Phase II Study of Concurrent Radiation Therapy, Temozolomide, and Bevacizumab Followed by Bevacizumab/Everolimus as First-Line Treatment for Patients With Glioblastoma

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Abstract: *Purpose*: To evaluate the efficacy of adding bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and everolimus, a mammalian target of rapamycin (mTOR inhibitor), to standard radiation therapy/temozolomide in the first-line treatment of patients with glioblastoma. *Patients and methods*: Following surgical resection or biopsy, patients with newly diagnosed glioblastoma received standard radiation therapy/temozolomide plus bevacizumab 10 mg/kg intravenously (IV) every 2 weeks. Four weeks after the completion of radiation therapy, patients began oral everolimus 10 mg daily, and continued bevacizumab every 2 weeks; therapy continued until tumor progression or unacceptable toxicity. *Results*: Sixty-eight patients were treated, 82% of whom had previously undergone partial or complete surgical resection. Sixty-four patients completed combined modality therapy, and 57 patients began maintenance therapy with bevacizumab/everolimus. Thirty-one of 51 patients (61%) with measurable tumor had objective responses. After a median follow-up of 17 months, the median progression-free survival (PFS) was 11.3 months (95% confidence interval [CI], 9.3–13.1 months); median overall survival was 13.9 months. Toxicity was consistent with the known toxicity profile of bevacizumab; grade 3/4 toxicities during maintenance therapy related to everolimus included fatigue (27%), pneumonitis (7%), and stomatitis (5%). *Conclusions*: The use of bevacizumab and everolimus as part of first-line combined modality therapy for glioblastoma was feasible and efficacious. The PFS compared favorably to previous reports with standard radiation therapy/temozolomide therapy, and is similar to results achieved in other phase II trials in which bevacizumab was added to fist-line treatment. Ongoing randomized phase III trials will clarify the role of bevacizumab in this setting.

Introduction

Glioblastoma, the most common primary brain tumor in adults, remains incurable, with a short expected survival. The standard treatment approach, which includes maximal surgical resection, concurrent radiation therapy and temozolomide, plus temozolo-

mide maintenance, produces a median survival of 14.6 months and a 2-year survival of 26.5%.[1]

Recently, several targeted agents have shown some activity in the treatment of glioblastoma. In particular, inhibition of angiogenesis has proved to be a clinically relevant approach. Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), has shown activity as a single agent and in combination with irinotecan in patients with relapsed glioblastoma, and is currently approved by the US Food and Drug Administration (FDA) for this indication.[2-6] In recurrent glioblastoma, bevacizumab (either alone or in combination) results in 6-month progression-free survival (PFS) ranging from 30–50%, and has been generally well-tolerated. The addition of bevacizumab to combined modality first-line treatment is also of interest; preliminary results from a phase II trial showed that the combination of bevacizumab, temozolomide, and radiation therapy was well-tolerated, with a high level of efficacy.[7] A definitive phase III trial is currently ongoing.

The phosphatidylinositol 3 (PI3) kinase/AKT/mammalian target of rapamycin (mTOR) pathway is also considered to be a relevant target in patients with glioblastoma. Constitutive activation of the PI3 kinase pathway is frequent in glioblastomas, and is associated with a poor prognosis.[8] Activation of the pathway is often caused by mutations in the *PTEN* gene, resulting in loss of suppressor function.[9] Therefore, inhibition of the PI3 kinase pathway may be clinically useful in the treatment of patients with glioblastoma.

In this phase II study, we evaluated the efficacy and feasibility of administering an angiogenesis inhibitor, bevacizumab, and an mTOR inhibitor, everolimus, as part of multi-modality first-line treatment for patients with glioblastoma. Following maximal surgical cytoreduction, bevacizumab was administered concurrently with standard radiation therapy/temozolomide. After completion of radiation therapy, bevacizumab was continued, and everolimus was administered concurrently. Previous phase I and phase II studies have shown the combination of bevacizumab and everolimus to be tolerable and active in selected malignancies.[10-12]

Patients and Methods

This phase II trial was initiated in February 2009, and was performed at selected sites in the Sarah Cannon Research Institute Oncology Research Consortium. The trial was approved at the institutional review boards of all participating sites prior to study activation.

Eligibility

Eligible patients for this trial had histologically-confirmed supratentorial glioblastoma (World Health Organization grade IV). Whenever feasible, patients had maximal surgical resection or debulking, although patients with inoperable glioblastomas were also eligible. No previous treatment with radiation therapy or systemic chemotherapy was permitted. However, local chemotherapy with a Gliadel wafer (polifeprosan 20 with carmustine implant) at the time of surgical resection was permitted. (Since Gliadel wafers have a minor impact on PFS and result in minimal systemic toxicity, it was believed that inclusion of patients receiving this therapy was unlikely to confound study results.) Additional eligibility criteria included age 18 years or older; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate kidney, liver, bone marrow, and cardiac function.

Patients were excluded if they had active cardiac disease or a history of myocardial infarction within 6 months; were pregnant or lactating; were unable to swallow whole pills; had uncontrolled hypertension; had history of thrombotic or embolic events within the last 6 months; had history of bleeding diathesis or coagulopathy; or had known human immunodeficiency virus (HIV) infection. Patients who were receiving warfarin for previous thromboembolic events were eligible, as long as the international normalized ratio (INR) was stable and within therapeutic range. Standard exclusions for patients receiving bevacizumab also applied (serious nonhealing wound, ulcer, or bone fracture; major surgery within 4 weeks of the initiation of treatment with bevacizumab; hemoptysis or other bleeding event within 4 weeks of study entry). Concurrent use of potent inducers or inhibitors of the CYP3A4 enzyme system were not allowed during treatment with everolimus. All patients provided written informed consent prior to entering this trial.

Pretreatment Evaluation

Prior to receiving any protocol treatment, all patients underwent complete blood counts, chemistry profile, complete medical history, prothrombin time, urinalysis, and physical examination. Magnetic resonance imaging (MRI) of the head was performed after surgical resection and prior to initiation of protocol therapy. All patients had tumor measurements performed prior to receiving protocol therapy.

Treatment

Protocol therapy included concurrent radiation therapy, temozolomide, and bevacizumab, followed by maintenance therapy with concurrent bevacizumab and everolimus (Figure 1).

Combined modality therapy included radiotherapy administered by standard techniques and standard doses of temozolomide.[1] Radiotherapy was administered in 2.0 Gy single daily fractions, Monday through Friday, to a total of at least 60 Gy. All patients received temozolomide

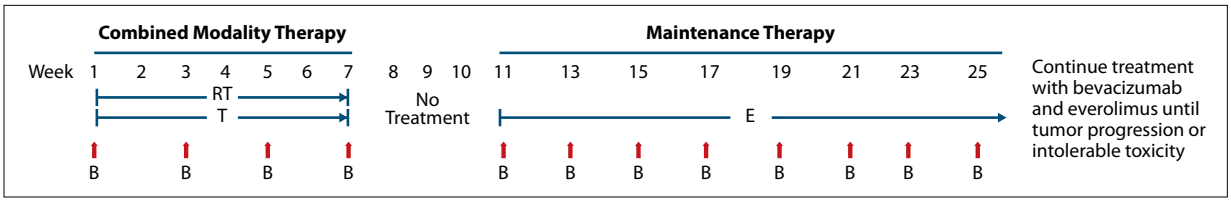

Figure 1. Treatment plan. Patients received 6 weeks of concurrent radiation therapy, temozolomide, and bevacizumab, followed by maintenance therapy with bevacizumab and everolimus.

Treatment schema:
Combined Modality Therapy: Radiation therapy (RT): 2 Gy/fraction, single daily fractions Monday through Friday, to a total of 60 Gy; Temozolomide (T): 75 mg/m^2 by mouth daily; Bevacizumab (B): 10 mg/kg IV every 2 weeks (Weeks 1, 3, 5, and 7); Beginning 4 weeks after the last dose of radiation therapy, patients with objective response or who are clinically stable will begin Maintenance Therapy.
Maintenance Therapy: Bevacizumab (B): 10 mg/kg IV every 2 weeks, beginning Week 11; Everolimus (E): 10 mg by mouth daily, beginning Week 11.

75 mg/m^2 orally daily and bevacizumab 10 mg/kg intravenously (IV) every 2 weeks (weeks 1, 3, 5, and 7), both beginning on day 1 of radiation therapy.

After the completion of combined modality therapy, patients had a 4-week break from treatment. Treatment then resumed (on week 11), with bevacizumab 10 mg/kg IV every 2 weeks and everolimus 10 mg orally daily. Treatment with bevacizumab and everolimus was continued until tumor progression or unacceptable toxicity occurred.

The use of steroids for treatment of cerebral edema was permitted during protocol therapy. The daily dose of steroids was decreased during treatment, if clinically appropriate.

Dose Modifications

Radiotherapy was administered without interruption, if possible. Patients with radiotherapy-related grade 4 toxicity had treatment interrupted for 1 week, or until the toxicity decreased to grade 3 or less. Radiotherapy was resumed at that time. Radiotherapy was also interrupted for a platelet count of less than 20,000/μL, and restarted when the platelet count rose above this level.

The most frequent toxicity anticipated with temozolomide was myelosuppression. Temozolomide was administered without interruption, as long as the absolute neutrophil count (ANC) remained greater than 1,500/μL and the platelet count remained greater than 100,000/μL. Temozolomide was decreased by 25% if the ANC decreased to 1,000–1,500/μL or the platelet count decreased to 75,000–100,000/μL. Temozolomide was stopped for 1 week if the ANC fell to less than 1,000/μL or the platelet count fell to less than 75,000/μL. Dosing was resumed at a 75% dose after the ANC increased to 1,500/μL or greater and the platelet count increased to 100,000/μL or greater. The temozolomide dose was reduced to 75% following any episode of neutropenic fever or a reversible grade 3 or 4 nonhematologic toxicity.

The dose of bevacizumab was not reduced or delayed for myelosuppression. Bevacizumab was delayed or discontinued according to standard guidelines for well-recognized bevacizumab toxicities (eg, hypertension, proteinuria, hemorrhage, venous or arterial thrombosis, gastrointestinal [GI] perforation, fistula, congestive heart failure, wound dehiscence, or reversible posterior leukoencephalopathy).

The dose of everolimus was modified on the basis of either hematologic or nonhematologic toxicity. Everolimus was interrupted if grade 3 or 4 toxicity occurred, and was held until the toxicity improved to grade 1 or less. At that time, dosing was resumed with a 1-level dose reduction (5 mg orally once daily). Patients were monitored for development of hyperlipidemia or hyperglycemia; if these events occurred, appropriate medical management was initiated.

Determination of Response

Patients were reassessed with MRI scanning following combined modality therapy. Patients with objective response or stable disease began treatment with concurrent bevacizumab and everolimus. Patients were reevaluated at 8-week intervals with MRI scans until tumor progression was documented. If MRI findings were equivocal, or pseudo-progression was considered a possibility after discussion with the neuroradiologist and radiation oncologist, the patient was continued on therapy and the MRI was repeated after a 2-month interval. Response to treatment was determined using the criteria from MacDonald and colleagues.[13]

Statistical Analysis

The primary objective of this phase II trial was to obtain efficacy data regarding this novel first-line treatment regimen. The primary efficacy endpoint was PFS. Objective response rate and overall survival were secondary endpoints.

When this trial was designed, there were no results from trials that incorporated bevacizumab into first-line combined modality therapy; therefore, the median PFS of 7 months obtained with concurrent radiation therapy/temozolomide

Table 1. Patient Characteristics (N=68)

Characteristic	Number of Patients (%)
Median age, years (range)	
59 (24–80)	
Sex	
Male	39 (57%)
Female	29 (43%)
ECOG performance status	
0	24 (35%)
1	44 (65%)
Previous surgical resection	
Complete	17 (25%)
Partial	39 (57%)
Biopsy only	12 (18%)

ECOG=Eastern Cooperative Oncology Group.

was used as a comparator. Improvement in the median PFS from 7 to 10 months was believed to be a clinically significant result. To detect such a difference, inclusion of 55 evaluable patients was necessary in this phase II trial (80% power, alpha = 0.05). To allow for a projected 15% inevaluable rate, a total accrual of 64 patients was planned.

The PFS was defined as the interval from the first date of study treatment until the date of disease progression or death. Overall survival was defined as the interval from the first day of study treatment until the date of death. The toxicity analysis included all patients who received at least 1 dose of therapy. Toxicity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 3.0). Survival curves were calculated using the Kaplan-Meier method.[14]

Results

Patient Characteristics

Between February 2009 and October 2009, 68 patients were entered into this clinical trial (Table 1). The median age of the patients was 59 years; 39 patients (57%) were male. Surgical resection or debulking of the glioblastoma had been performed prior to study entry in 56 patients; 17 patients had complete resection, and only 3 patients (4%) had been treated with Gliadel wafers. Twelve patients (18%) were unresectable and had only a biopsy performed. In these 12 patients, resection was not performed due to multifocal tumor (9 patients) or unfavorable tumor location (3 patients). Patients began combined modality treatment a median of 31 days after their surgical resection or biopsy (range, 27–63 days).

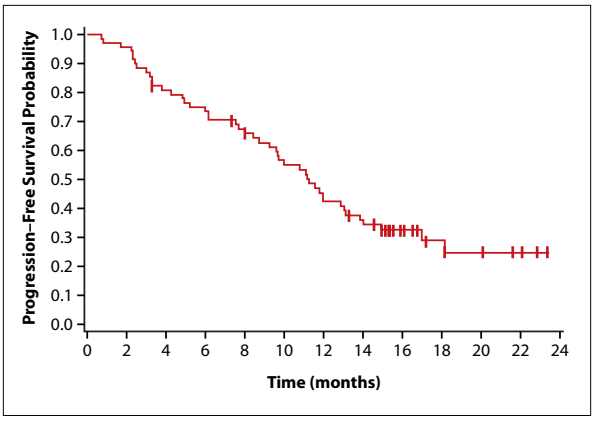

Figure 2. Estimated progression-free survival (PFS) for 68 patients treated. Median PFS was 11.3 months (95% confidence interval [CI], 9.3–13.1 months).

Treatment Received

Sixty-four of 68 patients (94%) completed combined modality therapy. Four patients (6%) did not complete this treatment for the following reasons: disease progression (2 patients); patient request (1 patient); and toxicity (GI perforation, 1 patient). The planned radiotherapy dose was delivered without interruptions to all patients who completed combined modality therapy.

After the 4-week interval without treatment, 57 of the 64 patients who completed combined modality therapy began maintenance therapy with bevacizumab and everolimus. Seven patients who completed combined modality therapy did not begin maintenance therapy for the following reasons: treatment-related toxicity (delayed wound healing, grade 5 myocardial infarction, persistent thrombocytopenia; 3 patients); intercurrent illness (alcohol/narcotics abuse, necrotizing fasciitis; 2 patients); physician discretion (1 patient); and progressive disease (1 patient).

The median duration of maintenance treatment with bevacizumab and temozolomide was 5 months (range, 0–13+ months). Twenty-three patients are currently continuing therapy. Of the 34 patients who stopped maintenance therapy, 13 patients (38%) did so because of tumor progression. Other reasons for discontinuation of therapy included intercurrent illness (7 patients), treatment-related toxicity (6 patients; febrile neutropenia, 2 patients; 1 patient each thrombotic thrombocytopenic purpura, pneumonitis, fatal central nervous system [CNS] hemorrhage, fatal pulmonary embolism), patient request (5 patients), symptomatic deterioration (2 patients), and withdrew consent (1 patient).

Efficacy

At the time combined modality therapy was initiated, 51 patients had measurable tumor on MRI scan, and were evaluable for response to treatment. After complet-

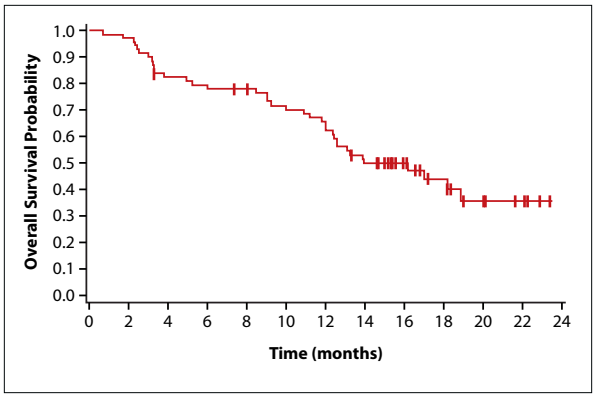

Figure 3. Estimated overall survival (OS) for 68 patients treated. Median OS was 13.9 months (95% confidence interval [CI], 12.4 months–not available).

ing combined modality treatment, 29 patients (57%) had partial responses. Two additional partial responses were seen during maintenance treatment (for an overall response rate of 61%), and 1 patient with a partial response improved to a complete response.

Figure 2 shows the estimated PFS for the entire group; 36 patients had progressed after a median follow-up of 17 months. The median PFS was 11.3 months (95% confidence interval [CI], 9.3–13.1 months). The 6-, 12-, and 18-month PFS rates were 73%, 42%, and 29%, respectively.

The estimated overall survival is shown in Figure 3. The median survival was 13.9 months (95% CI, 12.4–NA months). The overall survival rate at 18 months was 44%.

Toxicity

Treatment-related toxicity during combined modality therapy is detailed in Table 2. Most of the toxicity was consistent with the known toxicity profile of concurrent radiation therapy and temozolomide. Additional grade 3/4 toxicity that was possibly related to bevacizumab included venous thromboembolic events (4%), hypertension (3%), GI perforation (1%), and arterial thrombotic events (3%). These toxicities are consistent with the known toxicity profile of bevacizumab, and did not seem more severe or frequent in this combination regimen.

The toxicity observed during maintenance treatment with bevacizumab and everolimus is summarized in Table 3. Again, the toxicity profile was consistent with the known profiles of the 2 agents, and was also consistent with previous reports of this combination. The most common grade 3/4 toxicities related at least in part to everolimus included fatigue (27%), pneumonitis (7%), stomatitis/mucositis (5%), and hyperlipidemia (4%). During maintenance treatment, grade 3/4 bevacizumab toxicity included hypertension (14%), venous thromboembolism (13%), and proteinuria (5%).

Table 2. Treatment-Related Toxicity During Combined Modality Therapy (N=68)

	Number of Patients (%)		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic			
Neutropenia	1 (1%)	0	1 (1%)
Thrombocytopenia	4 (6%)	5 (7%)	2 (3%)
Anemia	2 (3%)	0	0
Febrile neutropenia	0	0	1 (1%)
Nonhematologic			
Fatigue	16 (24%)	2 (3%)	1 (1%)
Thrombosis/ embolism	0	2 (3%)	1 (1%)
Hypertension	2 (3%)	2 (3%)	0
Nausea/vomiting	7 (10%)	1 (1%)	0
Stomatitis/mucositis	7 (10%)	0	0
Skin rash	4 (6%)	0	0
Proteinuria	3 (4%)	0	0
CNS ischemia	0	0	1 (1%)
Deaths			
Gastrointestinal perforation	1 (1%)		
Myocardial infarction	1 (1%)		

CNS=central nervous system.

There were 4 patients who had fatal treatment-related toxicity. One patient experienced fatal GI perforation prior to completing combined modality therapy. One patient had a fatal myocardial infarction in the 4 weeks between combined modality and maintenance therapy. During maintenance bevacizumab/everolimus, 1 patient had a fatal pulmonary embolism, and 1 patient had a CNS hemorrhage that resulted in death.

Discussion

The ability to modulate the activity of several critical molecular pathways has improved prospects for the treatment of glioblastoma. Inhibition of angiogenesis has already shown therapeutic potential in patients with relapsed/refractory glioblastoma. To date, bevacizumab has produced the best results in this setting. The demonstration of objective tumor regressions in 50–60% of patients, with a 6-month PFS of 30–50%, resulted in the FDA approval of bevacizumab in this setting.[2-6] Several inhibitors of the VEGF receptor may also have activity in the treatment of relapsed/refractory glioblastoma.[15,16] The

Table 3. Treatment-Related Toxicity During Maintenance Treatment With Bevacizumab/Everolimus (N=57)

	Number of Patients (%)		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic			
Neutropenia	4 (7%)	0	0
Thrombocytopenia	8 (14%)	2 (4%)	0
Nonhematologic			
Fatigue	12 (21%)	13 (23%)	2 (4%)
Thrombosis/embolism	1 (2%)	2 (4%)	5 (9%)
Hypertension	14 (25%)	8 (14%)	0
Pneumonitis	1 (2%)	3 (5%)	1 (2%)
Proteinuria	8 (14%)	3 (5%)	0
Stomatitis/mucositis	4 (7%)	3 (5%)	0
Hyperlipidemia	3 (5%)	2 (4%)	0
Diarrhea	3 (5%)	1 (2%)	0
Skin rash	9 (16%)	0	0
Nausea/vomiting	3 (5%)	0	0
Deaths			
Pulmonary embolism	1 (1%)		
CNS hemorrhage	1 (1%)		

CNS=central nervous system.

PI3 kinase/AKT/mTOR pathway is also a target of great interest in the treatment of patients with glioblastoma. Although the relevance of this pathway as a therapeutic target has not been proven, the frequent constitutive activation seen in glioblastoma, often associated with *PTEN* mutation, strongly suggests that disorders in this pathway are important determinants of the malignant phenotype.

In this study, we added an angiogenesis inhibitor (bevacizumab) and an mTOR inhibitor (everolimus) to the first-line combined modality treatment of patients with glioblastoma. Bevacizumab treatment was initiated concurrently with standard radiation therapy/temozolomide. Everolimus was begun after radiation therapy was complete, and was administered in combination with bevacizumab until tumor progression occurred. While adding bevacizumab and everolimus to this combined modality regimen, we deleted the maintenance treatment with temozolomide, which has been part of the standard treatment regimen. The contribution of continued administration of temozolomide beyond the completion of concurrent radiotherapy/temozolomide independently has never been independently assessed. We believed that omission of maintenance temozolomide would not make a substantial change in efficacy, since single-agent temozolomide has a low level of efficacy against glioblastoma, and maintenance strategies using single-agent chemotherapy have been unsuccessful in many other, better-studied tumor types. Since we were concerned about the possible toxicity of adding bevacizumab and everolimus to temozolomide, we opted to substitute bevacizumab (a drug with substantial single-agent activity) and everolimus for temozolomide.

In this multicenter, community-based phase II trial, we found this novel regimen to be active and well tolerated. Objective responses occurred in 61% of patients, and the median PFS was 11.3 months (95% CI, 9.3–13.1 months). These results compare favorably with historical results achieved with standard radiation therapy/temozolomide (median PFS, 6.9 months).[1]

Since our trial was initiated, the preliminary results of several other phase II trials incorporating bevacizumab into first-line combined modality therapy have been reported. Lai and associates added bevacizumab concurrently with radiation therapy/temozolomide, and continued bevacizumab with temozolomide following completion of radiation therapy. In a group of 70 patients, the median PFS was 13.6 months, similar to the median PFS observed in our trial.[17] Vredenburgh and colleagues reported results of a similar regimen, with the exception that irinotecan was added to bevacizumab/temozolomide after radiotherapy was completed. In 125 patients, a median PFS of 14 months was achieved.[18] Two other smaller phase II studies have also reported similar median PFS.[7,19] In addition, all studies have demonstrated a favorable toxicity profile, with no suggestion of increased intracranial bleeding or other bevacizumab-related adverse events. In spite of consistent suggestion of improved PFS in these phase II studies, effects on overall survival have been less consistent when compared to historical results with radiation/temozolomide.[7,18-20] Difficulties in accurately measuring PFS in glioblastoma have been increasingly recognized (eg, effects of previous radiotherapy, peritumoral edema); therefore, demonstration of improved survival in randomized trials will be critical in establishing the role of bevacizumab in first-line therapy.

The substitution of everolimus for temozolomide in the maintenance phase of treatment was feasible and well tolerated, but the role of everolimus in the treatment of glioblastoma remains unclear. It is possible that retaining the maintenance temozolomide, with the addition of bevacizumab, would have resulted in a more active regimen. Several newer targeted agents are more efficient in blocking the PI3 kinase pathway, and may be preferable to everolimus in this setting. Several ongoing studies are evaluating PI3 kinase inhibitors, either as single agents or with bevacizumab, in patients with relapsed/refractory glioblastoma.

The combined evidence from several phase II studies strongly suggests a role for bevacizumab in combination with radiotherapy/temozolomide in the first-line treatment of glioblastoma. Two large phase III studies are currently comparing the efficacy of standard radiotherapy/temozolomide versus radiotherapy/temozolomide/bevacizumab, and will provide a definitive answer to this question. Continued development of angiogenesis inhibitors and exploitation of other critical pathways make further improvements of glioblastoma treatments likely in the near future.

Acknowledgment

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