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ORIGINAL REPORT

Randomized Phase II Study of Cilengitide, an Integrin-Targeting Arginine-Glycine-Aspartic Acid Peptide, in Recurrent Glioblastoma Multiforme

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ABSTRACT

Purpose
Cilengitide, an inhibitor of $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin receptors, demonstrated minimal toxicity and durable activity across a wide range of doses administered to adults with recurrent glioblastoma multiforme (GBM) in a prior phase I study. The current multicenter phase II study was conducted to evaluate the activity and safety of cilengitide in GBM patients at first recurrence.

Patients and Methods
Eligible patients were randomly assigned to receive either 500 or 2,000 mg of cilengitide twice weekly on a continuous basis. Patients were assessed every 4 weeks. The primary end point was 6-month progression-free survival (PFS) rate. Secondary end points included PFS, overall survival (OS), and radiographic response, as well as quality-of-life and pharmacokinetic assessments.

Results
Eighty-one patients were enrolled, including 41 on the 500-mg arm and 40 on the 2,000-mg arm. The safety profile of cilengitide was excellent, with no significant reproducible toxicities observed on either arm. Antitumor activity was observed in both treatment cohorts but trended more favorably among patients treated with 2,000 mg, including a 6-month PFS of 15% and a median OS of 9.9 months.

Conclusion
Cilengitide monotherapy is well tolerated and exhibits modest antitumor activity among recurrent GBM patients. Additional studies integrating cilengitide into combinatorial regimens for GBM are warranted.

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INTRODUCTION

The outcome of patients with glioblastoma multiforme (GBM), the most common adult primary CNS tumor, remains dismal. Despite current multimodality therapy integrating surgery, radiation therapy (XRT), and chemotherapy, the median progression-free survival (PFS) and overall survival (OS) for newly diagnosed patients are only 6.9 and 14.6 months, respectively.[1] Furthermore, no established therapy exists for recurrent patients. Increasing understanding of the molecular pathogenesis of malignant gliomas has led to the development of novel therapeutics targeting activated regulators critical to GBM cell growth, survival, invasion, and angiogenesis.[2,3] Exploiting such regulators therapeutically may provide more specific yet less toxic treatment compared with traditional cytotoxic approaches.

Composed of dimerized α and β domains, integrins are transmembrane receptors that bind multiple extracellular ligands via an arginine-glycine-aspartic acid (RGD) peptide. Ligand binding activates integrins to regulate tumor cell invasion, migration, proliferation, survival, and angiogenesis.[4] Integrins are widely expressed by both GBM cells and tumor vasculature.[5-7]

Cilengitide (EMD 121974; Merck KGaA, Darmstadt, Germany), a cyclic RGD peptide, competitively binds $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin receptors.[8] Cilengitide[9,10] and other integrin inhibitors are active against preclinical GBM models,[11-14] and clinical studies also demonstrate encouraging antitumor benefit. In a recent phase I study, 10% of recurrent GBM patients achieved radiographic responses, and 31% achieved stable disease for a median of 5.4 months across a wide range of cilengitide dose levels. Of note, systemic exposure at dose levels of 120

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mg/m^2 and higher was within the range achieved by cilengitide in preclinical studies for inhibition of integrin-mediated cell adhesion and angiogenesis.[15] Furthermore, cilengitide exhibits a highly favorable safety profile. No dose-limiting toxicities were observed in separate phase I studies of cilengitide administered up to 2,400 mg/m^2 twice weekly to adults with either advanced solid tumors or recurrent malignant glioma.[16,17] The current multicenter, open-label, randomized phase II study was conducted to further evaluate the efficacy and safety of cilengitide among recurrent GBM patients. Because neither a maximum-tolerated dose (MTD) nor a clear-cut dose-response relationship was determined in the prior phase I study,[16,17] two cilengitide dose levels were evaluated, including an intermediate-low (500 mg) dose and an intermediate-high (2,000 mg) dose relative to the administered doses in the prior phase I study.

PATIENTS AND METHODS

Patient Eligibility

Patients were required to have histologically confirmed GBM that recurred after surgery, XRT, and no more than one chemotherapy regimen. Additional eligibility requirements included the following: age $\geq$ 18 years; measurable, contrast-enhancing tumor; Karnofsky performance score (KPS) $\geq$ 70; stable corticosteroid dose for $\geq$ 1week; satisfactory hematologic (hematocrit $\geq$ 30%, hemoglobin $\geq$ 10 mg/dL, absolute neutrophil count $\geq$ 1,500 cells/μL, platelets $\geq$ 100,000 cells/μL, and normal prothrombin time and partial thromboplastin time) and biochemical results (serum creatinine $\leq$ 1.5 mg/dL, total bilirubin $\leq$ 1.5$\times$ the upper limit of normal, and AST and alkaline phosphatase $\leq$ 2.5$\times$ the upper limit of normal); more than 12 weeks from completion of XRT, more than 4 weeks from prior chemotherapy or investigational agent, and more than 2 weeks from prior surgery ($\geq$ 1 week for biopsy); and written, informed consent. Patients were excluded for pregnancy or nursing, prior antiangiogenic treatment, more than 66 Gy of prior XRT, significant concurrent medical illness or prior malignancy, and known underlying coagulation disorder.

Treatment Design

Patients were centrally randomly assigned to receive cilengitide at either 500 or 2,000 mg per dose. Stratification factors for random assignment included pre-enrollment surgery (none *v* biopsy/subtotal resection) and KPS (70 to 80 *v* 90 to 100). Within 96 hours of random assignment, cilengitide was infused intravenously over 1 hour twice weekly, with at least 72 hours between infusions. Four-week treatment cycles were repeated until unacceptable toxicity, progressive disease (PD), or consent withdrawal. Exclusive of unexpected and intercurrent illness, patients were permitted to miss $\leq$ two consecutive doses or seven total doses during the first 6 months of therapy and $\leq$ four doses over an 8-week period thereafter.

Assessments

A physical examination, CBC, urinalysis, and biochemistry profile were performed before every cycle. Brain magnetic resonance imaging (MRI) was obtained after every other cycle. Toxicity was graded according to National Cancer Institute Common Terminology Criteria of Adverse Events (version 3). There were no cilengitide dose modifications because prior clinical data revealed no correlation of dose to toxicity incidence or severity. Patients with grade 3 or 4 adverse events were allowed to resume cilengitide if the event resolved within 1 week and did not recur.

Independent, blinded central neuroradiology review determined response by contrast-enhanced MRI, neurologic examination, and corticosteroid dosing using the modified Macdonald criteria.[18] Quality-of-life assessment using the Functional Assessment of Cancer Therapy–Brain (version 4) survey, including the disease-specific, physical well-being, functional well-being, emotional well-being, additional concerns, and social/family well-being subscales, was completed at screening, after every other cycle, and at study discontinuation.

For cilengitide pharmacokinetics, blood (4 mL) was taken in cycles 1 and 2 on week 1, day 1 predose; at the end of infusion; and at 1.5, 2, 3, 4, 8, and 24 hours after infusion initiation. In addition, at one site, CSF (10 mL) was also obtained at these time points. Plasma was extracted immediately and stored at $-$20°C. Plasma and CSF sample analyses were performed using a validated liquid chromatography coupled with tandem mass spectrometry method. The validated calibration range was 200 to 100,000 ng/mL.

Calculation of pharmacokinetic parameters via noncompartmental standard methods using the pharmacokinetic software program KINETICA (version 4.1; Thermo Scientific, Waltham, MA) included maximum serum concentration (C_{max}), time to maximum concentration, area under the curve from time zero to infinity ($AUC_{0\text{-}inf}$), apparent terminal elimination half-life associated with the negative terminal slope, total body clearance of drug from plasma, and volume of distribution during terminal phase.

Statistical Considerations

The 21% (95% CI, 13% to 29%) 6-month PFS rate achieved by temozolomide in GBM patients at first recurrence is an established efficacy benchmark of salvage therapy.[19] Thus, the primary objective of our study compared the lower 95% CI of 6-month PFS for each stratum. The exact binomial method was used to calculate 95% CIs. Approximately 40 patients were randomly assigned to each arm for a study population of 33 patients per arm in anticipation of a 15% dropout rate within 6 months. With a planned sample size of 33 patients, a two-sided 95% CI for a single proportion will extend 15% from an expected 6-month PFS of 25%, thereby ensuring that the lower 95% CI is no less than the uninteresting level of 10%.

Time to PD was measured from date of random assignment to PD or death, and survival time was defined from date of random assignment to death. Kaplan-Meier survival curves were plotted for both OS and PFS.

The association between clinical antitumor activity and prognostic factors was explored via a logistic regression model using 6-month PFS as the dependent variable and cilengitide dose (500 *v* 2,000 mg), baseline KPS ($\leq$ 80 *v* $>$ 80), age, baseline tumor size ($<$ 3 *v* 3 to 6 *v* $>$ 6 cm), and time from diagnosis as independent variables. The Cox regression model was used to explore the prognostic value of the same independent variables in a stepwise procedure on OS.

Associations between PFS, OS, and clinical prognostic factors were explored in a univariate manner. The Cox model was first used for comparing age and baseline tumor size in continuous scales. The proportional hazard assumptions were examined via the observed score process component, and the functional form in the original scale was examined via the observed cumulative martingale residuals. Kaplan-Meier curves were plotted by categories of age ($\leq$ 50 *v* $>$ 50 years) and baseline tumor size ($\leq$ 6 *v* $>$ 6 cm). KPS categories and treatment after recurrence were compared using the nonparametric log-rank test and Kaplan-Meier curves. Drug safety and pharmacokinetic parameters were descriptively compared for each stratum.

RESULTS

Patient Characteristics

Between October 2004 and October 2005, 81 patients were enrolled from 15 institutions, including 41 on the 500-mg arm and 40 on the 2,000-mg arm (Fig 1). Patient demographic and pretreatment characteristics were similar in both arms (Table 1). All patients underwent central histopathologic review. A diagnosis of GBM was confirmed in 93% of patients, 5% of patients had anaplastic astrocytoma, and 2% of patients had low-grade glioma. All patients received prior XRT, 99% received prior temozolomide, and 15% received other chemotherapy agents in addition to temozolomide.

Study Drug Administration and Safety

Study drug administration and compliance with treatment for the intent-to-treat study population were excellent (Table 2). Patients

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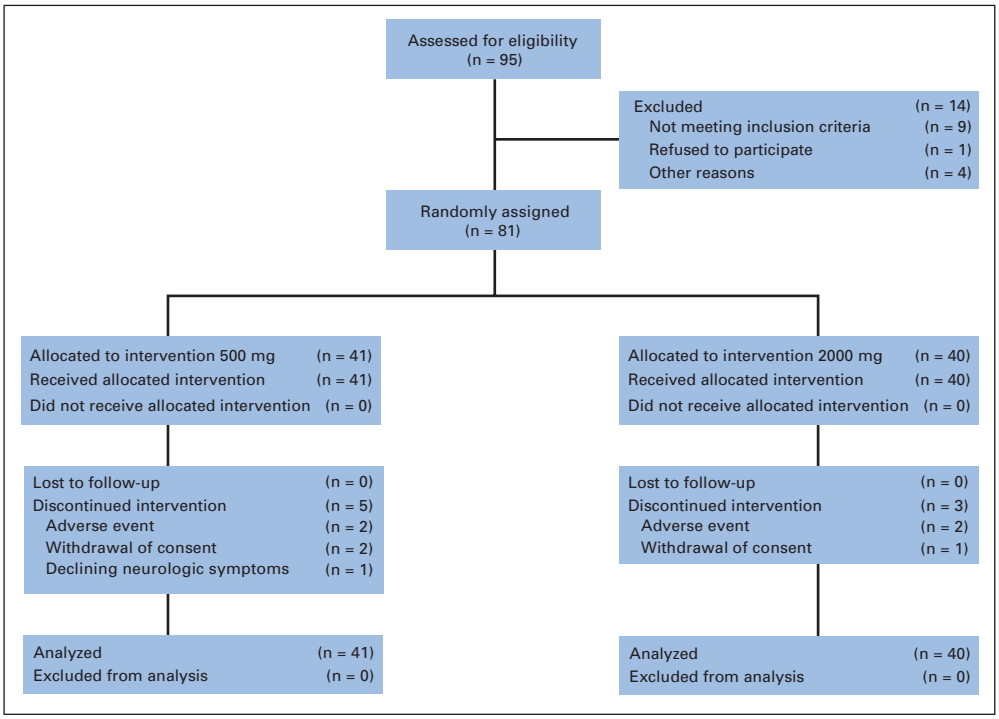

Fig 1. CONSORT diagram.

received a median of 16 infusions, and the mean infusion number was similar in both arms.

All patients were assessable for toxicity. Significant hematologic toxicity was uncommon (Table 3). Four patients experienced grade 3 nonhematologic toxicities that were possibly related to cilengitide therapy. In the 500-mg arm, one patient had transaminase elevation and one patient experienced arthralgia. In the 2,000-mg arm, one patient developed weight gain and one patient experienced headache and altered mental status. There were no grade 4 or 5 study-related, nonhematologic events. Five deaths occurred during treatment or

Table 1. Patient Characteristics

Characteristic	Arm A: 500 mg/d (n = 41) No.	%	Arm B: 2,000 mg/d (n = 40) No.	%	All Patients (N = 81) No.	%
Age, years						
Median	51.0		54.5		52.0	
Range	29.0-78.0		35.0-81.0		29.0-81.0	
Sex						
Female	18	44	12	30	30	37
Male	23	56	28	70	51	63
KPS						
100	6	15	5	13	11	14
90	11	27	12	30	23	28
70-80	24	59	23	58	47	38
Histopathology (independent review)						
GBM	37	90	38	95	75	93
Anaplastic astrocytoma	2	5	2	5	4	5
Low-grade glioma/other	2	5	0	0	2	2
Time from diagnosis to enrollment, months						
Median	9.4		9.8		9.6	
SD	7.25		7.87		7.52	
Prior temozolomide treatment	40	98	40	100	80	99
Prior chemotherapy (not temozolomide)	6	15	6	15	12	15
Resection before enrollment	6	15	4	10	10	12
Baseline corticosteroid use	38	93	34	85	72	89

Abbreviations: KPS, Karnofsky performance score; GBM, glioblastoma multiforme; SD, standard deviation.

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Table 2. Study Drug Administration and Compliance

Drug Administration and Compliance With Regimen	Arm A: 500 mg/d (n = 41)		Arm B: 2,000 mg/d (n = 40)		All Patients (N = 81)	
	No.	%	No.	%	No.	%
Total No. of infusions						
Mean	35		37		36	
Range	4-184		4-189		4-189	
Duration of therapy, days						
Mean	118		106		112	
Range	11-659		12-447		11-659	
0-3 months	28	68	24	60	52	64
> 3-6 months	5	12	11	28	16	20
> 6-12 months	5	12	2	5	7	9
> 12-24 months	3	7	3	8	6	7
> 24 months	0	0	0	0	0	0
% of prepared doses fully infused	98		99		98	
Patients who missed any scheduled dose	11	27	11	28	22	27
Patients who had > 120 hours between any 2 doses during the first 6 months	12	29	7	18	19	24
Patients who withdrew consent	2	5	1	3	3	4
Patients who violated required infusion guidelines*	2	5	2	5	4	5

*The required infusion guidelines were as follows. Exclusive of unexpected or intercurrent illness, patients were not permitted to miss more than two consecutive doses or more than seven total doses during the first 6 months of therapy and no more than four doses during any 8-week interval after 6 months of therapy.

within 28 days of cilengitide discontinuation, including four patients with PD and one patient with aspiration pneumonia. One patient, who was treated in the 500-mg arm, experienced an intracranial hemorrhage (grade 2) with PD.

Quality of Life

Functional Assessment of Cancer Therapy–Brain compliance at screening, before every other cycle of therapy, and at study discontinuation was 91%, 100%, and 49%, respectively. Assessment scores during therapy and at study discontinuation were within 1 standard deviation of the screening value at each time point (data not shown).

Pharmacokinetics

Samples for plasma and CSF pharmacokinetic analyses were available from three and one patient on each arm, respectively (Table 4). In both arms, cilengitide pharmacokinetics were independent of time, and no accumulation after repeated doses was observed. Patients treated with 2,000 mg had higher cilengitide exposures than patients treated with 500 mg; C_{max} was 2.6 to 4.8 times greater, and the $AUC_{0\text{-inf}}$ was 3.9 to 5.1 times greater. Of note, cilengitide did reach the CSF in a dose-dependent manner (Table 4). The CSF C_{max} was reached approximately 2 hours later than the plasma C_{max} and was approximately 1/100 of the plasma C_{max}, although the ratio varied with time from 0.002 to 0.128. In addition, the CSF terminal elimination half-life was approximately two-fold longer than that in plasma.

Efficacy

Outcomes for the intent-to-treat population are listed in Table 5 and shown in Figure 2. Although no complete responses were observed, seven patients (9%) achieved a partial response (Fig 1). All responders remained progression free for at least 10 months (median, 17 months; range, 10.8 to > 36 months). The study was not powered to detect statistically significant differences in outcomes between the two arms, and none of the outcome measures achieved statistical significance, including the primary end point of PFS (hazard ratio [HR] = 0.9; 95% CI, 0.57 to 1.49; $P = .74$). However, several outcome measures trended more favorably in patients treated with 2,000 mg,

Table 3. Hematologic Toxicity

Hematologic Toxicity	Arm A: 500 mg/d (n = 41)				Arm B: 2,000 mg/d (n = 40)				Total (N = 81)			
	Grade 1-2		Grade 3-4		Grade 1-2		Grade 3-4		Grade 1-2		Grade 3-4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Anemia	13	32	0		6	15	0		19	23	0	
Leukopenia	5	12	0		9	23	0		14	17	0	
Lymphopenia	9	22	5	12	5	13	2	5	14	17	7	9
Neutropenia	1	2	0		1	3	1	3	2	2	1	1
Thrombocytopenia	6	15	0		8	20	0		14	17	0	
Febrile neutrophia	0		0		0		0		0		0	

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Table 4. Pharmacokinetic Parameters of Cilengitide per Dose Level

Dose and Cycle	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{0-\mu}$ (ng/mL · h)	$t_{1/2}$ (hours)	CL (L/h)	V_{ss} (L)
Plasma						
500 mg						
Cycle 1 (n = 2)						
Mean	40,350	1.0	86,454	2.22	8.93	20.5
SD	24,395	0.0	72,592	0.58	7.50	12.9
% CV	60.5	0.0	84.0	26.2	84.0	62.9
Cycle 2 (n = 3)						
Mean	35,433	1.0	84,285	2.41	6.98	19.9
SD	20,557	0.0	35,536	0.76	3.77	9.7
% CV	58.0	0.0	42.2	31.5	54.0	48.9
2,000 mg						
Cycle 1 (n = 3)						
Mean	105,700	1.2	337,129	3.43	5.99	23.8
SD	14,145	0.3	38,540	0.18	0.71	3.7
% CV	13.4	24.7	11.4	5.1	11.8	15.5
Cycle 2 (n = 3)						
Mean	169,667	1.0	430,498	3.28	4.66	15.8
SD	20,744	0.0	28,586	0.12	0.32	1.0
% CV	12.2	0.0	6.6	3.7	6.9	6.5
CSF						
500 mg, cycle 1 (n = 1)	138	4.0	2394	9.96		
2,000 mg, cycle 1 (n = 1)	410	3.0	5506	7.25		

Abbreviations: C_{max}, maximum concentration; t_{max}, time to maximum serum concentration; $AUC_{0-\mu}$, area under the concentration-time curve from time zero to infinity; $t_{1/2}$, terminal half-life; CL, mean systemic clearance; V_{ss}, apparent volume of distribution at steady-state; SD, standard deviation; CV, coefficient of variation.

and none favored the 500-mg arm. Specifically, the radiographic response rate, the 6-month PFS rate, and the number of patients completing ≥ 12 cycles of therapy were all higher for the 2,000-mg arm. Furthermore, although both arms were evenly matched for demographic, pretreatment, and postrecurrence treatment factors, the median OS was also higher for the 2,000-mg arm.

Logistic regression revealed that the only variable to predict 6-month PFS was baseline KPS. Specifically, 6-month PFS was fivefold higher in patients with a KPS of 90 to 100 than in patients with a KPS of 80 or less, independent of cilengitide dose. None of the other evaluated variables, including cilengitide dose level, age, tumor size, and time from original diagnosis, correlated with 6-month PFS (data not shown). Similar results were obtained for OS by the Cox regression model. A KPS ≥ 90 reduced the risk of death by 55.5% (HR = 0.445; 95% CI, 0.249 to 0.798) compared with a KPS less than 90.

Table 5. Efficacy of Single-Agent Cilengitide by Dose Level

Outcome or Response	Arm A: 500 mg/d (n = 41)	Arm B: 2,000 mg/d (n = 40)
Patients with a radiographic response		
No.	2	5
%	5	13
Time to progression, weeks		
Median	7.9	8.1
95% CI	7.7 to 15.6	7.9 to 15.0
6-month PFS rate	10	15
95% CI	2.8 to 23.7	5.7 to 29.8
Overall survival, months		
Median	6.5	9.9
95% CI	5.2 to 9.3	6.4 to 15.7
HR	0.70	
95% CI	0.43 to 1.14	
P	.15	
Patients completing ≥ 12 cycles		
No.	3	5
%	7	13
Patients completing ≥ 24 cycles		
No.	2	2
%	5	5

Abbreviation: PFS, progression-free survival.

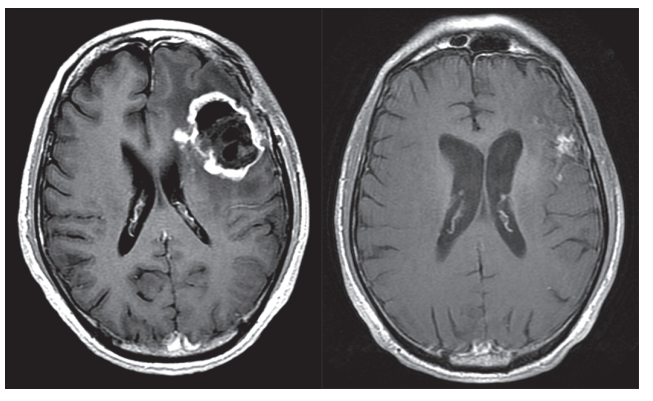

Fig 2. T1-weighted magnetic resonance imaging after gadolinium administration of a representative radiographic response to cilengitide in a patient with recurrent glioblastoma multiforme who achieved a partial response.

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DISCUSSION

The current study was designed to evaluate the antitumor activity of single-agent cilengitide, a cyclic RGD-containing peptide inhibitor of $\alpha V\beta 3$ and $\alpha V\beta 5$ integrin receptors, in recurrent GBM patients. Of note, to our knowledge, this represents the first phase II study of an integrin-targeting therapeutic administered as a single agent in human brain tumor patients. Two dose levels of twice-weekly cilengitide were evaluated because neither a maximum-tolerated dose nor a clear-cut dose-response relationship was determined in a prior phase I study.[17] Specifically, patients were randomly assigned to receive either an intermediate-low (500 mg) or an intermediate-high (2,000 mg) cilengitide dose relative to the dosing range of the prior GBM phase I study. Flat dosing was used in our study because the prior phase I trial did not suggest a relationship between body-surface area and either cilengitide pharmacokinetics or toxicity.

The current study supports many findings of the prior phase I trial.[17] First, we confirmed higher plasma and CSF cilengitide exposures after treatment with the 2,000-mg than the 500-mg dose. Second, the overall excellent safety profile of cilengitide was confirmed with only sporadic instances of relevant nonhematologic and hematologic toxicities. Furthermore, we noted stable qualify-of-life measures among responding patients, providing further support of the good tolerability of cilengitide in this population. We also observed evidence of antitumor activity in each treatment stratum. Nine percent of patients achieved a radiographic response (5% in 500-mg arm, 12.5% in 2,000-mg arm), which essentially replicates the response rate of the prior phase I study (10%)[17] and compares favorably with the 5% radiographic response rate reported for temozolomide in GBM patients at first recurrence,[19] particularly because nearly all patients on our study had PD after prior temozolomide. In addition, a subset of patients achieved prolonged disease control in response to single-agent cilengitide therapy including 10% and 5% of patients who remained progression free for more than 12 and 24 months, respectively, and 10% of patients on the prior phase I study who remained progression free for 8 to 29 months.[17]

Although the current study was not powered to detect a difference between the arms, several factors favor using the 2,000-mg dose in future cilengitide trials. First, higher cilengitide plasma and CSF exposures are achieved with 2,000 mg. Second, the safety profiles of the two arms in our study were comparable. Third, all measures of antitumor activity trended higher in our study in patients on the 2,000-mg dose, including radiographic response rate, PFS, and OS. Finally, pharmacodynamic data from the prior phase I study in GBM revealed that cilengitide AUC inversely correlates with tumor relative cerebral blood flow quantified by dynamic susceptibility contrast MRI.[17,20]

Our 6-month PFS rate with 2,000 mg was within the range reported for temozolomide,[19] even though nearly all patients had experienced treatment failure with prior temozolomide. Furthermore, our study's 6-month PFS rate is comparable to or better than that achieved with other newly developed therapeutics targeting key mediators of cell signaling pathways, including epidermal growth factor receptor, mammalian target of rapamycin, and platelet-derived growth factor receptor, administered as single agents to recurrent GBM patients.[21-25]

OS at the 500-mg dose level also seemed similar to the OS achieved with temozolomide at first progression.[19] Although statistical significance was not achieved, patients in the 2,000-mg arm had a higher median OS time, with a 30% reduction in HR, compared with patients treated with 500 mg. Improved OS seems to be related to the higher cilengitide dose because both arms were evenly matched for demographic, pretreatment, and postrecurrence treatment variables. Two strategies to increase the potential benefit of cilengitide for GBM patients are currently being investigated. First, intratumoral delivery and the ability to modulate integrin signaling within primary brain tumors are being determined in a North American Brain Tumor Consortium trial.[26] Preliminary results from this study suggest that cilengitide is effectively delivered into GBM tumors yielding elevated tumor-to-plasma ratios for up to 24 hours.

Second, several lines of evidence suggest that integrin antagonists, including cilengitide, may have enhanced antitumor benefit when administered in combinatorial therapeutic regimens. Integrins are critically involved in many tumor-promoting activities, such as proliferation, survival, invasion, and angiogenesis. Therefore, effective integrin inhibition may enhance other therapeutics targeting regulators of these processes. In addition, recent evidence suggests that integrin inhibitors may potentiate the activity of cytotoxic agents. Furthermore, its low-toxicity profile suggests that cilengitide can be administered safely with cytotoxic therapy. In preclinical models, integrin antagonists such as cilengitide enhance the antitumor activity of XRT, including synergy in some models.[27-29] Although integrin antagonists plus chemotherapeutics have produced mixed clinical outcomes, the combination did not elicit unexpected or increased toxicity.[30,31]

For these reasons, a trial combining cilengitide with XRT and temozolomide for newly diagnosed GBM patients was recent ly performed.[32] Fifty-two patients received cilengitide 500 mg twice weekly during XRT with daily temozolomide and then during six post-XRT monthly temozolomide cycles. With a median follow-up time of 14 months, the 6-month PFS and 1-year OS rates were 69% and 67%, respectively. In comparison, patients treated with the same regimen without cilengitide have 6-month PFS and 1-year OS rates of 54% and 62%, respectively.[1] Furthermore, patients treated on the cilengitide study whose tumors lacked methylguanine methyltransferase expression had a particularly favorable outcome. A similar study being conducted by the New Approaches to Brain Tumor Therapy Consortium, which randomly assigns newly diagnosed GBM patients to either 500 or 2,000 mg of cilengitide twice weekly during XRT with temozolomide and during post-XRT temozolomide dosing, will further define the value of integrating cilengitide into multimodality regimens for this patient population. In addition, a randomized phase III study comparing XRT plus temozolomide versus the same regimen plus cilengitide in newly diagnosed GBM patients with methylated methylguanine methyltransferase tumors is planned.

In contrast to cancers, such as chronic myelogenous leukemia or gastrointestinal stromal tumors, that can be effectively treated with single-agent targeted therapeutics as a result of critical dependence on a specific genetic abnormality, the vast majority of solid tumors, including GBM, exhibit a multitude of genetic abnormalities that contribute to marked heterogeneity and redundant expression of tumor-promoting mediators. Not surprisingly, in this setting, the clinical benefit of single-agent therapy of targeting therapeutics

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among unselected patients is limited. In this context, the excellent safety profile and modest activity of cilengitide monotherapy noted in our study are encouraging. Additional efforts to optimize the antitumor activity of cilengitide, including its integration into rationally designed combination regimens, and to determine biologic factors that identify patient subsets with a heightened likelihood of therapeutic benefit are warranted. Furthermore, although prior pharmacodynamic data[17,20] and trends favoring improved outcome with higher cilengitide dosing across several studies suggest that higher dosing is appropriate, future studies to determine an optimal biologic dose of integrin antagonists such as cilengitide for GBM may guide more effective use of these agents.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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