 33)	BV + CT	NA			42%	NA		GB + AG: 8.2
Nghiempfu ⁴⁷	GB (N = 123)	BV + CT (n = 44); CT or other agent(s) [control] (n = 79)	NA			BV + CT: 41%; control: 18%	NA		BV + CT: 9.0; control: 6.1
Gilbert ³⁷	GB (N = 57)	BV + irinotecan	NA			37%	NA		NA
Bevacizumab + radiation therapy									
Gutin ⁴⁸	GB (n = 20)	BV + HFSRT	50%		NA	65%	NA		12.5
Single-agent bevacizumab									
Friedman ³⁴	GB (N = 167)	BV alone (n = 85); BV + irinotecan (n = 82)	BV alone: 28%		NA	BV alone: 42.6%	NA		BV alone: 9.2
Kreisl ³⁶	GB (N = 48)	BV → BV + irinotecan	Levin criteria: 71%; MacDonald criteria: 35%		NA	29%	NA		7.2
Chamberlain ⁴⁹	GB (N = 50)	BV	42%		42%				8.5
Raizer ⁵⁰	GB (n = 50), AA (n = 5); AO/AOA (n = 6)	BV	0%	25%	50%	32	22%	NA	6.6



Key studies in recurrent AG	BV + CT	34%	59%	GB + AG:	32%	NA	GB + AG:
Bevacizumab + chemotherapy							
Norden ⁴⁶	AG (N = 21)			5.5			8.2
Desjardins ³⁵	AG (N = 33)	9%	33%	8.1	55%	39%	15
Single-agent bevacizumab							
Chamberlain ⁵¹	AA (N = 25)	0%	8%	6.7	60%	20%	9.0
Chamberlain ⁵²	AO (N = 22)	0%	5%	6.75	68%	23%	8.5

Note: ^aMedian PFS and median OS that were reported in weeks were standardized to months using the following formula: weeks/52 × 12.
Abbreviations: AA, anaplastic astrocytoma; AG, anaplastic glioma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; BV, bevacizumab; CR, complete response; CT, chemotherapy; GB, glioblastoma; HFSRT, hypofractionated stereotactic radiotherapy; HGG, high-grade glioma; NA, not available; PR, partial response; SD, stable disease.

single-agent bevacizumab was 28% (24/85), with a median duration of response of 5.6 months.³⁴ When responses in this study were calculated on the basis of MacDonald response criteria (including stable or improved clinical assessment as well as steroid dose) by an independent radiology review, 25.9% (95% CI, 17.0%–36.1%) of patients were found to have responded to bevacizumab monotherapy.⁹ The PFS-6 rate with single-agent bevacizumab was 42.6% (95% CI, 29.6%–55.5%), and the median OS was 9.2 months (95% CI, 8.2–10.7 months).³⁴ In the single institution, prospective phase 2 NCI 06-C-0064E study of 48 patients with recurrent GBM treated with single-agent bevacizumab, 71% and 35% of patients achieved radiographic response based on Levin and MacDonald criteria, respectively.³⁶ When employing an outside and independent response assessment, the objective response rate was 19.6% (11/56; 95% CI, 10.9%–31.3%).⁹ The median PFS was 16 weeks (95% CI, 12–26 weeks), the PFS-6 rate was 29% (95% CI, 18%–48%), and the median OS was 31 weeks (95% CI, 21–54 weeks).³⁶ The response data established by the BRAIN and NCI 06-C-0064E studies resulted in the FDA accelerated approval of single-agent bevacizumab for patients with recurrent GBM following prior upfront, TMZ-based chemoradiotherapy. Two additional studies (a prospective phase 2 trial and a retrospective analysis) have also evaluated single-agent bevacizumab in recurrent GBM with response rates of 25% and 42%, and PFS-6 rates of 32% and 42%, respectively further supporting the activity of bevacizumab for recurrent GBM.^{49,50} Nonetheless and as demonstrated by the European drug regulatory agency, EMEA (European Medicines Agency), approval of bevacizumab for recurrent GBM is dependent upon interpretation of the above mentioned data. European regulatory agencies were unconvinced by these studies and consequently, bevacizumab was not approved in Europe for this indication. It was suggested following completion of bevacizumab vs. an active control treatment such as a nitrosourea in a prospective randomized trial, further consideration of approval of bevacizumab for this indication would be entertained.

Safety Profile of Bevacizumab

In general, bevacizumab treatment is generally well tolerated in patients with recurrent GBM, and



the bevacizumab-related toxicities are comparable to those that have been characterized in other solid cancers. Reported rates of grade 3 or higher adverse events with bevacizumab in patients with recurrent GBM have ranged between 18% and 66%, and it appears that the rate of serious treatment-related adverse events is lower when bevacizumab is used as a single agent.^{34,36,37,49} In the randomized, non-comparative phase 2 BRAIN study in patients with recurrent GBM, the rate of grade 3 or higher adverse events was 46% in patients treated with bevacizumab monotherapy and 66% in patients treated with bevacizumab plus irinotecan.³⁴ Cross-trial comparisons also suggest that single-agent bevacizumab is associated with a lower rate of grade 3 adverse events than bevacizumab-containing combinations for GBM; however, these observations are subject to differences in study design and patient populations.^{37,49}

The most common adverse events attributable to bevacizumab treatment in recurrent GBM include low-grade bleeding (ie, epistaxis), hypertension, impaired wound healing, and proteinuria,^{32–34} which are similar to bevacizumab associated toxicities in other cancer types.^{26,28,29} The majority of these toxicities appear to be due to on-target, class-specific actions of angiogenic inhibition, and reflect disruption of VEGF in normal tissue. The rates of serious adverse events such as gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS), cardiac failure, and wound-healing complications in GBM studies are low (each $\leq 2\%$ incidence).^{31–34,46,48,50,53} While the reported rate of grade 2 or higher bleeding events has been as high as 5.3%, life-threatening intracranial hemorrhages have occurred in only a small percentage ($\leq 3\%$) of patients treated with bevacizumab.^{31–34,37,46,50} This latter incidence rate falls within the expected range for spontaneous events in patients with GBM (approximately 2%–3%).^{54,55} Relatively high rates of thromboembolism ie, deep vein thrombosis and pulmonary embolism have been reported in studies evaluating bevacizumab-containing therapy in recurrent GBM (ranging from 1.6%–12.5%). However, these rates must be considered in the context of the significant risk of thromboembolism that is inherent in patients with GBM.⁵⁶ Thus, the cumulative data from clinical trials suggest that despite small risks of life-threatening complications, including

intracranial hemorrhages and thromboembolism, bevacizumab-containing therapy is well tolerated with manageable, class-specific toxicities.

Practical Issues Regarding Bevacizumab Administration

There are a number of practical issues related to treatment administration, combination therapy, contraindications and other safety-related issues, response evaluation, and disease course that are relevant to the use of bevacizumab for GBM. With regard to administration, the recommended dose and schedule of single-agent bevacizumab is 10 mg/kg intravenously every 2 weeks in patients with recurrent GBM.⁹ While most studies in recurrent GBM have evaluated bevacizumab (in combination with irinotecan) on a schedule of 10 mg/kg every 2 weeks or a weekly equivalent dose of 15 mg/kg every 3 weeks, it is not clear what the ideal treatment schedule or dosage of bevacizumab should be because no direct comparisons of different treatment schedules or dose-response studies have been conducted.^{57,58} Consequently, until a benefit in efficacy or tolerability has been established with an alternative dosing regimen, bevacizumab should be administered as a single agent according to the prescribing information, at a dose of 10 mg/kg every 2 weeks.

It is also unclear as to which therapeutic agent, if any, should be combined with bevacizumab to improve efficacy in recurrent GBM. The similar response and PFS-6 rates observed with bevacizumab monotherapy relative to bevacizumab plus chemotherapy (predominantly irinotecan but also including carboplatin, BCNU, CCNU, TMZ, fotemustine, erlotinib, and etoposide), combined with the limited single-agent activity of irinotecan in recurrent GBM, have led many but not all investigators and the FDA to argue that it is unclear whether irinotecan (or other agents) contributes additional clinical benefit to bevacizumab-based regimens in recurrent GBM.^{36,59–65} For these reasons, as well as the observation of higher rates of grade 3 or higher adverse events that are associated with the combination of chemotherapy and bevacizumab, the addition of irinotecan or other agents outside of clinical trials does not appear to be justified at this time. The identification of an alternative partner for bevacizumab is currently an active area of research.



As an example, in Australia, a randomized phase 2 study (the Cabaret trial) is comparing bevacizumab with or without carboplatin to determine if there is any benefit to using carboplatin in combination with bevacizumab.

Clinical experience suggests that bevacizumab is not contraindicated in patients on other concomitant medications and in particular enzyme-inducing antiepileptic drugs (EIAEDs) and anticoagulants. Dose modifications of bevacizumab are generally not required, even when administered to patients taking EIAEDs such as phenytoin or carbamazepine.^{32,33} Additionally, there does not appear to be an appreciable increased risk of hemorrhage (intracranial or extracranial) with or without concurrent use of bevacizumab with anticoagulants.^{46,66} In a retrospective review of thromboembolic events and anticoagulation in patients with GBM, the investigators concluded that the use of anticoagulants did not lead to any major hemorrhages and did not appear to prohibit the initiation or continuation of bevacizumab therapy though the risk of hemorrhage was modestly increased (2–3 fold).⁶⁶

There are, however, specific severe adverse events that occur at a relatively low incidence but which require dose delays or cessation of bevacizumab. Compelling indications for discontinuing bevacizumab therapy include intracranial hemorrhage (CTC grade 2 or higher), bowel perforation, cardiac failure, stroke and wound dehiscence,⁵³ and temporary suspension of bevacizumab is recommended 4 weeks prior to surgery, as well as in patients with evidence of moderate to severe proteinuria or severe hypertension that is not controllable with medication.⁹ The blockade of VEGF has been shown to impair wound healing, and several studies have indicated a small risk for wound dehiscence, either at the site of the craniotomy or the central venous line.^{31–34,45,46,67} In practice, this observation mandates that antiangiogenic therapy not commence until the craniotomy (or surgical wound) is healed, which may require 4 to 6 weeks. Of note, there are differences in the frequency of monitoring for select bevacizumab-related side effects such as proteinuria, between clinical trials and current clinical practice; based on clinical trial protocols, it is recommended that the urine protein be tested either with every or every other cycle of bevacizumab. In patients with >2+ proteinuria, a 24-hour urine

collection is suggested to quantify and classify by CTC the degree of proteinuria.

A unique challenge in using bevacizumab (as well as other angiogenic inhibitors) for recurrent GBM is determining radiographic response as the one consequence of angiogenic inhibition is a decrease in blood brain barrier disruption. As a direct result of the anti-permeability effect of bevacizumab, contrast enhancing tumor conspicuity is diminished radiographically. Therefore what appears to be a responding GBM by way of decrease in contrast enhancement (and tumor diameters) predominantly represents a secondary steroid like effect, a phenomenon termed a pseudo response. Using alternative MRI sequences such as FLAIR and T2W demonstrate typically little to no change in tumor dimensions on bevacizumab treatment. These findings suggest bevacizumab is predominantly a cytostatic agent and re-emergence of contrast enhancement appears either with discontinuance of bevacizumab or with acquisition of resistance to angiogenic inhibition. The recently published radiology assessment in neuro-oncology (RANO) criteria attempt to improve upon MacDonald response criteria as well as recognize post-bevacizumab radiologic changes that confound interpretation.^{36,68}

At present, there is no consensus as to the most effective method for a priori determination of response to bevacizumab treatment. Common practice in patients with recurrent GBM treated with bevacizumab involves magnetic resonance imaging (MRI) evaluations following 2 cycles of treatment and, if stable or responding, after every subsequent 4 cycles of bevacizumab. Proposed research methods for evaluating response to bevacizumab include assaying for angiogenic factors (eg, serum or urinary VEGF, basic fibroblast growth factor, matrix metalloproteinase, or urokinase plasminogen activator) or ex vivo markers (eg, circulating endothelial cells); biopsy analysis (to determine tumor density and drug–target interactions); and radiographic assessment (calculating fluoro-L-thymidine-PET response, changes in the apparent diffusion coefficient, or the ratio of fluid-attenuated inversion-recovery [FLAIR] volume to contrast-enhancing tumor volume).^{67,69–73}

As a secondary benefit, bevacizumab has been shown to decrease both tumoral and peritumoral edema in patients with GBM, thereby reducing the



requirement for chronic corticosteroid use. Several studies have reported that corticosteroid reductions were feasible in 33% to 59% of patients with recurrent GBM following bevacizumab treatment,^{32,34,36,46,49,74} and 2 trials have reported average corticosteroid dose reductions of 72% and 59%,^{36,74} respectively. The ability of bevacizumab-based therapy to reduce corticosteroid usage is an important benefit, as chronic corticosteroid use in patients with GBM is associated with significant morbidity and numerous side effects, including a cushingoid pattern of weight gain; hyperglycemia, skin fragility and bleeding; myopathy; lymphopenia; infection; and thromboembolism.^{75–77}

Interestingly, a recent retrospective analysis in recurrent GBM that compared outcomes in patients treated with bevacizumab ($n = 44$) with those in a control group ($n = 79$) suggested that the effect of bevacizumab is greater in patients with advanced age.⁴⁷ In the older cohort of patients (≥ 55 years), bevacizumab treatment was associated with a significant improvement in both PFS ($P = 0.02$) and OS ($P = 0.03$) relative to the control group. By contrast, no treatment-related differences in outcomes were observed in younger patients (< 55 years). The authors hypothesized that this age-dependent response may be reflective of biological differences (eg, VEGF-expression levels) in GB in various age groups.⁴⁷ At a minimum, these results support the applicability of bevacizumab for older patients with GBM, a cohort of patients with the highest GBM-related mortality.

Notwithstanding evidence of bevacizumab activity in recurrent GBM, not all patients respond to treatment, and no biomarkers for patients responsive to antiangiogenic therapies have been identified. One explanation for the lack of response after bevacizumab treatment is that antiangiogenic therapy only treats one of several tumor compartments—the angiogenic-dependent contrast-enhancing component—and does not target the highly infiltrative migratory angiogenic-independent compartment (eg, the leading edge of infiltrating glioma cells [FLAIR-defined tumor volume]).^{53,68} In a retrospective analysis, a diffuse, infiltrative pattern of recurrence was seen in 20% of patients (8/40; 95% CI, 9%–36%) treated with salvage bevacizumab for recurrent GBM.⁷⁸ While the authors noted that this pattern of recurrence appears

to be more prevalent with bevacizumab treatment, the analysis, in lacking a control arm, did not provide a corresponding baseline value to establish a more definitive association for this recurrence pattern. Two recently published studies, one conducted retrospectively in the prospective BRAIN trial and the other retrospective, suggest that an increase in the non-contrast enhancing infiltrative GBM compartment is not promulgated by bevacizumab treatment but rather longer survival and failure of bevacizumab to treat this compartment are causative.^{79,80} Importantly, in a subset of patients failing bevacizumab, the first radiographic evidence of disease progression is enlargement in the infiltrative non-contrast enhancing compartment that is best visualized by comparing sequential FLAIR MR images.^{45,46,51,52,68} However, in the majority of patients disease progression on bevacizumab is manifested as the re-emergence of contrast enhancing tumor. A recent study however contends that the majority of patients (75%) failing bevacizumab therapy, regardless if given upfront or at recurrence demonstrate a diffuse pattern of recurrence though the pattern of recurrence does not impact post-bevacizumab survival.⁸¹ The issue of whether diffuse disease is more common following bevacizumab treatment remains controversial. It was also postulated that abrupt cessation of anti-VEGF therapy results in rebound edema and clinical deterioration (so-called flare response), however this has not been shown in clinical studies evaluating off-bevacizumab radiographic progression.

Determining treatment options for patients with GBM who progress following bevacizumab treatment is particularly challenging as at present there is no consensus on the optimal treatment. Strategies used include continuing bevacizumab and adding another agent for example carboplatin (the most common strategy), discontinuing bevacizumab and treatment with either an investigational agent or alternative cytotoxic chemotherapy. In 2 retrospective studies, it was observed that patients who progress (after an initial response) following frontline treatment with a bevacizumab-containing regimen rarely respond to bevacizumab plus an alternative chemotherapy upon progression—with a reported PFS-6 rate of 2% and long-term disease control in 9.5% of patients, respectively.^{46,82} Additional studies have reported that



patients receiving bevacizumab plus irinotecan or an alternative cytotoxic therapy following progression on single-agent bevacizumab have poor outcomes—0 of 19 patients had radiographic responses in a prospective phase 2 study, and a median OS of 2.0 months (range, 1.0–5.0 months) was reported in a retrospective analysis.^{36,49} In a recent study of 35 patients with GBM that progressed following treatment with bevacizumab and irinotecan, continuous low-dose TMZ was added to bevacizumab and irinotecan. The authors concluded that this regimen appears to have activity in previously treated GBM (partial responses in 11.4%, stable disease \geq 2 months in 40%, and a median survival of 5 months [range, 2–13 months]).⁸³ Further investigation is necessary, however, to confirm these preliminary results. Patients with GBM who progress after an initial response to bevacizumab represent a particularly challenging patient population. These patients are and will increasingly be offered novel investigational treatments such as vascular disrupting agents, therapies targeting cell migration (Src), and alternative antiangiogenic therapies (ie, therapeutics that target basic fibroblast growth factor [bFGF], stromal cell-derived factor-1 α [SDF1 α], Tie2, hepatocyte growth factor [HGF], and the c-Met receptor).⁸⁴

Projections

Because of positive clinical results seen in recurrent GBM, bevacizumab continues to be evaluated in additional treatment settings. Most notably in the Dutch BELOP trial and the recently opened EORTC trial (EORTC 2601) are prospectively evaluating bevacizumab vs. CCNU (lomustine) vs. combination therapy in patients with recurrent GBM that will likely define the benefit of bevacizumab in comparison to lomustine, the standard of care in Europe. These studies represent the first attempt to confirm bevacizumab activity in recurrent GBM in a prospective randomized trial. In addition, there continues to be interest in optimizing bevacizumab by way of partnering with another agent. Duke University has proposed a trial of bevacizumab in combination with the anti-integrin inhibitor, cilengitide, both as initial therapy for recurrent disease as well as in the challenging situation of recurrent GBM failing bevacizumab. Increasingly investigators are appreciating the need

for investigational trials in recurrent GBM both for patients that are bevacizumab naïve as well as experienced. There is in addition new studies evaluating and comparing bevacizumab with standard treatment ie, a nitrosourea in recurrent contrast enhancing WHO Grades 2 and 3 gliomas (EORTC TAVAREC trial). These new trials in part are based upon retrospective studies of bevacizumab for recurrent anaplastic gliomas.^{35,46,51,52}

Because of the improved radiographic response to bevacizumab in recurrent GBM relative to historical treatments (20%–25% vs. 5%–6%) and improvement in PFS-6 (40% vs. 15%), it was logical that up-front studies of bevacizumab were designed and executed.^{85–87} Early efficacy results in 2 studies evaluating bevacizumab with radiotherapy and TMZ for the treatment of newly diagnosed GBM compare favorably to data from a historical EORTC (European Organization for Research and Treatment of Cancer)/NCIC (National Cancer Institute of Canada Clinical Trials Group) trial.^{1,86,87} The study by Lai represents the first published such trial using bevacizumab in combination with standard up-front TMZ treatment for newly diagnosed GBM.⁸⁵ Using an institutional control group of patients treated with standard TMZ-based chemoradiation and post-radiation TMZ followed by bevacizumab at time of first recurrence, no difference in OS was seen. Notably the study results by Lai with respect to the primary endpoint ie, OS were very similar to trials using non-bevacizumab containing regimens such as poly-ICLC or talampanel.² These studies suggest that an improvement in OS is seen in newly diagnosed GBM patients irrespective of the add-on therapy in part reflecting the effectiveness of bevacizumab as a salvage therapy. The most striking difference in bevacizumab administered early (upfront) vs. late (salvage) is seen in the improvement in median PFS (13.6 months vs. 7.6 months). Unclear is whether this difference in median PFS is clinically relevant. Bevacizumab mechanistically acts in part as a permeability modifying agent that decreases tumor contrast enhancement, the primary measure of tumor response. Consequently measuring radiographic response by amount of tumor contrast enhancement is problematic (eloquently discussed in the new RANO criteria) and is the likely explanation of the



prolongation of PFS.⁶⁸ Less clear from the study by Lai was whether early bevacizumab compared to delayed bevacizumab resulted in an improvement in quality of life as no instruments such as neurocognitive testing were employed. It is recognized that bevacizumab administered to patients with recurrent GBM regardless of response, benefit from the steroid-like effect of bevacizumab permitting steroid withdrawal or reduction and improvement or resolution of steroid toxicity. The challenge of tumor-related vasogenic edema and steroid dependency are more clinically relevant in the recurrent GBM setting with potentially two exceptions ie, patients with large unresectable tumors that are steroid dependent and the elderly with newly diagnosed GBM. A prospective trial evaluating quality of life throughout the course of a GBM would help clarify these issues. Importantly, 2 large phase 3 trials—RTOG-0825 (a US-based study sponsored by the Radiation Therapy Oncology Group) and AVAglio (a global study sponsored by Roche Pharmaceuticals)—are nearing completion and will prospectively evaluate bevacizumab-containing regimens in patients with newly diagnosed GBM. The results of these studies are needed to establish the safety, including the potential for wound-healing complications, and efficacy of combining bevacizumab with radiotherapy and TMZ in the frontline setting for newly diagnosed GBM. In addition, these studies will answer the question, does the timing of bevacizumab treatment (upfront at initial diagnosis or at recurrence) matter in the management of patients with GBM?

Because a secondary benefit of bevacizumab therapy is a marked improvement of peritumoral edema, leading to reductions in or discontinuance of corticosteroid use, bevacizumab may also be useful in the management of symptomatic patients with suspected pseudo progression following concurrent TMZ and radiation for newly diagnosed GBM,^{88–90} as well as in patients with inoperable, newly diagnosed GBM complicated by large corticosteroid-dependent tumor masses. Additionally, there are indications that bevacizumab may be beneficial in patients with other brain tumors and CNS disorders, such as radiation-induced necrosis with mass effect,^{74,91,92} highly angiogenic non-glioma recurrent primary brain tumors such as meningioma, medulloblastoma, ependymoma,⁹³ oligodendroglial

tumors,^{52,94,95} neurofibromatosis 2 (NF2)-related vestibular schwannomas,⁹⁶ and radiation-induced myelopathy.⁹⁷

Discussion

Angiogenic inhibition holds great promise for the treatment of GBM, a malignant disease associated with an impoverished survival.^{89,98} Bevacizumab is the best characterized antiangiogenic therapy and recently received FDA approval as a single agent for the treatment of patients with recurrent GBM following prior upfront, TMZ-based chemoradiotherapy. Overall, treatment with bevacizumab in multiple GBM studies appears to be well tolerated with toxicity (ie, bleeding, hypertension, wound dehiscence, proteinuria, intracranial hemorrhage and thromboembolism), similar to that seen with other solid cancers treated with bevacizumab-containing therapies.

Because of the extensive clinical experience with bevacizumab, practical issues regarding its administration, safety profile, and response to treatment have been described.^{89,98,99} Notwithstanding this knowledge, several important questions about the use of bevacizumab in GBM still remain unanswered—for example, the optimal therapeutic partner, dosage, treatment schedule, treatment duration in responding patients (ie, in the BRAIN trial 38% of patients continue on treatment at 1-year and 16% at 2-years) and radiographic response criteria of bevacizumab are all unknown, as are the treatment options that should be offered to patients who progress on bevacizumab-based therapy. Many of these unanswered questions are addressed in on-going clinical trials and results of these trials will likely to continue to drive improvements in the treatment of patients with GBM.

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the speaker's bureau for Genentech/Roche, for which he has received honoraria. The author confirms that they have permission to reproduce any copyrighted material.

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