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Phase I/II study of sorafenib in combination with temsirolimus for recurrent glioblastoma or gliosarcoma: North American Brain Tumor Consortium study 05-02

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The activity of single-agent targeted molecular therapies in glioblastoma has been limited to date. The North American Brain Tumor Consortium examined the safety, pharmacokinetics, and efficacy of combination therapy with sorafenib, a small molecule inhibitor of Raf, vascular endothelial growth factor receptor 2, and platelet-derived growth factor receptor–β, and temsirolimus (CCI-779), an inhibitor of mammalian target of rapamycin. This was a phase I/II study. The phase I component used a standard 3 × 3 dose escalation scheme to determine the safety and tolerability of this combination therapy. The phase II component used a 2-stage design; the primary endpoint was 6-month progression-free survival (PFS6) rate. Thirteen patients enrolled in the phase I component. The maximum tolerated dosage (MTD) for combination therapy was sorafenib 800 mg daily and temsirolimus 25 mg once weekly. At the MTD, grade 3 thrombocytopenia was the dose-limiting toxicity. Eighteen patients were treated in the phase II component. At interim analysis, the study was terminated and did not proceed to the second stage. No patients remained progression free at 6 months. Median PFS was 8 weeks. The toxicity of this combination therapy resulted in a maximum tolerated dose of temsirolimus that was only one-tenth of the single-agent dose. Minimal activity in recurrent glioblastoma multiforme was seen at the MTD of the 2 combined agents.

Keywords: anaplastic glioma, glioblastoma, malignant glioma, sorafenib, temsirolimus.

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults.[1] Despite surgery, radiation, and chemotherapy, the prognosis remains poor, with a median overall survival of 12–15 months.[2,3] Over the past decade, several molecular alterations in signaling pathways commonly found in GBM have been uncovered, including the pathways of phosphatidylinositol-3 kinase–Akt–mammalian target of rapamycin (PI3K/Akt/mTOR), Ras–Raf–mitogen-activated protein kinase (Ras/Raf/MAPK), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).[4,5] Sorafenib (BAY 43-9006) is a potent inhibitor of

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several receptor tyrosine kinases (RTKs) and intracellular signaling molecules, including Raf, VEGF receptor (VEGFR)2, and PDGF receptor (PDGFR)–β.[6] Temsirolimus (CCI-779), an analogue of sirolimus, targets the mTOR pathway with improved aqueous solubility and pharmacokinetic properties compared with sirolimus.[7]

Like many other single agents in trials for recurrent GBM, temsirolimus has not demonstrated significant single-agent activity despite promising preclinical data.[8] Two multicenter phase II studies of temsirolimus monotherapy in recurrent GBM demonstrated 6-month progression-free survival (PFS6) rates of 2.3%–7.8%.[9,10] Moreover, the addition of adjuvant sorafenib to standard therapy for newly diagnosed GBM did not improve treatment efficacy over historical controls in a multicenter phase II study.[11] Potential reasons for lack of response include coactivation of multiple RTKs[12] and redundant signaling pathways. Combining targeted agents inhibiting parallel pathways (horizontal blockade) is one strategy to improve the effectiveness of targeted molecular therapy.

The North American Brain Tumor Consortium (NABTC) conducted a phase I/II study of sorafenib in combination with erlotinib, temsirolimus, or tipifarnib in patients with recurrent GBM or gliosarcoma (NABTC 05-02). Both the phase I and phase II components used a sequential accrual design. In this design, the first 3 patients accrued to the phase I trial were enrolled into arm 1 (sorafenib in combination with erlotinib), the next 3 patients into arm 2 (sorafenib in combination with temsirolimus), the next 3 patients into arm 3 (sorafenib in combination with tipifarnib), and so on. Patients were enrolled sequentially in groups of 3 into each arm until the maximum tolerated dose (MTD) was determined for each arm. Similarly, patients were accrued in groups to each arm of the phase II component. Details of this study design will be discussed elsewhere. The results from arm 2 of this phase I/II study—sorafenib in combination with temsirolimus—are presented here.

Materials and Methods

Patient Eligibility

Adults (≥18 y old) with histologically confirmed GBM or gliosarcoma with unequivocal tumor recurrence by MRI scan were eligible. A baseline MRI was performed within 14 days of registration on a stable steroid dosage for ≥5 days. Patients must have had progressive disease following prior radiotherapy and have had an interval of ≥42 days from the completion of radiotherapy to study entry. Phase I patients may have had any number of prior relapses; phase II patients may have had treatment for no more than 2 prior relapses. Patients receiving any enzyme-inducing antiepileptic drugs were excluded. Additional eligibility criteria included Karnofsky performance score ≥60, life expectancy ≥8 weeks, adequate bone marrow function (absolute neutrophil count ≥1500/mm^3, platelet count ≥100 000/mm^3, hemoglobin ≥10/dL), adequate liver function (alanine aminotransferase and alkaline phosphatase ≤2 times the upper limit of normal; bilirubin <1.5 mg/dL), adequate renal function (blood urea nitrogen or creatinine ≤1.5 times the upper limit of normal), fasting cholesterol <350 mg/dL (9.0 mmol/L), and fasting triglycerides <400 mg/dL (4.56 mmol/L). Due to potential teratogenicity of sorafenib and temsirolimus, all patients of childbearing potential were required to use adequate birth control. Pregnant women and patients with serious intercurrent medical illnesses and conditions that could alter drug metabolism were excluded.

The study was approved by the institutional review board of each participating institution and conducted in accordance with institutional and federal guidelines for human investigations. Patients were informed of the investigational nature of the study and signed institutional review board–approved informed consent forms before enrollment.

Evaluation during Study

Medical history and physical examination were performed at baseline and at the start of each 4-week cycle. MRI was obtained at baseline and before every other cycle (every 8 wk). Determination of tumor response was made using the Macdonald criteria.[13] Central review of radiology was conducted at the University of California–San Francisco, and central review of pathology was conducted by K.A.

Treatment Plan

Both sorafenib and temsirolimus were supplied by the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, under a cooperative research and development agreement with Bayer HealthCare and Pfizer Pharmaceuticals. Patients were administered sorafenib orally twice per day and temsirolimus intravenously once weekly.

Phase I study.—As previously mentioned, this study was part of a sequential accrual study design of sorafenib in combination with tipifarnib, temsirolimus, or erlotinib (NABTC 05-02). The phase I component used standard dose escalation enrolling 3 patients per cohort, although groups of 3 patients were enrolled sequentially into 1 of the 3 arms: arm 1 (sorafenib and tipifarnib), arm 2 (sorafenib and temsirolimus), or arm 3 (sorafenib and erlotinib).

In arm 2, patients initially received sorafenib at a dosage of 400 mg/d in combination with temsirolimus 25 mg intravenously once weekly. Subsequent dosages of sorafenib remained at 400 mg/d or increased to 800 mg/d. If the initial dose of temsirolimus was well tolerated, subsequent dosages were increased by 25 mg/wk. Escalations were planned in groups of 3 patients, with an additional 3 patients to be added at the first indication of a dose-limiting toxicity (DLT).

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 4 (http://ctep.info.nih.gov/reporting/ctc.html). DLTs were defined as any grade 4 hematologic toxicity; grade 3 thrombocytopenia lasting more than 7 days; any grade ≥3 nonhematologic toxicity (except asymptomatic grade ≥3 lipase unless associated with grade ≥3 amylase or symptoms consistent with pancreatitis); any intolerable grade 2 nonhematological or grade ≥3 hematological toxicity requiring dose reduction during the first 28 days of treatment; or any toxicity resulting in treatment delay greater than 1 week during the first 28 days of treatment. MTD was based on the tolerability observed during the first 28 days of treatment. The MTD of each agent in each arm was that dosage at which fewer than one-third of patients experienced DLT (ie, the dosage at which 0 or 1 of 6 patients experienced DLT, with the next-higher dosage having at least 2 of 3 or 2 of 6 patients encountering DLT).

Phase II study.—Phase II was conducted as a 2-stage design with sequential accrual. The first 19 patients, enrolled in stage I of the 2-stage design, were to be accrued into the first combination completing phase I, with subsequent enrollment into the second and third combinations completing phase I. Nineteen patients were to be accrued into stage I for each arm. The plan was to accrue the next 14 patients into the first arm that passed the efficiency endpoint of stage I allowing accrual to stage II, the next 14 patients to the second arm that passed the efficiency endpoint of stage I, and so on (see Statistical section).

Pharmacokinetic Studies

Sample collection.—Whole blood samples—6 mL for sorafenib, 7 mL for temsirolimus—were collected in heparinized and EDTA-containing nonseparator tubes, respectively, by venipuncture (heparin lock) or by central venous catheter if in place. At the time of sampling, the first 1 mL of blood was discarded and the following 6–7 mL were collected. Serial samples were collected on days 1, 15, and 28 at the following times: baseline, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h post-administration. Temsirolimus was started on day 1 followed by sorafenib on day 2 after the 24-h post-temsirolimus sample. The 7 mL of whole blood was divided for determination of temsirolimus and sirolimus. The sorafenib blood samples were centrifuged within 30 min at 3000 revolutions per minute for 15 min. Plasma and whole blood samples were stored at −70°C until analysis.

Analytical methods.—Analytical standards for temsirolimus, its deuterated internal standard (IS) and sirolimus, and its IS (desmethoxyrapamycin) were obtained from Wyeth-Ayerst Research. Analysis of temsirolimus and sirolimus in whole blood was performed by 2 validated high-performance liquid chromatography (HPLC) assays using electrospray ionization mass spectrometry as previously reported.[14] Analytical standards for sorafenib and sorafenib amine oxide (N-oxide) were obtained from Toronto Research Chemicals. Tolnaflate (IS) was obtained from Sigma-Aldrich. An HPLC assay previously published was implemented and validated.[15] Briefly, duplicate calibration standards, quality control (QC), or patient samples were spiked with the IS followed by acetonitrile protein precipitation, then double extracted with diethyl ether. The absolute recoveries of sorafenib and sorafenib N-oxide were 70% and 75%, respectively. After evaporation, the residue was reconstituted with methyl alcohol and subjected to a linear gradient elution on a reverse phase C18 column with UV detection (254 nm). Calibration curves (7 points) were linear ($R2 > 0.99$) from 0.5 μg/mL (lower limit of quantitation) to 12 μg/mL for sorafenib and 0.08–4 μg/mL for the N-oxide metabolite. The interday precisions for sorafenib/N-oxide were 7.1%/7.5%, 7.5%/11%, and 8.5%/7.3% for the low, medium, and high QC samples, respectively.

The pharmacokinetic parameters for temsirolimus, sorafenib, and their respective metabolites were analyzed by noncompartmental analysis. Peak concentrations (C_{max}) were determined by inspection of each individual's concentration-time curve. The area under the concentration-time curve was calculated using the linear trapezoidal rule up to the last measurable time point ($AUC_{0\text{-}t}$). Differences among the kinetic variables were evaluated using an unpaired 2-tailed *t*-test. Two-tailed $P < .05$ was regarded as statistically significant.

Statistical Considerations

Each arm of the study was evaluated separately. The primary endpoints for the phase I component were to determine the MTD for sorafenib in combination with temsirolimus and to characterize the toxicities and pharmacokinetics of combination therapy. The primary endpoint in the phase II component was PFS6 from time of registration. In a retrospective review of 8 consecutive negative phase II trials in recurrent malignant gliomas from The University of Texas MD Anderson Cancer Center, PFS6 was 15% for GBM (95% confidence interval [CI], 10%–19%).[16] The study was designed as 2-stage phase II and was sized to discriminate between 15% and 35% rates of PFS6. Based on these parameters, the design was to accrue 19 patients to the first stage of each arm sequentially. If 4 of the initial 19 patients were stable at 6 months, then that arm of the study would continue to stage II and accrual would continue, to a total of 33 patients. The combination regimen was considered effective in phase II testing (with a 1-tailed binomial test of a single proportion) if more than 7 of 33 patients had not progressed at 6 months. This provides a 1-tailed alpha <0.1 with power of 90% for the 35% alternative.

Results

Phase I Component

Patient characteristics.—Thirteen eligible patients were enrolled into the phase I component (sorafenib +

temsirolimus). Patient characteristics are summarized in Table 1. There were 9 men and 4 women. Median age was 50 years (range, 32–59 y) and median KPS was 80 (range, 60–100). All patients had GBM. Patients had had a median of 2 prior chemotherapy regimens (range, 1–3); none had previously received bevacizumab.

MTDs and toxicities.—MTDs were sorafenib 800 mg/d and temsirolimus 25 mg/wk. At this dosage, 1/6 patients experienced DLT (grade 3 thrombocytopenia). Emerging data from other ongoing phase I studies of this combination suggested that additional dose escalation would not be tolerated and therefore no further dose escalation was attempted. Other grade 3 or 4 treatment-related toxicities included lymphopenia, elevated aspartate aminotransferase, hypercholesterolemia, hypertriglyceridemia, hemorrhoids, diarrhea, and hypophosphatemia (Table 2).

Pharmacokinetic results.—The mean pharmacokinetic parameters for temsirolimus and its metabolite sirolimus for days 1 and 15 are displayed in Table 3. We have also provided data for temsirolimus at the dose levels of 25 mg from one of our recent trials of temsirolimus in combination with erlotinib for comparison.[17] The steady-state concentrations (C_{pmax}) and area under the plasma time curve ($AUC_{0\text{-}12}$) for sorafenib and its N-oxide metabolite for the dose levels of 200 mg and 400 mg on days 15 and 28 are summarized in Table 4.

Table 1. Patient characteristics

Patient Characteristic	Patients, *n* (%)	
	Phase I	Phase II
No. evaluable patients	13	18
Sex		
Male	9 (69.2)	9 (50)
Female	4 (30.8)	9 (50)
Age (y)		
Median	50	50
Range	32–59	24–64
KPS		
Median	80	90
100	1 (7.7)	3 (16.7)
90	5 (38.5)	9 (50.0)
80	4 (30.8)	4 (22.2)
70	2 (15.4)	1 (5.6)
60	1 (7.7)	1 (5.6)
Histology		
Glioblastoma	13 (100)	18 (100)
Prior chemotherapy regimens		
Median	2	1
1	6 (46.2)	9 (50.0)
2	4 (30.8)	6 (31.6)
3	3 (23.0)	3 (15.7)

Table 5 contains the geometric means comparisons of the kinetic parameters for sorafenib for the current trial and from 3 published trials.[18–20]

There were no statistical differences in the kinetic parameters for either temsirolimus/sirolimus or sorafenib/N-oxide between days 1 and 15 or days 15 and 28, respectively. Likewise, there were no discernible differences in the kinetic parameters of either temsirolimus or sorafenib in combination compared with published reports.[17–20] We did observe a couple of apparent drug interactions between concomitant medications and sorafenib. In a patient receiving sorafenib 200 mg bid who started fluconazole, a moderate inhibitor of cytochrome $P_{450}3A4$, the patient's sorafenib $AUC_{0\text{-}12}$ on day 15 was 134 $\mu g \times h/mL$ compared with a population mean of 32 $\mu g \times h/mL$. An additional patient receiving sorafenib 400 mg bid who started sertraline had a sorafenib day 28 $AUC_{0\text{-}12}$ of 181 $\mu g \times h/mL$ compared with the population mean of 33 $\mu g \times h/mL$.

Phase II Component

Patient characteristics.—Nineteen patients were accrued into the phase II component, but 1 patient was ultimately deemed ineligible on central pathology review. Among the 18 evaluable patients, there were 9 men and 9 women, with a median age of 50 years (range, 24–64 y; Table 1). Median KPS was 90 (range, 60–100). The patients had had a median of 1 prior chemotherapy regimen (range, 1–3); none had received bevacizumab prior to treatment on protocol. All patients treated on protocol had GBM. Patients received sorafenib 400 mg p.o. bid in combination with temsirolimus 25 mg i.v. weekly.

Toxicity data.—In the 18 evaluable patients for toxicity data, sorafenib and temsirolimus were well tolerated in the phase II study at the doses used (Table 6). No patients developed intratumoral hemorrhage. One patient stopped treatment prior to 26 weeks for cerebral ischemia. Two patients required dose reductions: one for grade 3 lipase and another for grade 3 rash and pruritis. The most common grade ≥ 3 adverse events were hypercholesterolemia, fatigue, hypophosphatemia, lymphopenia, and thrombocytopenia.

Efficacy data.—Seventeen patients were evaluable for radiographic response; there were no complete responses and 2 partial responses. Two patients were removed from the study for reasons other than progression (1 for alternative therapy and 1 for cerebral ischemia). No patients remained progression free at 6 months (ie, PFS6 = 0%). Median PFS was 8 weeks (95% CI, 5–9 wk). Median number of 4-week cycles was 2 (range, 1–4). The sorafenib + temsirolimus arm of the study was terminated due to lack of activity and did not proceed to stage II.

Table 2. Grade ≥2 adverse events with relationship possible or higher to sorafenib and/or temsirolimus according to dosage level in phase I component

Adverse Event	Dosage Level 0 (starting dose; sorafenib 200 mg bid + temsirolimus 25 mg i.v. weekly)			Dosage Level 1 (MTD; sorafenib 400 mg bid + temsirolimus 25 mg i.v. weekly)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hematologic						
Anemia	1	0	0	0	0	0
Leukopenia	0	0	0	3	0	0
Lymphopenia	2	1	0	1	1	0
Neutropenia	0	0	0	1	0	0
Thrombocytopenia	3	0	0	2	1	0
Nonhematologic						
ALT, SGPT (high)	1	0	0	2	0	0
Anorexia	1	0	0	0	0	0
AST, SGOT (high)	0	1	0	1	0	0
Bilirubin (high)	0	0	0	1	0	0
Cholesterol (high)	3	1	0	2	0	0
Diarrhea	1	0	0	2	1	0
Dry skin	0	0	0	1	0	0
Fatigue	1	0	0	1	0	0
Fever	0	0	0	1	0	0
Gum infection/gingivitis	1	0	0	0	0	0
Hand-foot syndrome/palmar-plantar erythrodysesthesia syndrome	1	0	0	1	0	0
Heartburn/dyspepsia	1	0	0	0	0	0
Hemorrhoids	0	0	0	1	1	0
Hyperglycemia	1	0	0	0	0	0
Hypertension	1	0	0	1	0	0
Hypertriglyceridemia	3	1	0	1	0	0
Hypoalbuminemia	1	0	0	0	0	0
Hypophosphatemia	4	1	0	2	1	0
Infection	1	0	0	0	0	0
Laryngitis	0	0	0	1	0	0
Lipase (high)	2	0	0	1	0	0
Mucositis	2	0	0	0	0	0
Nausea	0	0	0	1	0	0
Pain (oral cavity)	1	0	0	0	0	0
Rash, maculopapular	1	0	0	0	0	0

Abbreviations: ALT, alanine aminotransferase; SGPT, serum glutamic pyruvic transaminase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase.

Table 3. Pharmacokinetic values of temsirolimus and its metabolite sirolimus, mean values (SD), in comparison with another study

Temsirolimus						Sirolimus					
C_{max}, ng/mL		Trough, ng/mL		Auc_{0-24}, μg × h/mL		C_{max}, ng/mL		Trough, ng/mL		AUC_{0-24}, μg × h/mL	
D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15
530	616	24	20	1.53	1.35	43	48	30	32	0.74	0.83
(±101)	(±209)	(±6.92)	(±7.05)	(±0.27)	(±0.28)	(±20.5)	(±15.2)	(±15.9)	(±19.0)	(±0.34)	(±0.32)
$n = 13$	$n = 12$	$n = 12$	$n = 5$	$n = 12$	$n = 5$	$n = 12$	$n = 10$	$n = 10$	$n = 2$	$n = 11$	$n = 2$
Reference Study: Chang et al.[17]											
Course 1	Course 2			C1	C2	C1	C2			C1	C2
428	544	–	–	1.36	1.48	46	82	–	–	0.79	1.17
(±115)	(±110)			(±0.22)	(±0.28)	(±23)	(±5)			(±0.47)	(±0.64)
$n = 6$	$n = 4$										

Table 4. Pharmacokinetic values of sorafenib and its metabolite N-oxide at sorafenib dosages of 200 mg bid and 400 mg bid, mean (SD)

Sorafenib 200 mg bid				Sorafenib 400 mg bid			
C_{pmax}, μg/mL		AUC_{0-12}, μg × h/mL		C_{pmax}, μg/mL		AUC_{0-12}, μg × h/mL	
D15	D28	D15	D28	D15	D28	D15	D28
Bay/N-oxide Bay/N-oxide	Bay/N-oxide	Bay/N-oxide	Bay/N-oxide	Bay/N-oxide	Bay/N-oxide	Bay/	N-oxide
4.04/0.54 (±1.68)/ (±0.153)	3.20/0.37 (±1.34)/ (±0.10)	35.45/5.02 (±18.10)/ (±1.86)	29.0/2.93 (±12.32)/ (±0.825)	7.49/1.29 (±3.46)/ (±0.812)	6.24/1.27 (±4.03)/ (±1.45)	42.32/ 8.39	32.98/4.18 (±7.01)/ (±0.318)
$n = 4$	$n = 4$	$n = 3$	$n = 4$	$n = 4$	$n = 3$	$n = 1$	$n = 2$

Table 5. Pharmacokinetic values, geometric means, of sorafenib doses of 200 mg bid and 400 mg bid in comparison with other studies

	Sorafenib 200 mg bid				Sorafenib 400 mg bid			
	C_{pmax}, μg/mL		AUC_{0-12}, μg × h/mL		C_{pmax}, μg/mL		AUC_{0-12}, μg × h/mL	
	D14-15	D28	D14-15	D28	D14-19	D28	D14-19	D28
Current study	3.7	3.0	32	27	7.0	6.0	42	33
Sorafenib, Furuse et al.[18]	3.4	4.2	26	32	4.7	3.3	34	29
Sorafenib, Strumberg et al.[19]		4.0		35		5.4		48
Sorafenib + carboplatin + paclitaxel, Okamoto et al.[20]					6.0		39	

Discussion

In this study, the MTDs for combination therapy were sorafenib 800 mg/d and temsirolimus 25 mg/wk. Although the recommended dosage of single-agent temsirolimus is 25 mg/wk in renal cell carcinoma,[21] the single-agent MTD of temsirolimus in GBM studies is 170–250 mg/wk.[9,14,22] However, DLTs led to a maximum tolerated dose of temsirolimus that was only one-tenth of the single-agent dose for GBM. Pharmacokinetic studies showed no significant interactions between these 2 agents to suggest that overlapping toxicities unrelated to drug levels may account for the lower than expected MTDs. These results highlight the increased toxicity of combination therapy in this patient population.

Other studies combining temsirolimus with sorafenib have also found that only lower doses of temsirolimus could be tolerated when the 2 drugs were used together. The North Central Cancer Treatment Group also conducted a phase I/II study of sorafenib in combination with temsirolimus in recurrent high-grade gliomas.[23] The MTDs from this study were also less than expected, with sorafenib 400 mg/d and temsirolimus 25 mg/wk. DLTs were fatigue, anorexia, rash, and bowel perforation. Recently, Davies et al.[24] reported the results of a phase I study of sorafenib and temsirolimus in 25 patients with malignant melanoma. The MTDs were sorafenib 600 mg/d and temsirolimus 25 mg/wk. Dose-limiting toxicities included thrombocytopenia, hand-foot syndrome, serum transaminase elevation, and hypertriglyceridemia. In that study no patient achieved a clinical response, and pharmacodynamic studies of tumor biopsies failed to show inhibition of phospho–extracellular signal-regulated kinase.[24]

Combinations of temsirolimus with other targeted agents have also been associated with increased toxicity. In a phase I study of temsirolimus in combination with erlotinib for malignant glioma, the MTD for temsirolimus was only 15 mg/wk despite the lack of interaction between erlotinib and temsirolimus by pharmacokinetic analysis.[17] Recently published results from a phase I study adding temsirolimus to standard therapy with radiation and temozolomide for newly diagnosed GBM demonstrated an MTD for temsirolimus of 50 mg/wk and increased infectious complications over standard therapy.[25]

In the phase II component, PFS6 from stage 1 of this 2-stage study was 0%, leading to early termination. There are several potential reasons for these disappointing results. First, the toxicity of combination therapy resulted in a dose of temsirolimus that was much lower than expected based on single-agent temsirolimus studies in GBM. Second, CNS penetration of sorafenib is limited. CNS distribution studies have demonstrated that transport of sorafenib across the blood–brain barrier is restricted predominantly by the breast cancer resistance protein (ABCG2/BCRP).[26] Moreover, even in systemic tumors, sorafenib does not appear to inhibit the mitogen-activated protein kinase pathway significantly.[24] It should be noted, however,

Table 6. Grade ≥2 adverse events with relationship possible, probable, or definite to sorafenib and/or temsirolimus in phase II component

Adverse Event	Grade 2	Grade 3	Grade 4
Hematologic			
Anemia	1	0	0
Lymphopenia	6	2	0
Neutropenia	1	0	0
Thrombocytopenia	3	5	2
Nonhematologic			
Cholesterol (high)	6	2	0
Diarrhea	1	1	0
Fatigue	5	2	0
Hyperglycemia	3	0	0
Hypertension	1	0	0
Hypertriglycermidemia	4	0	0
Hypocalcemia	2	0	0
Hypokalemia	0	1	0
Hyponatremia	1	1	0
Hypophosphatemia	5	3	0
Infection–urinary tract/bladder	1	0	0
Lipase (high)	1	1	0
Nausea	1	0	0
Pain–joint/arthralgias	2	0	0
Pharyngeal mucositis	0	1	0
Pneumonia/lung infection	1	0	0
Pruritis	1	1	0
Rash	3	1	0
Seizures	0	1	0
Vomiting	1	0	0

that one would still expect an anti-angiogenic effect from sorafenib through VEGFR and PDGFR-β inhibition regardless of the lower doses. Third, the combination of sorafenib and temsirolimus at current doses may be insufficient to overcome the coactivation of multiple RTKs[12] and redundant signaling pathways found in GBM. Finally, temsirolimus inhibition of mTOR may lead to loss of feedback inhibition and paradoxical Akt activation, as seen with its analogue rapamycin (sirolimus).[27,28] In a study comparing Akt activity using pre- and posttreatment tissues in GBM patients deficient in phosphatase and tensin homolog, rapamycin treatment led to Akt activation in 7 of 14 patients associated with shorter time to progression.[29]

In conclusion, the combination of sorafenib 800 mg/d and temsirolimus 25 mg/wk had minimal activity in recurrent GBM and substantial toxicity. Despite the disappointing results of the current study, combination therapy using targeted agents to inhibit parallel pathways (horizontal inhibition) or several steps in the same signaling pathway (vertical inhibition) may be worthwhile, although more potent and specific agents with less overlapping toxicities and good penetration across the blood–brain barrier will be necessary.

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