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Phase II study of carboplatin, irinotecan and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy[1]

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Abstract

BACKGROUND—We evaluated the efficacy of carboplatin, irinotecan and bevacizumab among recurrent glioblastoma (GBM) patients after prior progression on bevacizumab therapy in a phase 2, open-label, single-arm trial.

METHODS—Eligible patients received carboplatin (area under the plasma curve [AUC] 4 mg/ml-min) on day one, while bevacizumab (10 mg/kg) and irinotecan (340 mg/m2 for patients on CYP3A-enzyme inducing anti-epileptics [EIAEDs] and 125 mg/m2 for patients not on EIAEDs) were administered on days 1 and 14 of every 28-day cycle. Patients were evaluated after each of the first two cycles and then after every other cycle. Treatment continued until progressive disease, unacceptable toxicity, non-compliance or voluntary withdrawal. The primary endpoint was progression-free survival at six months (PFS-6) and secondary endpoints included safety and median overall survival (OS).

RESULTS—All patients had progression on at least one prior bevacizumab regimen and 56% enrolled after either second or third overall progression. The median OS was 5.8 months (95% confidence interval [CI]: 4.0, 7.0 months) and PFS-6 rate was 16% (95% CI: 5.0, 32.5%). The

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CONFLICT OF INTEREST DISCLOSURES

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most common grade 3 or 4 events were hematologic and occurred in 29% of cycles. Nine patients (38%) required dose modification. There were no treatment related deaths.

CONCULSION—Carboplatin, irinotecan and bevacizumab is associated with modest activity and adequate safety among recurrent GBM patients who progressed on bevacizumab previously.

Keywords

Glioblastoma; angiogenesis; bevacizumab; vascular endothelial growth factor; irinotecan; carboplatin

INTRODUCTION

Outcome for glioblastoma (GBM), the most common malignant primary brain tumor, remains poor with median overall survival of only 14.6 months following current standard therapy that includes maximum safe resection followed by involved-field radiation with temozolomide and adjuvant temozolomide.[1] Salvage therapies following recurrence have had limited activity.[2–4] Initial clinical trials with bevacizumab, a humanized monoclonal antibody (MAb) against vascular endothelial growth factor (VEGF), were conducted among recurrent GBM patients because GBM tumors are highly angiogenic[5, 6] and secrete high levels of VEGF.[7–9] In addition, VEGF targeting MAbs inhibit growth in *in vivo* orthotopic GBM xenograft models[10, 11] and can enhance the anti-tumor activity of cytotoxic therapy.[12–14] Furthermore, significant clinical benefit associated with bevacizumab plus chemotherapy had been noted in other aggressive solid tumors.[15–20] Encouraging rates of radiographic response and improved survival reported by initial studies in recurrent GBM[21, 22] triggered follow-up studies which ultimately led to accelerated approval by the U.S. Food and Drug Administration (FDA) of single-agent bevacizumab based on durable radiographic responses.[23–25]

However, the survival benefit following bevacizumab with or without other systemic agents is modest with most patients developing progressive disease within 8–10 months and dying from refractory tumor soon thereafter.[22–24, 26–30] Thus effective therapy for GBM patients following progression on bevacizumab-based therapy represents a major unmet need.

Carboplatin and irinotecan exhibit modest anti-tumor activity when administered separately among recurrent malignant glioma patients.[31–38] In addition, both agents impair DNA replication via potentially complementary mechanisms and are associated with primarily non-overlapping toxicities. We therefore hypothesized that a regimen combining carboplatin and irinotecan may be adequately tolerated and associated with greater anti-tumor benefit than either agent alone. Studies evaluating this regimen in other cancer populations were the basis for the dosing schedule utilized in the current study.{Hermes, 2008 #10764;Jones, 2003 #9143} The rationale for continuing bevacizumab was to avoid rebound, fulminant progressive tumor following bevacizumab discontinuation[39] and to potentially normalize tumor vasculature to allow enhanced chemotherapy delivery.[40]

PATIENTS AND METHODS

Protocol Objectives

Our primary objective was to evaluate the activity, defined by progression-free survival at six months (PFS-6) of carboplatin and irinotecan combined with bevacizumab among adults with recurrent GBM who progressed on prior bevacizumab therapy. In addition, we sought to evaluate the safety of this regimen in this patient population.

Patient Eligibility

Patients were required to have histologic confirmation of WHO grade IV malignant glioma (GBM or gliosarcoma) that progressed after prior bevacizumab based therapy. Patients with prior low-grade glioma were eligible if histologic transformation to grade IV malignant glioma was confirmed. Eligible patients were also: at least 18 years of age; had a KPS ≥ 70, and were on a stable corticosteroid dose for at least 1 week. Additional enrollment criteria included: hematocrit >29%; absolute neutrophil count >1000 cells/μl; platelet count >100,000 cells/μl; and serum creatinine, aspartate aminotransferase and bilirubin within 1.5 times the institutional upper limit of normal. At least 4 weeks between surgical resection or chemotherapy, and at least 12 weeks between radiotherapy and enrollment were required. All patients provided informed consent. There were no limits based on either the number of prior episodes of progression or therapeutic regimens received.

Patients were excluded for: grade ≥ 3 toxicity on prior bevacizumab; progressive disease or grade ≥ 3 toxicity on prior carboplatin or irinotecan; uncontrolled hypertension; acute hemorrhage on baseline MRI; urine protein:creatinine ratio > 1; homozygosity for the *28UGT1A1 allele; pregnancy or nursing; active infection requiring intravenous antibiotics; therapeutic anti-coagulation with warfarin; and prior stereotactic radiosurgery, radiation implants, or radiolabeled monoclonal antibody therapy unless there was unequivocal disease progression (such as a new lesion or biopsy-proven recurrence).

Treatment Design

Eligible patients for this open-label phase II study received bevacizumab at 10 mg/kg intravenously every 14 days. Carboplatin was administered at an AUC of 4 on day one of each 28-day cycle. Irinotecan was administered on days 1 and 14 at 340 mg/m^2 for patients receiving cytochrome P450 CYP3A enzyme-inducing anti-epileptics (EIAEDs; phenytoin, phenobarbital, carbamazepine, oxcarbazepine and primidone) and at 125 mg/m^2 for those not on EIAEDs. Study therapy continued until progressive disease, unacceptable toxicity, non-compliance with study protocol guidelines or withdrawal of consent.

Response Evaluation

Study investigators determined response by neurologic examination and contrast-enhanced MRI after the first two treatment cycles and then prior to every other cycle based on the recently published Response Assessment in Neuro-Oncology criteria.[41] A complete response (CR) required disappearance of all enhancing and non-enhancing tumor on consecutive MRIs at least 4 weeks apart, with corticosteroid discontinuation and neurologic stability or improvement. A partial response (PR) required ≥ 50% reduction in size (product of largest perpendicular diameters) of enhancing tumor with stability or improvement of neurologic status and corticosteroids. Progressive disease (PD) included ≥ 25% increase of enhancing tumor, a new enhancing lesion, significant worsening of non-enhancing tumor including that detected by FLAIR or T2 sequences, or clinical decline. Stable disease (SD) was defined as any assessment not meeting CR, PR, or PD criteria. Partial responses and stable disease also required stable or improved signal abnormality on fluid-attenuated inversion recovery (FLAIR) sequences.

Dose Modification and Retreatment Criteria

Chemotherapy doses were held for grade 3 or 4, related, non-hematologic toxicity, grade 3 thrombocytopenia, grade 4 neutropenia, and fever and neutropenia (any grade) until the event resolved to grade 1 or pre-treatment baseline. Thereafter, chemotherapy doses were reduced by 25%. Chemotherapy doses were also reduced by 25% for any related event that required > 2 weeks to satisfy re-treatment criteria. Patients who required more than 3

chemotherapy dose reductions were allowed to remain on study and receive bevacizumab alone. Bevacizumab was discontinued for uncontrollable hypertension, grade 2 or greater hemorrhage, arterial thrombosis, wound dehiscence requiring surgical intervention, intestinal perforation or grade 4 venous thrombosis, proteinuria or congestive heart failure. Bevacizumab was held until other related grade 3 events resolved to grade ≤ 1.

Initiation of each cycle required: an ANC ≥ 1000/mm^3; a platelet count ≥ 100,000/mm^3; creatinine ≤ 1.5 times the upper limit of normal (× ULN), bilirubin ≤ 2 × ULN and AST ≤ 2.5 × ULN; proteinuria <3+ on urinalysis or urine protein:creatinine ratio ≤ 1.0; and resolution of any related grade ≥ 3 event to grade ≤ 1.

Statistical Considerations

Our primary goal was to evaluate the PFS-6 rate of carboplatin, irinotecan and bevacizumab among recurrent GBM patients who had progressed on prior bevacizumab therapy. At the time this study was designed, benchmarks for outcome among recurrent GBM patients who had progressed on prior bevacizumab therapy had not been established, therefore we chose to use the historical benchmark established with temozolomide at first recurrence. Hence, given a PFS-6 rate of 21% among recurrent GBM patients treated with temozolomide at first recurrence,[42] a sample size goal of 24 recurrent GBM patients was chosen to allow 88% power to differentiate between 6-PFS rates of 5% and 25% with a type I error rate of 0.03.

An interim efficacy analysis after 16 patients were accrued to each arm was planned *a priori*. If 12 or more of these 16 patients progressed or died within 2 months of study initiation, further accrual would be suspended. The interim efficacy threshold was met and therefore the study completed accrual as specified.

For this study among heavily pretreated patients with an extremely poor prognosis, rates of unacceptable toxicity, defined as grade ≥ 2 CNS hemorrhage or grade 4 or 5 non-hematologic toxicity, of 15% or less were considered desirable, while rates of 40% or greater were considered undesirable. Stopping rules for unacceptable toxicity based upon boundaries proposed by Pocock were used to monitor this study after each group of 4 patients.[43] Accrual was not suspended to formally assess the toxicity profile unless the following thresholds of unacceptable toxicity were satisfied: ≥3/4; ≥4/8; ≥5/12; ≥6/16; ≥7/20; ≥7/24. The type I and type II errors associated with this monitoring were 0.05 and 0.07, respectively. These guidelines did not adjust for differential length of follow-up of accrued patients.

Progression-free survival (PFS) was defined as the time between the cycle one start date and the date of disease progression or death. PFS was censored at the time of last follow-up if the patient remained alive without disease progression, or at the start of non-study treatment if initiated before disease progression. Overall survival (OS) was calculated from the start of therapy until death or last contact if censored. PFS and OS were summarized using Kaplan-Meier estimator including 95% CIs.

RESULTS

Patient Characteristics

Characteristics of the 25 patients who enrolled on this study between September 2009 and July 2010 are summarized in Table 1. Patients were relatively young (median age, 52 years), over half had a KPS of at least 90, and 10 (40%) were on corticosteroids at enrollment. Patients were moderately pretreated with 14 (56%) having 2–3 episodes of prior progression. All patients had progressed after standard therapy with radiation and temozolomide chemotherapy as well as prior bevacizumab. Most patients (96%) had

progressed on one prior bevacizumab regimen, while one patient enrolled after progression on two prior bevacizumab regimens. Thirteen patients (52%) enrolled after having progressed on bevacizumab used at recurrence while twelve patients (48%) enrolled after progressing on bevacizumab incorporated into adjuvant therapy for newly diagnosed GBM patients. Sixty percent of patients progressed previously on bevacizumab in combination with chemotherapy, while 36% progressed on bevacizumab monotherapy and one patient progressed on bevacizumab with a targeted agent (sorafenib). Nearly all patients (92%) enrolled while progressing on bevacizumab therapy, however two (8%) progressed on bevacizumab and then received either single agent temozolomide or XL-184, a dual VEGFR-2/met tyrosine kinase inhibitor, for 2–4 months prior to study enrollment. Median duration of initial bevacizumab therapy was nine months with a range of 2–34 months.

As of January 1, 2011, one patient continues to receive study therapy in cycle 6 while all other patients have discontinued study therapy. Two patients remain free of progression including one patient who completed 12 cycles of therapy and remains off study and one patient who discontinued study therapy due to recurrent hematologic toxicity after 4 cycles, and is currently receiving her fifth cycle of non-study irinotecan and bevacizumab with stable disease. Eight patients (32%) remain alive including the two described above and six who are progressed on study therapy and are currently receiving additional salvage therapy. Seventeen patients (68%) have died.

Study Drug Administration and Safety

Study drug administration and compliance with treatment for the intent-to-treat study population were excellent. A total of 80 cycles of therapy were administered including a median of 3 cycles (range, 1– 12) per patient. Twenty-one patients (84%) discontinued study therapy due to progressive disease. Single patients discontinued study therapy due to completion of one year of therapy with no evidence of active disease, recurrent grade 3–4 hematologic toxicity, non-compliance and voluntary withdrawal, respectively.

All patients were assessable for toxicity. Table 2 summarizes the frequency of grade ≥ 2 adverse events that were at least possibly related to the study regimen as a percentage of the total number of cycles administered during the study. Most adverse events were grade 2 while the most common grade 3 or 4 events were hematologic. Grade 3 or 4 neutropenia occurred in 6 (24%) and 2 (8%) patients, while grade 3 or 4 thrombocytopenia occurred in 3 patients (13%), and grade 3 anemia occurred in 2 patients (8%). Among non-hematologic events, grade 3 events were limited to fatigue in 3 patients (13%) and hypertension in 2 patients (8%). Nine patients (36%) required one dose reduction of carboplatin and irinotecan, while two patients (8%) required two dose reductions. There were no study related deaths or episodes of intra-cranial hemorrhage.

Outcome

The median follow-up for all patients was 7.99 months (95% CI, 6.25, 11.02). Outcome analysis was based on the intent-to-treat population and includes one patient who discontinued study therapy on day 2 of cycle 1 due to voluntary withdrawal. Median OS, PFS and PFS-6 rate are summarized in Table 3 and Figure 1. Best radiographic response was stable disease in twenty patients (80%), and progressive disease in four (16%) while one patient was not evaluable. None of the patients met criteria for radiographic response. Among 10 patients who were on dexamethasone at study initiation, five were able to taper by an average of 4.6 mg per day, including two patients who were able to completely discontinue dexamethasone. There was no difference in either PFS or OS among patients who received adjuvant bevacizumab compared to those who received bevacizumab at recurrence. nor was there a difference in OS for patients who progressed on bevacizumab

monotherapy compared to bevacizumab in combination with chemotherapy. However, PFS was improved for patients who progressed on bevacizumab monotherapy compared to those who progressed on bevacizumab plus chemotherapy (p=0.0356). Specifically, 44.4% of patients who were treated after bevacizumab monotherapy remained progression-free after 6 months, compared to 0% of patients who were treated after progression on bevacizumab plus chemotherapy.

DISCUSSION

Bevacizumab is indicated for the treatment of recurrent GBM patients in the United States, Canada and a growing number of countries worldwide.[25] In addition, bevacizumab is currently being evaluated for newly diagnosed GBM patients in two multinational, blinded placebo-controlled randomized phase III studies as well as additional phase II studies.[44, 45] Thus a high percentage of GBM patients are currently receiving bevacizumab either at recurrence or following initial diagnosis. Although bevacizumab substantially improves rates of radiographic response and PFS, all patients ultimately progress. Furthermore, survival after bevacizumab progression is poor.

To date, effective treatment after bevacizumab progression has not been identified (Table 3). Two prospective studies have been reported. Among 19 patients with recurrent GBM who progressed on single-agent bevacizumab, median PFS following initiation of bevacizumab plus irinotecan was only 1.1 months. Overall survival was not reported for these patients.[24] Similarly, among 23 recurrent GBM patients treated with bevacizumab plus protracted daily (metronomic) chemotherapy using either temozolomide or etoposide after bevacizumab failure, the median OS was 4.1 months (95% CI: 2.8, 5.8) and PFS-6 was 4.4% (95% CI, 3.1,18.2).[46] Several relatively small retrospective series (range of evaluated patients, 19–35) report median OS and PFS-6 probability of 2.2–4.1 months and 0–4.4%, respectively.[26, 27, 48]{Torcuator, 2010 #10972; Lu-Emerson 2010} Of note, a retrospective review reported that patients who received stereotactic radiosurgery with bevacizumab and chemotherapy achieved a median PFS of 2.6 months and a median OS of 7.2 months after prior bevacizumab failure; in comparison, patients who received bevacizumab and chemotherapy alone, without a radiosurgical boost, had a median PFS of 1.7 months and a median OS of 3.3 months.{Torcuator, 2010 #10972} These results suggest that stereotactic radiosurgery may improve outcome for some patients following progression on bevacizumab; however, these findings require prospective evaluation.

Our phase II study demonstrates that continuation of bevacizumab with carboplatin and irinotecan is associated with a modest improvement in outcome compared to historical data for recurrent GBM patients who have progressed on bevacizumab therapy. Although prospective, this small series enrolled patients with relatively favorable prognostic factors including younger age and good performance status, thus further evaluation of this regimen should be considered in a randomized, controlled trial. Another concern is that our study design precludes determination of whether therapeutic benefit required combination of all three study agents or if a subset of the study regimen may have been sufficient to render therapeutic benefit. Specifically, we did not evaluate whether either carboplatin alone or carboplatin and irinotecan without bevacizumab may have improved outcome on our study. However, it is unlikely that irinotecan alone, irinotecan plus bevacizumab or carboplatin plus bevacizumab were responsible for therapeutic benefit in our study based on the lack of benefit observed with these regimens in previously reported series.[24, 26, 27, 48]

The rationale for this study regimen was based on several considerations. Bevacizumab was included to avoid fulminant “rebound” tumor re-growth that has been reported upon abrupt bevacizumab discontinuation,[39] and because anti-VEGF therapy can normalize tumor

vasculature and improve chemotherapy delivery.[49] Furthermore, a retrospective registry series reported that bevacizumab continuation after progression on a bevacizumab regimen improves survival in patients with metastatic colorectal cancer.[50] The combination of carboplatin and irinotecan was considered attractive for several reasons. First each of these agents has modest anti-tumor activity when administered separately among recurrent malignant glioma patients.[31–36, 38, 51] Second, the mechanisms of cytotoxicity of each agent are potentially complementary. Specifically, irinotecan inhibits DNA replication by blocking topoisomerase 1 while carboplatin induces DNA cross-links and adducts. Third, the primary toxicities of each agent, gastrointestinal for irinotecan and hematologic for carboplatin, are non-overlapping; thus combining the two agents is expected to be associated with acceptable toxicity. Fourth, pharmacologic metabolism paths of each agent differ suggesting that detrimental pharmacologic interactions associated with a combined regimen are not expected. Finally, studies using carboplatin plus irinotecan for patients with other aggressive solid tumors have generated encouraging evidence of anti-tumor activity and overall adequate tolerance.[52–54]

Our study demonstrates that the combination of carboplatin, irinotecan and bevacizumab is associated with adequate safety, despite enrolling patients who were moderately pretreated. The type, frequency and severity of encountered toxicity was similar to that which has been reported for each agent when administered separately,[31–36, 38, 51] thus the combination did not cause unexpected events. One factor that may have contributed to the acceptable safety profile we observed was the exclusion of patients homozygous for the *28 UGT1A1 allele since such patients are predicted to be at increased risk of irinotecan toxicity.[55, 56]

Treatment of GBM patients who progress on bevacizumab therapy is currently a dire unmet need in neuro-oncology. We demonstrate that carboplatin, irinotecan and bevacizumab is associated with modest anti-tumor benefit and adequate safety in moderately pre-treated GBM patients who have progressed on bevacizumab. Further evaluation of this regimen is warranted and the identification of effective therapies for GBM patients who progress on bevacizumab should be highly prioritized.

Abbreviations List

MG	malignant glioma
ITT	intent-to treat
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CNS	central nervous system
CR	complete response
GBM	glioblastoma
KPS	Karnofsky performance status
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
SD	stable disease

VEGF vascular endothelial growth factor

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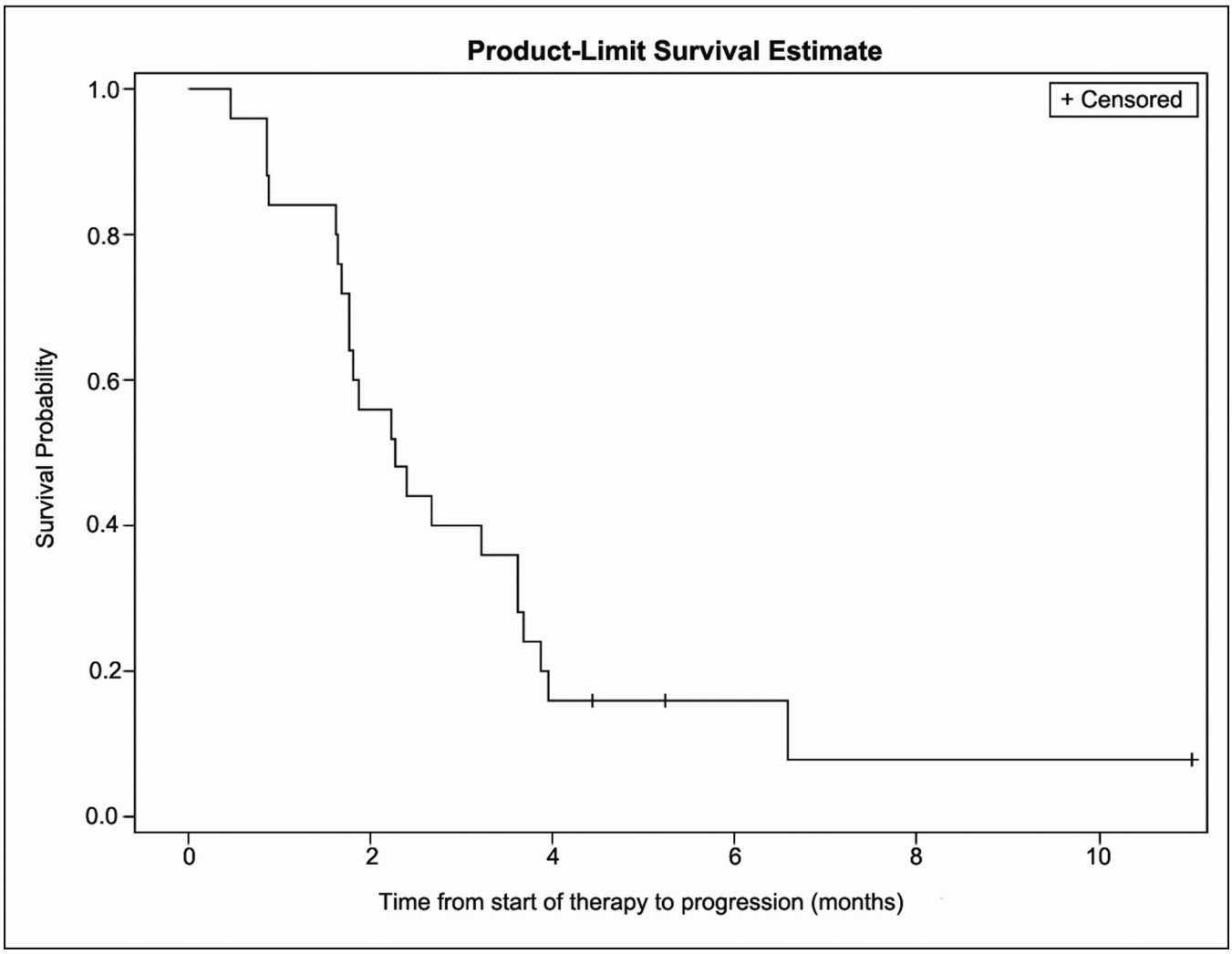
1a



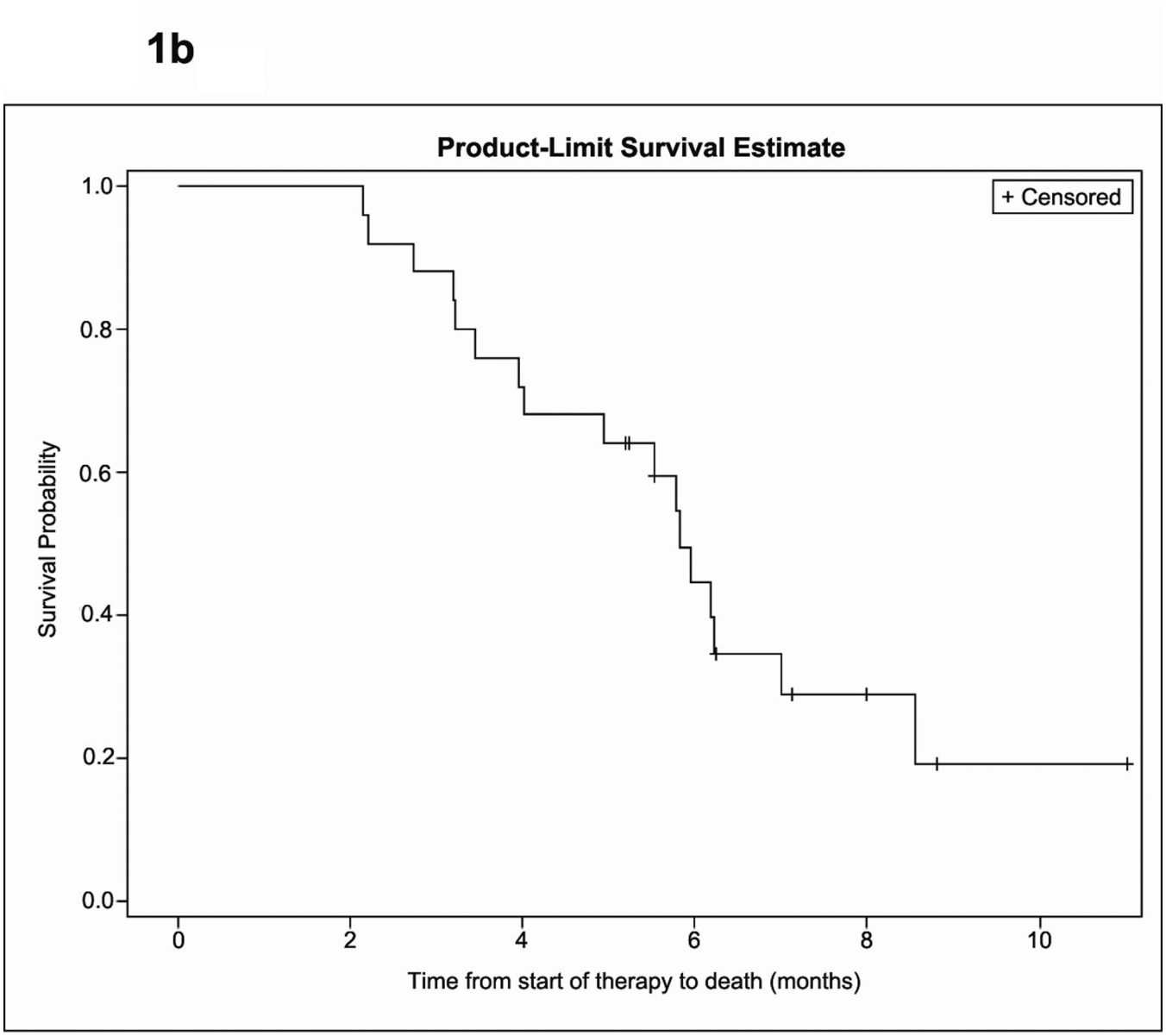


Figure 1.
Kaplan-Meier estimate of time to progression (A) and overall survival (B).

Table 1

Patient Characteristics

Age (years)	
Median	52
Range	19 – 76
Gender	
Male	17 (68)
Female	8 (32)
KPS	
90–100	13 (52)
80	10 (40)
70	2 (8)
Time from Diagnosis (weeks)	
Median	58.1
Range	29.9–260.9
EIAED	
Yes	1 (4)
No	24 (96)
Corticosteroids	
Yes	10 (40)
Average Dose (mg/day)	2.8
Range (mg/day)	0–16
No	15 (60)
Surgery Prior to Enrollment	
None	22 (88)
Biopsy	2 (8)
STR	1 (4)
Number Prior PD	
1	11 (44)
2	13 (52)
3	1 (4)
Progression on BV at Enrollment	
No	2 (8)
Yes	23 (92)
BV Partner at Prior Progression	
None	9 (36)
Chemotherapy	15 (60)
Etoposide	2
Temozolomide	13
Sorafenib	1 (4)
Number Prior BV PD	
1	24 (96)

2	1 (4)
Number months on prior BV	
Median	9
Range	2–34

Abbreviations: BV, bevacizumab; EIAED, CYP3A enzyme inducing anti-epileptic drugs; KPS, Karnofsky performance status; mg, milligram; PD, progressive disease; STR, subtotal resection

Table 2

Frequency of grade ≥ 2 adverse events at least possibly related to the study regimen as a percentage of total cycles administered (n=80).

Event	Grade		
	2	3	4
Anemia	7 (9%)	2 (3%)	-
Anorexia	2(3%)	-	-
Dehydration	-	1 (1%)	-
Diarrhea	2 (3%)	-	-
Fatigue	4 (5%)	3 (4%)	-
Hypertension	2(3%)	2 (3%)	-
Hyponatremia	-	1 (1%)	-
Hypophosphatemia	-	1(1%)	-
Infection	1(1%)	-	
Mucositis	-	1 (1%)	-
Nausea/emesis	4 (5%)	1(1%)	-
Neutropenia	14 (18%)	10 (13%)	3 (4%)
Proteinuria	5 (6%)	-	-
Thrombocytopenia	13 (16%)	7 (9%)	3(4%)
Thrombosis	-	1 (1%)	-
Transaminase elevation	2 (3%)	1 (1%)	-
Weight loss	2 (3%)	-	-

Table 3

Summary of outcome in the current study relative to previously reported series of GBM patients treated with bevacizumab therapy after progression on prior bevacizumab-based treatment.

Study Design	Regimen	Number patients	Median PFS, months (%% CI)	PFS-6, % (95% CI)	Median OS, months (95% CI)	Citation
Prospective	BV + carboplatin + CPT-11	25	2.3 (1.8, 3.6)	16 (5.0, 32.5)	5.8 (4.0, 7.0)	Current Study
Prospective	BV + CPT-11	19	1.1 (CI – NR)	NR	NR	Kreisl[24]
Prospective	BV + daily TMZ or VP-16	23	1.8 (1.0, 2.1)	4.4 (3.1, 18.2)	4.1 (2.8, 5.8)	Reardon, in press[46]
Retrospective	BV + miscellaneous agents	54 (35 GBM)	1.3 (1.2, 1.5)	2 (CI – NR)	2.9 (CI – NR)	Quant[27]
Retrospective	BV + miscellaneous agents	19	2 (1.2, 3.3)	0	5.2 (3.3, 8.4)	Iwamoto[48]
Retrospective	BV + miscellaneous agents	23	1.8 (CI - NR)	NR	NR	Norden[26]
Retrospective	BV + SRS + chemotherapy	23	2.6 (CI – NR)	NR	7.2 (CI – NR)	Torcuator[47]
Retrospective	BV + chemotherapy	23	1.7 (CI- NR)	NR	3.3 (CI – NR)	Torcuator[47]

Abbreviations: BV, bevacizumab; CI, confidence interval; CPT-11, irinotecan; GBM, glioblastoma; NR, not reported; OS, overall survival; PFS, progression-free survival; SRS, stereotactic radiosurgery; TMZ, temozolomide; VP-16, etoposide