VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma

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Submitted September 8, 2008; accepted March 19, 2009; published online ahead of print at www.jco.org on August 31, 2009.

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Genentech Inc provided support for manuscript preparation.

Presented in part at the 12th Annual Meeting of the Society for Neuro-Oncology, November 15-18, 2007, Dallas, TX, and at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/09/2728-4733/$20.00

DOI: 10.1200/JCO.2008.19.8721

ABSTRACT

Purpose
We evaluated the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with recurrent glioblastoma in a phase II, multicenter, open-label, noncomparative trial.

Patients and Methods
One hundred sixty-seven patients were randomly assigned to receive bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m^2 or 125 mg/m^2 (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) once every 2 weeks. Primary end points were 6-month progression-free survival and objective response rate, as determined by independent radiology review. Secondary end points included safety and overall survival.

Results
In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month progression-free survival rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively; and median overall survival times were 9.2 months and 8.7 months, respectively. There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. Of the patients treated with bevacizumab alone or bevacizumab plus irinotecan, 46.4% and 65.8%, respectively, experienced grade $\geq$ 3 adverse events, the most common of which were hypertension (8.3%) and convulsion (6.0%) in the bevacizumab-alone group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the bevacizumab-plus-irinotecan group. Intracranial hemorrhage was noted in two patients (2.4%) in the bevacizumab-alone group (grade 1) and in three patients (3.8%) patients in the bevacizumab-plus-irinotecan group (grades 1, 2, and 4, respectively).

Conclusion
Bevacizumab, alone or in combination with irinotecan, was well tolerated and active in recurrent glioblastoma.

J Clin Oncol 27:4733-4740. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Glioblastoma is the most aggressive malignant primary brain tumor in adults and is nearly always fatal. Standard treatment for newly diagnosed glioblastoma is surgical debulking followed by radiotherapy and temozolomide (TMZ) with additional maintenance TMZ.[1] At the time of disease recurrence, few treatment options are available. Procarbazine and nitrosoureas are modestly effective as systemic agents, although they were evaluated before routine use of first-line TMZ. For selected patients, salvage surgery and prolifeprospan 20 with carmustine wafers are indicated. Single-agent irinotecan (CPT-11; Camptosar; Pfizer, New York, NY), a topoisomerase I inhibitor, is commonly used in the relapse setting, albeit with response rates of 15% or less.[2-5] Despite therapy, 6-month progression-free survival (PFS) for relapsed or progressive glioblastoma is 9% to 21%, objective response (OR) rate is less than 10%, and median overall survival (OS) is 30 weeks or less.[2-8] Thus, recurrent glioblastoma remains a largely unmet medical need, which highlights the need for novel and effective therapies.

Significant progress has been made in understanding the molecular characteristics of glioblastoma and the potential of targeted therapeutic approaches to the disease. Grade 4 gliomas have long been associated with pathologic hallmarks of extensive tumor necrosis; intense vascular proliferation; and increased expression of angiogenic factors, the most notable of which is vascular endothelial growth factor (VEGF). VEGF is an important regulator of angiogenesis and has been implicated in pathologic

angiogenesis associated with tumor growth.[9] It is highly expressed in glioblastoma, and overexpression correlates with high-grade malignancy and poor prognosis.[10-12] Consistent with being hypoxia driven, VEGF expression is localized to regions of glioblastoma that border areas of necrosis.[13-15]

Bevacizumab (BV; Avastin; Genentech, South San Francisco, CA) is a humanized monoclonal antibody that inhibits VEGF and is the first antiangiogenic therapy to be approved for use in patients with cancer. In combination with chemotherapy or biologics, BV was associated with prolonged OS in phase III trials of metastatic colorectal[16] and non–small-cell lung[17] cancers and with prolonged PFS in metastatic breast[18] and renal[19] cancers compared with placebo or chemotherapy alone. In a single-institute, phase II trial of patients with recurrent glioblastoma, BV in combination with CPT-11 demonstrated 46% 6-month PFS and 57% OR rates.[20] We sought to confirm these findings in a phase II, multicenter, randomized, noncomparative trial that evaluated safety and efficacy of BV alone and in combination with CPT-11 in patients with glioblastoma who were experiencing first or second relapse after they experienced failure with TMZ.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed glioblastoma in first or second relapse and had disease progression confirmed by magnetic resonance imaging (MRI) $\leq$ 14 days before the first study treatment. Contrast-enhancing, bidimensionally measurable disease was required. Patients had been treated with standard radiotherapy and had received TMZ. Other key inclusion criteria were Karnofsky performance status (KPS) $\geq$ 70%; life expectancy greater than 12 weeks; and adequate hematologic (ie, platelet count $\geq$ 100,000/μL, absolute neutrophil count $\geq$ 1,500/μL), hepatic, and renal function. Patients taking corticosteroids were required to be on a stable or decreasing dose for 5 or fewer days before baseline MRI. Therapeutic systemic anticoagulation with low molecular weight heparin or warfarin was allowed.

Exclusion criteria included previous treatment with prolifeprospan 20 with carmustine wafer, CPT-11, or anti-VEGF agents; MRI evidence of recent intracranial hemorrhage; history of bleeding diathesis or coagulopathy; clinically significant cardiovascular disease; arterial thromboembolism less than 6 months before the first study treatment; and uncontrolled hypertension.

Study Design

Eligible patients were randomly assigned to receive BV or BV + CPT-11 and were stratified by KPS (70% to 80%, 90% to 100%) and by first or second relapse (Fig 1). All patients received BV 10 mg/kg intravenously every other week. Patients in the BV + CPT-11 group received CPT-11 340 mg/m^2 (if taking enzyme-inducing antiepileptic drugs [EIAEDs]) or 125 mg/m^2 (if not taking EIAEDs) intravenously over 90 minutes every other week. A treatment cycle was defined as 6 weeks of therapy.

Reduction in BV dose was not permitted. If toxicity necessitated holding BV, the dose level was not changed once treatment resumed. If a patient given BV + CPT-11 experienced grades 3 or 4 toxicity, all drugs were held until resolution to grade 1 or less, and CPT-11 dose was reduced by 25%. If no additional toxicity occurred, the reduced dose was maintained for all subsequent treatments. If grade 3 or 4 toxicity occurred at the reduced CPT-11 dose, the dose was reduced by an additional 25%. Additional dose reductions were not permitted. The maximum allowable length of treatment interruption was 30 days.

Patients in both groups were treated for 104 weeks or until disease progression or discontinuation (ie, planned treatment period). Patients in the BV group who experienced disease progression could enter a postprogression phase and could receive CPT-11 in combination with BV. Patients who experienced disease progression a second time or who experienced unmanageable toxicity were discontinued from study treatment and were observed for survival. Patients in the BV + CPT-11 group who experienced unmanageable toxicity could discontinue the toxicity-causing agent and could continue receiving the remaining single agent for the balance of the 104-week treatment period. Patients in the BV + CPT-11 group who demonstrated radiographic or clinical disease progression at any time were discontinued from study treatment and were observed for survival. The appropriate local institutional review boards approved the protocol. All patients provided written, informed consent before study participation.

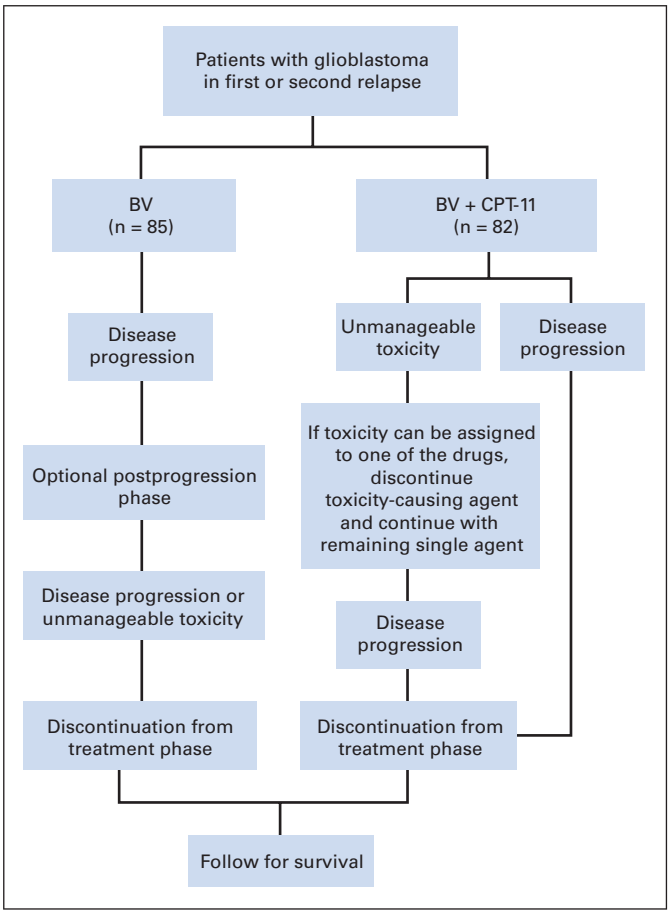

Fig 1. Study design. Patients with recurrent glioblastoma were randomly assigned to receive bevacizumab (BV) or BV plus irinotecan (CPT-11) and were stratified by Karnofsky performance status (70% to 80%, 90% to 100%) and by first or second relapse. BV-group patients who experienced disease progression could receive CPT-11 in combination with BV in an optional postprogression phase for the remainder of the 104-week treatment period.

Efficacy

Primary end points were 6-month PFS and OR rates. Six-month PFS was defined as the percentage of patients who remained alive and progression free at 24 weeks. OR was defined as a complete or partial response observed on two consecutive MRIs obtained 4 or more weeks apart. Secondary end points included OS, PFS, and response duration. Patients lost to follow-up were censored at the date they were last known to be alive.

Safety

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[21] AEs included abnormal laboratory values relative to universal normal ranges.

Assessments

All patients underwent clinical, laboratory, and MRI assessments before beginning each treatment cycle. Progression and OR were assessed by a blinded, independent radiology facility according to WHO Response Evaluation Criteria,[22] and corticosteroid dose was taken into account.[23] In addition to meeting MRI criteria for complete response, a patient could not be taking corticosteroids greater than physiologic levels (ie, equivalent to 20 mg/d hydrocortisone) at the time of MRI. In addition to meeting MRI criteria for partial response, the corticosteroid dose at the time of MRI could not be greater than the maximum dose taken during the first 6 weeks of study treatment. Corticosteroid dose did not affect determination of stable and progressive disease. Complete and partial responses were classified according to confirmatory MRI performed 4 or more weeks after an observed response. Only contrast-enhancing lesions were measured. Non–contrast-enhancing lesions were considered nontarget lesions in tumor assessment. Progression was determined by contrast-enhancing and non–contrast-enhancing lesions. Any new area of nonenhancing T2 or fluid-attenuated inversion-recovery signal consistent with tumor was considered progressive disease. Index lesions were not considered in the qualitative assessment of enhancement intensity. In the absence of radiographic documentation, clinical progression was used to determine progression. All patients were observed until discontinuation from the study, loss to follow-up, study termination, or death.

Statistical Analysis

Statistical analyses were performed after randomly assigned patients had been observed for ≥ 6 months. Efficacy analyses included the intent-to-treat population, which was defined as all randomly assigned patients. The primary efficacy analyses of 6-month PFS and OR rates were performed at a two-sided .025 level of significance to control for overall type-I errors at ≤ .05 for each treatment group. Exact 97.5% CIs for OR were calculated by using the Blyth-Still-Casella method.[24] Kaplan-Meier methods[25] were used to estimate 6-month PFS, median PFS, and median OS; the corresponding CIs (97.5% for 6-month PFS and 95% for median PFS and median OS) were calculated by using Greenwood's formula.[26] Data from patients who began alternative antitumor therapy before they experienced disease progression were censored at the last tumor assessment before the patients received the alternative therapy. Data from patients who experienced progression or who died greater than 42 days after their last dose of study drug were censored at the date of the last tumor assessment before their last dose of study drug plus 42 days.

On the basis of historical data,[2-7] 6-month PFS with salvage therapy or single-agent CPT-11 was assumed to be 15.0%, and the OR rates were assumed to be 5.0% with salvage therapy and 10.0% with single-agent CPT-11. A sample of approximately 80 patients in each treatment group provided approximately 80.0% power to detect ≥ 13.0% improvement in 6-month PFS and ≥ 90.0% power to detect ≥ 13.0% improvement in OR rate at a two-sided significance level of .025. Between-group comparisons of 6-month PFS and OR rates were not performed.

Safety analyses were performed by using descriptive statistics, and these analyses included randomly assigned patients who received at least one dose of study drug.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	% of Patients by Treatment Group	
	BV (n = 85)	BV + CPT-11 (n = 82)
Age, years		
Median	54	57
Range	23-78	23-79
Sex		
Male	68.2	69.5
Female	31.8	30.5
Ethnicity		
White	90.6	89.0
Black	3.5	2.4
Asian/Pacific Islander	2.4	0
Hispanic	3.5	6.1
Other	0	2.4
Prior diagnosis of glioma		
Glioblastoma	91.8	92.7
Other*	8.2	7.3
Relapse		
First	81.2	80.5
Second	18.8	19.5
KPS		
90-100	44.7	37.8
70-80	55.3	62.2
Initial surgery		
Partial resection	49.4	53.7
Complete resection	42.4	37.8
Biopsy only	8.2	8.5
Medication use at baseline		
EIAEDs	21.2	36.6
Corticosteroids	50.6	52.4
Anticoagulants	10.6	12.2
Median weeks to study treatment		
From last radiotherapy†	27.0	28.7
From last surgery†	32.2	34.4
Enrollment		
≤ 3 months (13 weeks) after last radiotherapy†	8.3	12.7
≤ 3 months (13 weeks) after last surgery†	20.2	10.1

Abbreviations: BV, bevacizumab; CPT-11, irinotecan; KPS, Karnofsky performance status; EIAEDs, enzyme-inducing antiepileptic drugs.
*Prior anaplastic astrocytoma or other histology progressing to grade IV glioblastoma.
†Treated patients were as follows per group: BV, n = 82; BV + CPT-11, n = 79.

RESULTS

Data analysis was prespecified to occur after all enrolled patients had been observed for 6 months. Efficacy and safety analyses included all study data collected through September 15, 2007. Subsequent follow-up provided an additional 2 months of survival data. Thus, the OS analysis and the safety analysis of death included data collected through November 15, 2007.

Patient Baseline Characteristics

Between June 2006 and February 2007, 167 patients were randomly assigned to receive BV (n = 85) or BV + CPT-11 (n = 82; Table 1). One hundred fifty-four (92.2%) of the randomly assigned patients had an initial diagnosis of glioblastoma. The remaining patients had an initial diagnosis of anaplastic astrocytoma or other lower-grade glioma that had progressed to glioblastoma, as histologically confirmed at study entry. Site-determined histologic diagnosis of glioblastoma was subsequently confirmed by central pathology review in all but two patients, one of whom had disease that was centrally interpreted to be anaplastic astrocytoma and the other for whom histologic samples were not available. Thirty-two patients (19.2%) had second-relapse glioblastoma. Eighteen patients (21.2%) in the BV group and 30 patients (36.6%) in the BV + CPT-11 group were being treated with EIAEDs, and baseline corticosteroid use was similar in the two groups (BV, 50.6%; BV + CPT-11, 52.4%). The median time from initial diagnosis to study random assignment was 8.6 months for the BV group and 9.8 months for the BV + CPT-11 group.

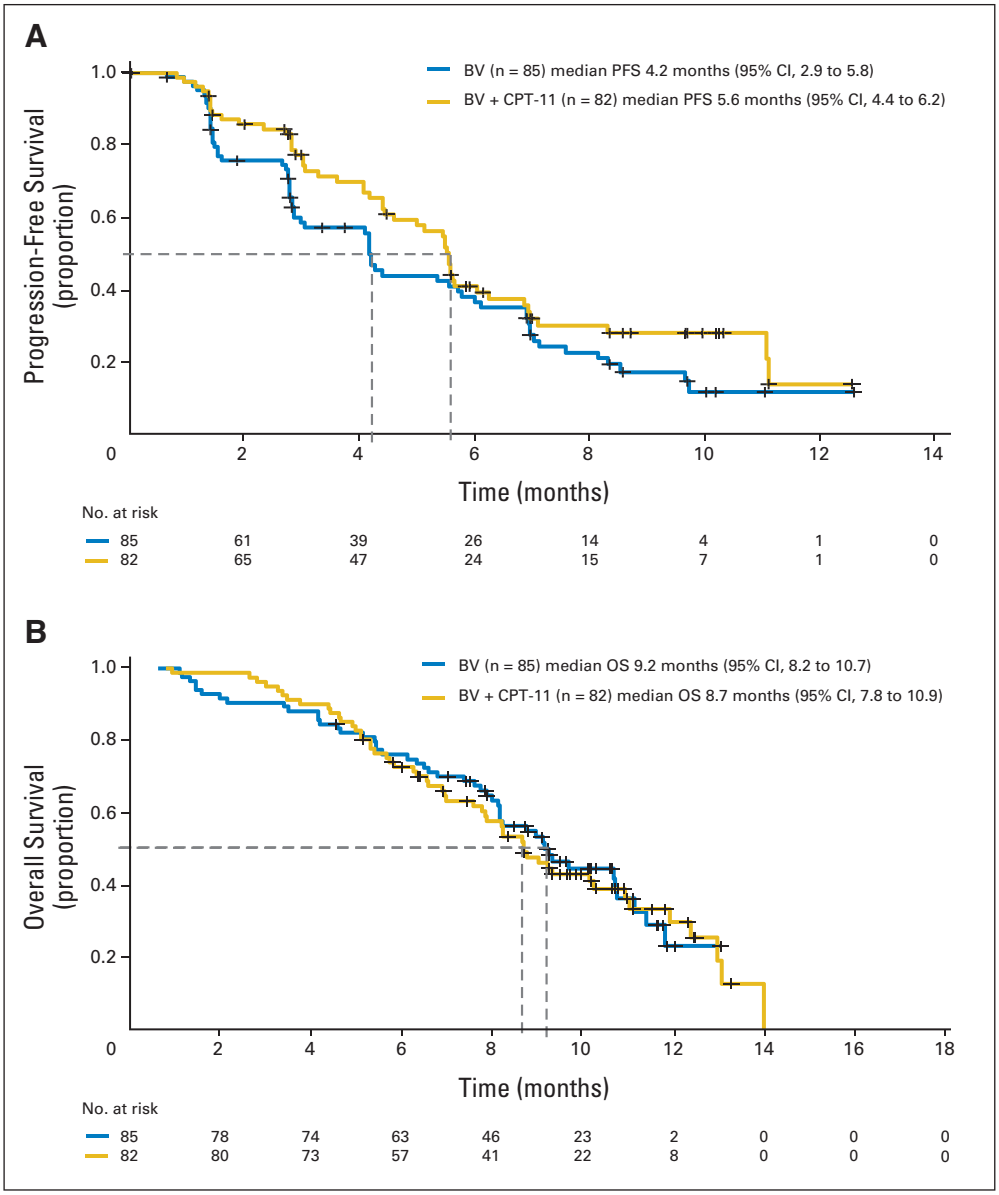

Fig 2. Survival analyses. (A) Progression-free survival (PFS) and overall survival (OS) for all randomly assigned patients were analyzed with Kaplan-Meier methods. PFS analysis included data collected through September 15, 2007. OS analysis included data collected through November 15, 2007. BV, bevacizumab; CPT-11, irinotecan.

Treatment

One patient in the BV group and three patients in the BV + CPT-11 group were not treated because of disease progression after random assignment but before the first treatment. The median number of BV doses was nine in the BV group and 12 in the BV + CPT-11 group. The median number of CPT-11 doses in the BV + CPT-11 group was 11. Forty-four patients (51.8%) in the BV group entered the postprogression phase and had CPT-11 added to their treatment regimens.

Efficacy

The estimated 6-month PFS rates were 42.6% (97.5% CI, 29.6% to 55.5%) in the BV group and 50.3% (97.5% CI, 36.8% to 63.9%) in the BV + CPT-11 group (Fig 2), and these exceeded the 15% rate assumed for salvage chemotherapy and CPT-11 alone ($P < .0001$). The 6-month PFS rates for patients in first and second relapse were 46.4% and 27.8%, respectively, for patients in the BV group and 49% and 57.1%, respectively, for patients in the BV + CPT-11 group. No investigator-determined clinical progressions (ie, patient discontinuation for progressive disease in the absence of radiographic progression) were reported.

Twenty-four patients (28.2%; 97.5% CI, 18.5% to 40.3%) in the BV group and 31 patients (37.8%; 97.5% CI, 26.5% to 50.8%) in the BV + CPT-11 group had an OR (Table 2). The OR rate differed from that assumed for salvage chemotherapy (5%) in the BV group ($P < .0001$) and CPT-11 alone (10%) in the BV + CPT-11 group ($P < .0001$). The OR rates for patients in first and second relapse were 31.9% and 12.5%, respectively, for patients in the BV group and 39.4% and 31.3%, respectively, for patients in the BV + CPT-11 group. The majority of patients experienced tumor shrinkage during the treatment period (Fig 3).

The median PFS times were 4.2 months (95.0% CI, 2.9 to 5.8 months) for the BV group and 5.6 months (95.0% CI, 4.4 to 6.2 months) for the BV + CPT-11 group (Fig 2). The median PFS times

Table 2. Response Rates

	Patients by Treatment Group			
	BV (n = 85)		BV + CPT-11 (n = 82)	
Response Data	No.	%	No.	%
Objective response	24	28.2	31	37.8
97.5% CI	18.5 to 40.3		26.5 to 50.8	
Complete response	1	1.2	2	2.4
Partial response	23	27.1	29	35.4

Abbreviations: BV, bevacizumab; CPT-11, irinotecan.

for patients in first and second relapse were 4.4 and 3.1 months, respectively, in the BV group and 5.5 and 5.6 months, respectively, in the BV + CPT-11 group. The median response durations were 5.6 months (95.0% CI, 3.0 to 5.8 months) in the BV group and 4.3 months (95.0% CI 4.2 months to not reached) in the BV + CPT-11 group.

The median OS times from the time of random assignment were 9.2 months (95.0% CI, 8.2 to 10.7 months) for the BV group and 8.7 months (95.0% CI, 7.8 to 10.9 months) for the BV + CPT-11 group (Fig 2). The median OS times for patients in first or second relapse were 9.1 and 9.2 months, respectively, in the BV group and 8.7 and 7.0 months, respectively, in the BV + CPT-11 group. As of November 15, 2007, 49 patients (57.6%) randomly assigned to the BV group and 53 patients (64.6%) randomly assigned to the BV + CPT-11 group had died. No patients were lost to follow-up. There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time (Fig 4).

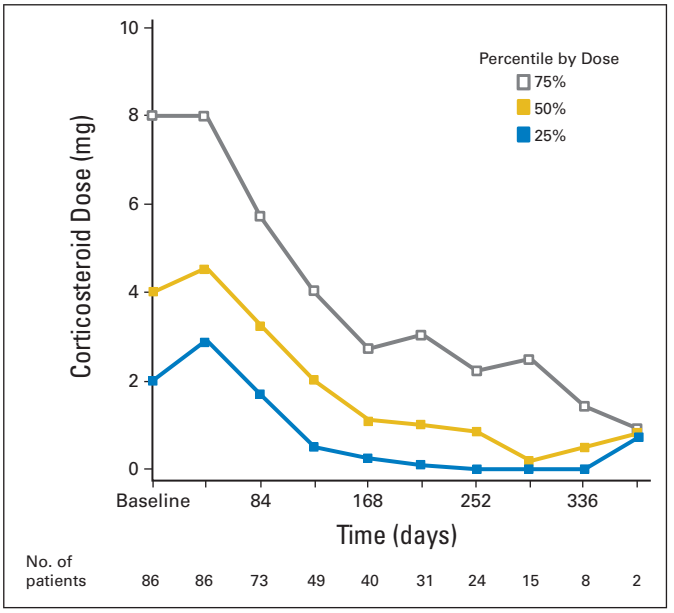

Fig 4. Change in corticosteroid dose across time. Forty-two–day averages of corticosteroid dose were calculated for each patient for whom data were available from baseline until disease progression or final study dose, whichever occurred first. The median (ie, 50th-percentile), 25th-percentile, and 75th-percentile doses are shown for each time point. The number of patients included in the analysis at each time point is noted below the *x*-axis.

Safety

One hundred sixty-three patients (84 in the BV group and 79 in the BV + CPT-11 group) who received study drug were included in the safety analysis (Table 3). This report includes AEs that occurred at any time from the first treatment dose through 30 days after the last treatment dose during the planned treatment period. For patients who received postprogression treatment, only those AEs that occurred before the addition of CPT-11 are included. The most common AEs (all grades) were fatigue (45.2%), headache (36.9%), and hypertension (29.8%) in the BV group and fatigue (75.9%), diarrhea (74.7%), and nausea (67.1%) in the BV + CPT-11 group. Thirty-nine patients (46.4%) in the BV group and 52 patients (65.8%) in the BV + CPT-11 group experienced grade 3 or greater AEs, the most common of which were hypertension (8.3%) and convulsion (6.0%) in the BV group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the BV + CPT-11 group.

Selected AEs associated with BV treatment included arterial thromboembolism (grade ≥ 3; BV, 2.4%; BV + CPT-11, 2.5%),

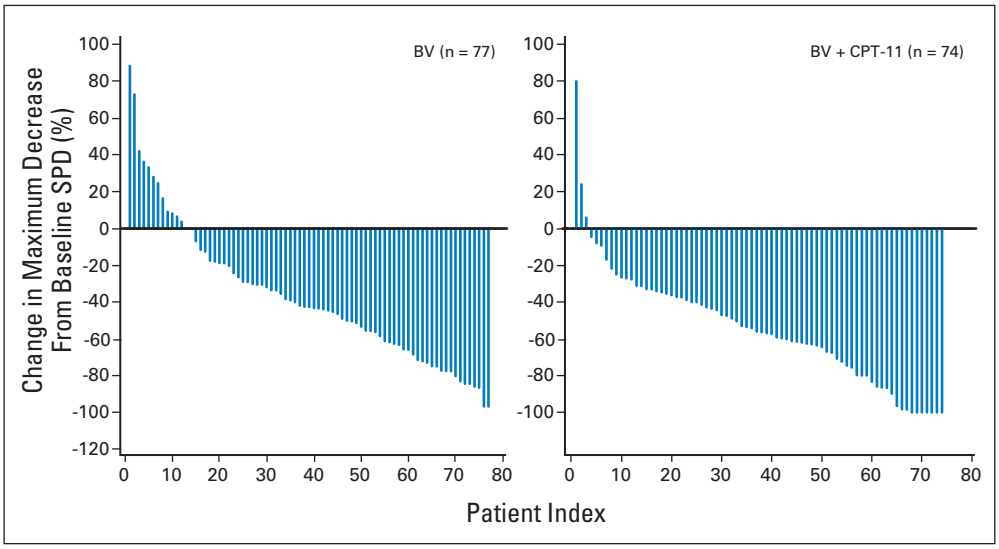

Fig 3. Independent radiology facility (IRF) –determined maximum decrease from baseline sum of the products of diameters (SPD). The maximum percent decrease from baseline SPD was defined as the percent change in SPD from baseline to the minimum postbaseline SPD. Patients who had IRF-determined measurable disease at baseline and at least one postbaseline tumor assessment were included. BV, bevacizumab; CPT-11, irinotecan.

Table 3. Adverse Events

Event	Patients by Treatment Group and Adverse Event Grade							
	BV (n = 84)				BV + CPT-11 (n = 79)			
	All		Grade ≥ 3		All		Grade ≥ 3	
	No.	%	No.	%	No.	%	No.	%
Any	83	98.8	39	46.4	79	100	52	65.8
Leading to death	2	2.4			1	1.3		
Leading to discontinuation of BV	4	4.8			14	17.7		
Leading to discontinuation of CPT-11	NA	NA	NA	NA	14	17.7		
Serious	22	26.2			34	43.0		
Selected								
Hypertension	30	35.7	7	8.3	21	26.6	1	1.3
Hemorrhage, overall	23	27.4	0	0	32	40.5	2	2.5
Hemorrhage, intracranial	2	2.4	0	0	3	3.8	1	1.3
Wound-healing complications	5	6.0	2	2.4	2	2.5	1	1.3
Venous thromboembolism	3	3.6	3	3.6	8	10.1	7	8.9
Arterial thromboembolism	4	4.8	2	2.4	5	6.3	2	2.5
Proteinuria	4	4.8	0	0	2	2.5	1	1.3
GI perforation	0	0	0	0	2	2.5	2	2.5
RPLS	0	0	0	0	1	1.3	0	0
Occurred in ≥ 5% of all patients*								
Aphasia			3	3.6			6	7.6
Confusional state			2	2.4			4	5.1
Convulsion			5	6.0			11	13.9
Deep vein thrombosis			2	2.4			5	6.3
Diarrhea			1	1.2			4	5.1
Fatigue			3	3.6			7	8.9
Hypertension			7	8.3			1	1.3
Pneumonia			1	1.2			4	5.1
Pyramidal tract syndrome			1	1.2			4	5.1
Somnolence			1	1.2			4	5.1
Hypokalemia			3	3.6			6	7.6
Leukopenia			0	0			5	6.3
Lympyhopenia			2	2.4			6	7.6
Neutropenia			1	1.2			7	8.9

NOTE. Adverse events that occurred during the planned treatment period were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events. For patients who received postprogression treatment (ie, CPT-11 added to BV), only those adverse events that occurred prior to CPT-11 treatment are included. For patients who experienced multiple occurrences of a specific adverse event, the adverse event was counted only once at the highest National Cancer Institute Common Terminology Criteria for Adverse Events grade that it occurred.

Abbreviations: BV, bevacizumab; CPT-11, irinotecan; NA, not applicable; RPLS, reversible posterior leukoencephalopathy syndrome.

*MedDRA preferred term was used.

venous thromboembolism (VTE; BV, 3.6%; BV + CPT-11, 8.9%), and wound-healing complications (grade ≥ 3; BV, 2.4%; BV + CPT-11, 1.3%). Two grade 3 or greater wound-dehiscence events were related to craniotomy sites. Two patients (2.5%) experienced grade 3 gastrointestinal perforation and one patient (1.3%) experienced serious reversible posterior leukoencephalopathy syndrome in the BV + CPT-11 group. Two patients (2.4%) who received BV alone experienced grade 1 intracranial hemorrhage, and three (3.8%) patients who received BV + CPT-11 experienced grades 1, 2, and 4 intracranial hemorrhage, respectively.

One patient who experienced a VTE was receiving concomitant anticoagulation prior to the VTE. Two of the five patients who developed intracranial hemorrhage were anticoagulated at the time of the hemorrhage; both hemorrhages were grade 1.

AEs led to BV discontinuation for four patients (4.8%) in the BV group and 14 patients (17.7%) in the BV + CPT-11 group and led to CPT-11 discontinuation for 14 patients (17.7%) in the BV + CPT-11 group. There were two (2.4%) AE-associated deaths (as a result of neutropenia infection, pulmonary embolism) in the BV group and there was one (1.3%) AE-associated death (as a result of convulsion) in the BV + CPT-11 group. For patients included in the safety analysis, the primary cause of death was disease progression for 44 patients (52.4%) in the BV group and for 48 patients (60.8%) in the BV + CPT-11 group.

DISCUSSION

The results demonstrated notable antitumor activity of single-agent BV and BV in combination with CPT-11 in pretreated patients with glioblastoma in first or second relapse. The majority of patients experienced tumor shrinkage during the treatment period, and ORs were durable. Furthermore, the observed 6-month PFS rate far exceeded the 15% rate assumed for salvage chemotherapy and CPT-11 alone,[2-5]

and the OS noted in the two groups was encouraging. The results are particularly noteworthy given that the inclusion criteria mandated disease progression after TMZ therapy, and efficacy was rigorously evaluated by a blinded, independent radiology facility. Finally, there was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. No formal comparisons of average corticosteroid dose at different time points were made because of differences in the size of the patient population across time. However, similar trends of stable or decreasing corticosteroid dose were observed in patients for whom data were available up to 36 weeks.

The 6-month PFS and OR values were numerically higher in patients experiencing first relapse compared with those experiencing second relapse. However, the number of patients in each relapse group was small, and the CIs overlapped when the relapse subgroups within each treatment group were compared. Although pseudoprogression is a potential confounder, it generally occurs $\leq$ 12 weeks after surgery or radiotherapy. A large majority of patients in this study enrolled greater than 12 weeks after surgery or radiotherapy. Furthermore, the study population was comparable to those in previous North American Brain Tumor Consortium clinical trials,[27] and the 6-month PFS, OR rate, and OS in the population on this study were greater than the same analyses reported in those comparable populations on other studies. It should also be noted that, in this study, OR required that patients had a sustained (ie, $\geq$ 4 weeks) response.

BV was well tolerated, and the incidence of targeted AEs in patients with glioblastoma was similar to that observed in previous BV trials.[16-19] The incidence of certain AEs, such as the rate of infection, increased with the addition of chemotherapy; however, no new safety issues related to BV or BV + CPT-11 were identified, and the incidence of intracranial hemorrhage was low.

The randomized design of the trial was intended only to prevent bias in treatment assignment, and there was no formal plan to compare outcomes in the two treatment groups. Determining the optimal utilization of BV therapy in recurrent glioblastoma, specifically as a single agent or in combination with CPT-11, either concurrently or sequentially after initial single-agent BV, or in combination with other chemotherapy agents, requires additional clinical investigation.

The benefit of BV in other grades of malignant glioma or as first-line glioblastoma therapy also requires additional study. In a previous, single-institution study of recurrent malignant glioma, BV had similar benefits in patients with grade 3 (ie, anaplastic astrocytoma) and grade 4 glioma.[28] Preliminary safety data regarding the addition of BV to concurrent radiation therapy and TMZ in the treatment of first-line glioblastoma have been reported[29] and support the Radiation Therapy Oncology Group study 0825, which will evaluate the addition of BV to standard therapy in newly diagnosed patients with glioblastoma. In summary, the results of this study suggest that BV is an active and important therapeutic agent in recurrent glioblastoma.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Jane Huang, Genentech (C); Maoxia Zheng, Genentech (C) **Consultant or Advisory Role:** Henry S. Friedman, Genentech (C); Michael D. Prados, Genentech (U); Patrick Y. Wen, Genentech (C), Schering-Plough (C); Tom Mikkelsen, Schering-Plough (C); David Schiff, Genentech (C); Lauren E. Abrey, Genentech (C); W.K. Alfred Yung, Schering-Plough (U), Novartis (U); James Vredenburgh, Genentch (C); Martin K. Nicholas, Genentech (C) **Stock Ownership:** None **Honoraria:** Henry S. Friedman, Genentech; Tom Mikkelsen, Genentech, Schering-Plough; Lauren E. Abrey, Genentech; W.K. Alfred Yung, Schering-Plough, Novartis; Timothy Cloughesy, Genentech **Research Funding:** Henry S. Friedman, Genentech; Michael D. Prados, Genentech; Patrick Y. Wen, Genentech; Tom Mikkelsen, Genentech; Lauren E. Abrey, Genentech, Pfizer; W.K. Alfred Yung, Genentech; Nina Paleologos, Genentech; Martin K. Nicholas, Genentech; James Vredenburgh, Genentech; Timothy Cloughesy, Genentech **Expert Testimony:** Michael D. Prados; Timothy Cloughesy **Other Remuneration:** None

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REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996, 2005
2. Friedman HS, Petros WP, Friedman AH, et al: Irinotecan therapy in adults with recurrent or progressive malignant glioma. J Clin Oncol 17:1516-1525, 1999
3. Cloughesy TF, Filka E, Kuhn J, et al: Two studies evaluating irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. Cancer 97:2381-2386, 2003
4. Raymond E, Fabbro M, Boige V, et al: Multicentre phase II study and pharmacokinetic analysis of irinotecan in chemotherapy-naive patients with glioblastoma. Ann Oncol 14:603-614, 2003
5. Prados MD, Lamborn K, Yung WK, et al: A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: A North American Brain Tumor Consortium study. Neuro Oncol 8:189-193, 2006
6. Ballman KV, Buckner JC, Brown PD, et al: The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol 9:29-38, 2007
7. Wong ET, Hess KR, Gleason MJ, et al: Outcomes and prognostic factors in recurrent glioma

patients enrolled onto phase II clinical trials. J Clin Oncol 17:2572-2578, 1999

8. Yung WK, Albright RE, Olson J, et al: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 83:588-593, 2000

9. Ferrara N, Gerber HP, LeCouter J: The biology of VEGF and its receptors. Nat Med 9:669-676, 2003

10. Godard S, Getz G, Delorenzi M, et al: Classification of human astrocytic gliomas on the basis of gene expression: A correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. Cancer Res 63:6613-6625, 2003

11. Lamszus K, Ulbricht U, Matschke J, et al: Levels of soluble vascular endothelial growth factor (VEGF) receptor 1 in astrocytic tumors and its relation to malignancy, vascularity, and VEGF-A. Clin Cancer Res 9:1399-1405, 2003

12. Jain HV, Nor JE, Jackson TL: Modeling the VEGF-Bcl-2-CXCL8 pathway in intratumoral agiogenesis. Bull Math Biol 70:89-117, 2008

13. Johansson M, Brannstrom T, Bergenheim AT, et al: Spatial expression of VEGF-A in human glioma. J Neurooncol 59:1-6, 2002

14. Phillips HS, Armani MP, Stavrou D, et al: Intense focal expression of vascular endothelial growth factor mRNA in human intracranial neoplasms: Association with regions of necrosis. Int J Oncol 2:913-919, 1993

15. Shweiki D, Itin A, Soffer D, et al: Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 359: 843-845, 1992

16. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004

17. Johnson DH, Fehrenbacher L, Novotny WF, et al: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. J Clin Oncol 22:2184-2191, 2004

18. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007

19. Yang JC, Haworth L, Sherry RM, et al: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 349:427-434, 2003

20. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al: Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25:4722-4729, 2007

21. Trotti A, Colevas AD, Setser A, et al: CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176-181, 2003

22. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

23. Macdonald DR, Cascino TL, Schold SC Jr, et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990

24. Cassella G: Refining binomial confidence intervals. Can J Stat 14:113-129, 1986

25. Meier P, Kaplan E: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

26. Greenwood M: Reports on public health and medical subjects, No.33, Appendix 1, in The Error of Sampling of the Survivorship Tables. London, United Kingdom, H.M. Stationary Office, 1926

27. Lamborn KR, Yung WK, Chang SM, et al: Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol 10:162-170, 2008

28. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al: Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13:1253-1259, 2007

29. Lai A, Filka E, McGibbon B, et al: Phase II pilot study of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme: Interim analysis of safety and tolerability. Int J Radiat Oncol Biol Phys 71:1372-1380, 2008

