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Effect of CYP3A-inducing anti-epileptics on sorafenib exposure: results of a phase II study of sorafenib plus daily temozolomide in adults with recurrent glioblastoma

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Abstract

Sorafenib, an oral VEGFR-2, Raf, PDGFR, c-KIT and Flt-3 inhibitor, is active against renal cell and hepatocellular carcinomas, and has recently demonstrated promising activity for lung and breast cancers. In addition, various protracted temozolomide dosing schedules have been evaluated as a strategy to further enhance its anti-tumor activity. We reasoned that sorafenib and protracted, daily temozolomide may provide complementary therapeutic benefit, and therefore performed a phase 2 trial among recurrent glioblastoma patients. Adult glioblastoma patients at any recurrence after standard temozolomide chemoradiotherapy received sorafenib (400 mg twice daily) and continuous daily temozolomide (50 mg/m^2/day). Assessments were performed every eight weeks. The primary endpoint was progression-free survival at 6 months (PFS-6) and secondary end points were radiographic response, overall survival (OS), safety and sorafenib pharmacokinetics. Of 32 enrolled patients, 12 (38%) were on CYP3-A inducing anti-epileptics (EIAEDs), 17 (53%) had 2 or more prior progressions, 15 had progressed while receiving 5-day temozolomide, and 12 (38%) had failed either prior bevacizumab or VEGFR inhibitor therapy. The most common grade ≥ 3 toxicities were palmer-planter erythrodysesthesia (19%) and elevated amylase/lipase (13%). Sorafenib pharmacokinetic exposures were comparable on day 1 regardless of EIAED status, but significantly lower on day 28 for patients on EIAEDs ($P = 0.0431$). With a median follow-up of 93 weeks, PFS-6 was 9.4%. Only one patient (3%) achieved a partial response. In conclusion, sorafenib can be safely administered with daily temozolomide, but this regimen has limited activity for recurrent GBM. Co-administration of EIAEDs can lower sorafenib exposures in this population.

Keywords

Sorafenib; Temozolomide; Glioblastoma; Raf; VEGF

Introduction

Recurrence among glioblastoma (GBM) patients following conventional therapy with surgical debulking, external beam radiotherapy and temozolomide chemotherapy remains essentially universal. The identification of effective salvage therapies continues to be an elusive yet paramount challenge. In the pre-temozolomide era, the 6-month progression-free survival rate (PFS-6) for salvage therapies was approximately 15% [1]. Unfortunately, treatments following recurrence in the modern, temozolomide era have yielded similarly poor PFS-6 rates [2, 3].

However, therapeutics targeting vascular endothelial growth factor (VEGF) [4–8] or its cognate receptor (VEGFR)[9], have recently been shown to achieve durable anti-tumor benefit among some patients with recurrent malignant glioma. In fact, the FDA granted bevacizumab, a humanized monoclonal antibody against VEGF, accelerated approval for recurrent GBM patients earlier this year based on durable radiographic response [7, 8]. However, improvements in OS were only modestly improved compared to historical benchmarks suggesting that rationally designed combinatorial strategies may further enhance the anti-tumor benefit of VEGF/VEGFR-targeted therapeutics.

Sorafenib (BAY 43-9006; Bayer Pharmaceuticals, Inc. Montville, N.J.), an orally bioavailable inhibitor of VEGFR, Raf-1 and wild-type B-Raf, as well as PDGFR, c-KIT and Flt-3 [10], is FDA-approved for the treatment of renal cell carcinoma as well as hepatocellular carcinoma [11, 12].

Temozolomide, a second generation imidazotetrazine derivative, induces glioma cell apoptosis by methylating specific DNA sites, the most critical being the O^6 position of

guanine [13, 14]. Multiple recent clinical studies evaluating a variety of “dose-dense” temozolomide schedules as a strategy to overcome methylguanine methyltransferase (MGMT)-mediated temozolomide resistance have shown preliminary evidence of encouraging anti-glioma benefit [15–25].

We hypothesized that the anti-tumor activity of sorafenib may be enhanced when administered with daily temozolomide. It is also possible, although unproven, that each of these agents may exert complementary anti-angiogenic effects which may also contribute to anti-tumor benefit. We therefore evaluated continuous daily dosing of sorafenib and temozolomide as a salvage regimen among recurrent GBM patients in the current single-arm phase 2 study.

Patients and methods

Protocol objectives

The primary objective of the study was to define the activity of sorafenib plus daily temozolomide in the treatment of adults with recurrent GBM as measured by PFS-6. Secondary objectives included: to further define the toxicity of this regimen; to evaluate other efficacy measures including radiographic response rate and overall survival (OS); and to determine the pharmacokinetics of sorafenib when combined with daily temozolomide among patients who are on and not on concurrently administered CYP3A-inducing anti-epileptics (EIAEDs).

Patient eligibility criteria

Patients were required to have histologically confirmed diagnosis of GBM that was recurrent following prior therapy as defined by the Macdonald criteria [26]. Eligibility also required: age ≥ 18 years; KPS ≥ 60%; stable corticosteroid dosing for at least 1 week prior to therapy initiation; adequate hematologic (hemoglobin ≥ 9 gm/dl; absolute neutrophil count ≥ 1500/mm^3; platelet count ≥ 100,000/mm^3), renal (serum creatinine ≤ 1.5 times the institutional upper limit of normal [X ULN]) and hepatic function (total bilirubin ≤ 1.5 X ULN, and AST and ALT ≤ 2.5 X ULN); PT/PTT within normal limits; at least 2 weeks between prior surgical resection (1 week for stereotactic biopsy), 4 weeks from prior chemotherapy or investigational therapy, and 12 weeks from prior radiotherapy, unless there was new radiographic enhancement outside the prior radiotherapy field or biopsy-proven recurrent tumor. All patients provided informed consent as approved by the Duke University Medical Center Institutional Review Board.

The following patients were excluded: pregnant or nursing women; those with reproductive potential and not using an effective contraceptive method; prior sorafenib therapy; prior bevacizumab therapy within 6 weeks of study enrollment; hypersensitivity to temozolomide; significant concurrent medical illness including NYHA class > 2 congestive heart failure, new onset angina within past 3 months or myocardial infarction or stroke within 6 months, cardiac dysrhythmia requiring anti-arrhythmic therapy, uncontrolled hypertension, bleeding diathesis or coagulopathy, gastrointestinal disease that could limit absorption, or infection requiring intravenous antibiotics. Patients who received prior temozolomide were eligible unless they had either hypersensitivity, unacceptable toxicity or progressive disease following daily temozolomide therapy. Patients who received prior anti-VEGF therapy were also eligible except for those who received bevacizumab within 6 weeks of study entry.

Treatment design

Sorafenib and temozolomide were administered orally on a continuous daily dosing schedule at 400 mg twice a day and 50 mg/m^2 once daily, respectively. Patients were

encouraged to take their temozolomide at either the same time or within 30 min of a sorafenib dose. Patients were advised to fast for 1 h before and 2 h after taking both temozolomide and sorafenib. Pneumocystis prophylaxis was recommended for all patients. For study purposes, a cycle consisted of 4 weeks of therapy.

Dose modification and retreatment criteria

Toxicity was graded according to NCI CTC version 2 (NCI 2004). Sorafenib was reduced to 400 mg once a day and then 400 mg every other day for grade 2 or greater palmer-plantar erythrodysesthesia (PPE), grade ≥ 3 neutropenia, thrombocytopenia or non-hematologic toxicity, or any attributable toxicity requiring greater than 2 weeks to satisfy re-treatment criteria. Temozolomide was reduced to 40 mg/m^2 per day and then to 50 mg/m^2 every other day for grade 4 neutropenia, grade 3 thrombocytopenia or any grade ≥ 3 non-hematopoietic attributable toxicity.

Retreatment after dose interruption or following each cycle required an ANC ≥ 500 cells/mm^3, platelets ≥ 500 cells/mm^3, SGOT and total bilirubin ≤ 2.5 X ULN and creatinine ≤_1.5 X ULN. In addition, all toxicities were required to resolve to grade ≤ 1 for retreatment.

Patients were removed from study for evidence of PD, grade 4 non-hematologic toxicity, more than 2 sorafenib dose reductions due to toxicity, noncompliance, or voluntary withdrawal.

Supportive care

Antiemetic therapy with serotonin antagonists were prescribed as needed. Loperamide was prescribed for diarrhea according to standard guidelines. Hematopoietic growth factors and blood products were administered according to institutional practice guidelines. Patients were encouraged to use skin emollients and protect pressure-sensitive areas early if they developed signs of PPE.

Evaluations prior to and during therapy

Patients underwent physical and neurologic examinations as well as MRI scans within 2 weeks of enrollment and before every other 4-week cycle. A complete blood count with differential was performed weekly, and a serum biochemistry profile as well as urinalysis were assessed every 4 weeks. A urinalysis and coagulation profile were performed prior to the first cycle, along with a beta human chorionic gonadotropin assay in women with reproductive potential.

Response evaluation

Response determination, performed by the study investigators, was based on neurologic examination and comparison of the baseline contrast-enhanced MRI scan with those performed before each cycle according to the Macdonald criteria [26]. A complete response (CR) was defined as the disappearance of all enhancing tumor from baseline on consecutive MRI scans at least 4 weeks apart, combined with discontinuation of corticosteroids and achievement of neurologic stability or improvement. A PR was defined as ≥50% reduction from baseline in the size (measured as the product of largest perpendicular diameters) of enhancing tumor maintained for at least 6 weeks with a stable or improved neurologic exam and a stable or reduced corticosteroid requirement. Patient response was defined based on the best response achieved at any point on study relative to the pre-treatment baseline MRI. Progressive disease was defined as more than 25% increase in size of enhancing tumor or

any new enhancing lesion compared to baseline or smallest post-treatment assessment. Stable disease was assigned for assessments not meeting criteria for CR, PR, or PD.

Pharmacokinetics

Blood sampling for sorafenib pharmacokinetics was performed on days 1 and 28 of cycle 1, and was obtained before and at 0.5, 1, 2, 4, 6, 8 and 24 h after the AM sorafenib dose. For each sample, plasma supernatants were separated by centrifugation and immediately frozen at −20°C. Plasma concentrations of sorafenib were analyzed using a validated liquid chromatograph tandem mass spectrometer assay with a lower limit of quantification of 0.01 μg/ml. Pharmacokinetic variables measured were area under the plasma concentration–time curve from 0 to 8 h ($AUC_{0–8}$), 0 to 24 h ($AUC_{0–24}$), maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max}). Plasma concentration–time data were evaluated by noncompartmental methods using WinNolin 4.0 (Pharsight, St. Louis, MO).

Statistical considerations

The primary goal of this study was to evaluate the PFS-6 of sorafenib and daily temozolomide in the treatment of patients with recurrent GBM. Given a 21% PFS-6 with 95% confidence interval of 13 to 29% for standard, 5-day temozolomide among patients at first relapse [27], we employed a single-stage phase 2 design to differentiate between a 5 and 20% PFS-6 rate among eligible patients with one or more relapses treated on the current study. The treatment regimen would be considered worthy of further evaluation if 4 or more of the total 32 patients remained progression-free for 6 months or longer. The following characteristics were true of this study design: (1) the type I error rate (α) or probability of erroneously concluding a treatment is active ($P \geq 0.2$) when it actually is ineffective ($P \leq 0.05$) was 0.074; (2) the type II error rate (β) or probability of erroneously concluding that the treatment is ineffective ($P \leq 0.05$) when the treatment actually is active ($P \geq 0.2$) was 0.093.

Efficacy and toxicity monitoring occurred after 16 patients were accrued to the study. If 10 or more patients died or developed disease progression, or 6 or more had developed grade 4 or 5 non-hematologic toxicity, accrual was to be suspended for a careful review of all data.

The product limit estimator developed by Kaplan & Meier was used to graphically describe the distribution of OS and PFS among patients. Survival was defined as the time between treatment initiation and death. For patients remaining alive, survival time was censored at the time of last follow-up. Progression free survival was defined as the time between treatment initiation and disease progression/relapse/death. Patients remaining alive and disease-free had PFS censored at last follow-up. Within the context of these plots/models, estimates of 6-month and 12-month survival and PFS were estimated.

The PFS and OS within subgroups defined by the following patient characteristics were compared using the logrank test: age (<50 vs. ≥50 years), KPS(<90 vs. ≥90%), number of prior episodes of progression (1 vs. >1), number of prior chemotherapeutics (1 vs. >1), prior bevacizumab (yes vs. no), prior bevacizumab or VEGFR tyrosine kinase inhibitor (yes vs. no), and concurrent use of EIAEDs (yes or no).

Due to the small sample sizes, non-parametric tests of statistical significance were used to compare AUC measurements between groups. The Sign test was used to compare day 1 AUC with Day 28 AUC for each group (i.e., two separate tests were performed—one for EIAC and one for non-EIAC). Only patients with measurements at both time points were included in this analysis. The Wilcoxon Rank Sum test was used to compare AUC values between groups. Separate tests were used to compare AUC at day 1 and day 28.

Results

Patient characteristics

Thirty-two patients with recurrent GBM were enrolled at Duke University Medical Center between October 2007 and November 2008 (Table 1). All patients were assessed for the primary endpoint and safety evaluations. One patient was not evaluable for radiographic response because he underwent a gross total resection immediately prior to enrollment. Twelve patients (38%) were on EIAEDs and 10 (31%) were on dexamethasone at study enrollment. Enrolled patients were moderately pre-treated; 17 (53%) had two or more prior episodes of progressive disease and had received two or more prior chemotherapy or investigational agents. Fifteen (47%) had progressive disease after prior 5-day temozolomide dosing and 12 (38%) had failed prior bevacizumab (n = 9) or VEGFR tyrosine kinase inhibitor therapy with vandetanib (n = 3). Following progression on the current study, 23 patients (72%) received salvage therapy with a bevacizumab-based regimen.

Toxicity

Seventy-three cycles of therapy were administered to patients enrolled on this study. Twenty-three patients (72%) received less than or equal to two cycles of therapy, 8 patients (25%) received 3–6 cycles and one patient received 13 cycles of therapy. Overall the regimen was well-tolerated (Table 2). Two patients experienced grade 4 events that included symptomatic elevation of amylase and lipase. For the first patient, this event developed during cycle 1 and required hospitalization, and resolved with treatment interruption and appropriate medical management. This patient had progressive disease at the end of cycle 1 and was taken off study. In the second patient, the amylase and lipase increased within 6 weeks of initiating study therapy, but resolved following a cholecystectomy. Following a brief interruption of therapy, sorafenib was increased to full dose in this patient and was tolerated during five additional cycles of therapy prior to the development of progressive disease. Of note, grade 2 and 3 elevation of amylase or lipase occurred in 2 and 4 patients, respectively. All of these patients were able to receive additional study therapy without further difficulty although the sorafenib dose was modified to 400 mg once daily in three of these patients. Reversible grade 2 and 3 palmar-plantar erythrodysesthesia (PPE) occurred in 1(3%) and 6 (19%) patients, respectively. Three of these patients required sorafenib dose modification, while the others responded to a brief (3–5 day) interruption of sorafenib dosing and supportive care. Other common adverse events included fatigue (25%), rash (22%) and infection (19%), but were limited to grade 2 in most patients. A variety of electrolyte disturbances, which responded to replacement therapy, were noted. As expected, hematologic abnormalities were uncommon. Only one patient developed an intracranial hemorrhage which was grade 1 and occurred at the time of tumor recurrence. There were no deaths on study attributable to study therapy.

Pharmacokinetics

Eight patients who were on EIAEDs had 24-h sorafenib concentration versus time profiles from both day 1 and day 28 of cycle 1. Fifteen patients who were not on EIAEDs underwent similar assessment for day 1 but only 11 of these patients had samples available for day 28 measurements (Table 3). Four patients who were on EIAEDs (50%) and five of those not on EIAEDs (33%) were also on dexamethasone during the period of their PK assessments. There were no noteworthy differences in other concomitant medications between patients on or not on EIAEDs. Of note, none of the patients on the EIAED arm who underwent PK sampling required sorafenib dose interruption or modification during cycle 1 of therapy. In contrast, five patients on the non-EIAED arm who underwent PK sampling required sorafenib dose interruption or modification during cycle 1. Sorafenib measures were

comparable on day 1 among patients on and not on EIAEDs. For patients not on EIAEDs, day 28 sorafenib $AUC_{0–24}$ was significantly higher compared to day 1 ($P = 0.0117$). This increase was expected based on established steady state kinetics, but may have also been mildly augmented by the discontinuation of dexamethasone (a mild CYP3A inducer) in 3 patients. Nonetheless, the day 28 increased exposure was noted despite one-third of the non-EIAED patients requiring decreased sorafenib dosing during cycle 1 due to toxicity compared to none of those on EIAEDs. In contrast, for patients on EIAEDs, sorafenib $AUC_{0–24}$ did not differ significantly between day 1 and day 28 ($P = 0.7266$). Furthermore, sorafenib $AUC_{0–24}$ was significantly higher on day 28 for patients not on EIAEDs compared to those who were on EIAEDs ($P = 0.0431$). For $AUC_{0–8}$ comparisons, similar findings were observed, however, this analysis was limited by small sample size ($n = 5$ per group) and wide standard deviations. There was no difference in day 1exposures between patients on and not on EIAEDs, nor was there a difference between day 1 and day 28 exposures for patients on EIAEDs. For patients not on EIAEDs, day 1 and 28 $AUC_{0–8}$ exposure did not achieve statistical significance when analyzed using the Sign test despite a nearly 5-fold difference in mean (day 1 = 11,082 vs. day 28 = 52061); however, the difference did achieve statistical significance using the paired *t* test ($P = 0.0334$).

Outcome

Confirmed partial response was observed in only 1 patient (3%). Fifteen patients achieved a best response of stable disease (47%), while 16 patients (50%) had progressive disease at first study assessment. With a median follow-up of 93 weeks (95% CI, 53.4, 106.3), the probability of remaining progression-free at 6 months was 9.4% (95% CI, 2.4, 22.3). The median progression-free and overall survivals were 6.4 weeks (95% CI, 3.9, 11.7 weeks) and 41.5 weeks (95% CI, 24.1, 55.1 weeks), respectively. The 1-year survival probability for patients with recurrent GBM was 34.4% (95% CI, 18.8, 50.6%).

Analyses provided no evidence that patient age, KPS, EIAED use, number of prior chemotherapy agents or prior bevacizumab treatment were associated with either PFS or OS; however, more than one prior PD was predictive of poorer OS ($P = 0.0051$).

Discussion

Despite potentially complementary direct and indirect mechanisms of anti-tumor activity, we demonstrate that sorafenib combined with daily temozolomide has minimal activity as a salvage regimen for recurrent GBM patients in this single-arm phase 2 study. Specifically, only one patient achieved a radiographic response and the PFS-6 was 9.4%. Sorafenib is an attractive therapeutic consideration in GBM because it can inhibit several biologically relevant oncogenic kinases including raf, a key mediator of the ras/MAPK kinase pathway [28]. Although mutations in ras or raf are uncommon in malignant gliomas [29], activation of the ras/MAPK pathway occurs frequently and may confer a poor prognosis [30]. Sorafenib can also block PDGFR, an oncogene associated with increased activity in malignant gliomas [31–33]. as well as c-KIT, which has recently been shown to be amplified or overexpressed in a subset of GBM tumors [34, 35]. Sorafenib also may exert a potent indirect anti-tumor effect by blocking angiogenesis via inhibition of VEGFR as well as PDGFR [28].

Despite its diverse spectrum of biologically relevant targets, at the time this study was initiated, there was no data evaluating sorafenib among recurrent GBM patients. However, several studies have been completed or are ongoing to better define the anti-tumor benefit of sorafenib among recurrent as well as newly diagnosed malignant glioma patients. Of note, preliminary results of a phase I dose escalation study of sorafenib monotherapy among recurrent malignant glioma patients reported limited toxicity up to doses of 800 mg bid with

further accrual ongoing to define an MTD [36]. Preliminary reports of additional studies combining sorafenib with either an mTOR inhibitor or an EGFR inhibitor reveal overall disappointing results and poor tolerance among recurrent malignant glioma patients [37, 38].

Protracted daily temozolomide was selected to partner with sorafenib in this study for two primary reasons. First, continuous daily dosing at 50 mg/m^2/day provides a 1.4–1.9 fold greater temozolomide exposure compared to standard dosing at 150–200 mg/m^2/day for 5 days each month. Although dose-dense schedules may enhance cytotoxicity simply due to greater tumor exposure, such schedules may also enhance anti-tumor activity by depleting MGMT. Although confirmation of this effect has not been proven in patient tumors, it has been demonstrated in peripheral blood mononuclear cells [39]. Furthermore, a wide array of "dose-dense" temozolomide schedules have shown promising anti-tumor benefit and acceptable toxicity in ongoing and completed clinical trials for malignant glioma patients [15–23, 40]. In addition, recent reports demonstrate that protracted temozolomide may have anti-tumor benefit among recurrent malignant glioma patients including some who were previously treated with standard, 5-day temozolomide dosing [24, 25]. In a formal phase 2 study of daily temozolomide administered at 50 mg/m^2/day, Perry and colleagues demonstrated that grade 3 malignant glioma patients and those who had progressed following completion of prior standard 5-day temozolomide achieved PFS-6 rates of 42 and 57%, respectively. In contrast, those who were treated with daily temozolomide following progression on standard 5-day temozolomide had a PFS-6 of only 17% [17]. These results led to a recently completed multicenter phase II study conducted by the NCIC. A preliminary analysis of outcome from this study of 120 patients confirmed that those with grade 3 histology as well as GBM patients who were treated 6 months after completing prior 5-day temozolomide therapy had PFS-6 rates of 38 and 28%, respectively, while those who were treated with daily temozolomide within 6 months of 5-day temozolomide dosing had a PFS-6 of only 9.5% [41].

In general, our study results affirm that daily temozolomide in combination with sorafenib has an acceptable toxicity profile. This finding is particularly relevant in that several ongoing studies are combing sorafenib with temozolomide for newly diagnosed GBM patients. Other studies have confirmed that sorafenib can be safely administered with a variety of chemotherapy agents for other malignancies [42–47]. Seven patients (22%) in the current study required dose modification or discontinuation of sorafenib due to adverse events and none of the patients required either dose modification or discontinuation of daily temozolomide. Elevated amylase and/or lipase has been reported with sorafenib and other VEGFR inhibitors. In our series, only two of the four patients who developed this complication were symptomatic and in one of these two patients, underlying gallstones were the likely etiology. Palmar-plantar erythrodysesthesia (PPE) was noted in seven patients (22%) but was manageable with brief sorafenib dose interruptions and supportive care in most patients.

There are several possible factors that may have contributed to the disappointing outcome observed on this study. First, in general patients on this study were heavily pre-treated. Thirteen patients (41%) had received at least 4 prior chemotherapy or investigational agents and 15 patients (47%) had progressed on prior 5-day temozolomide. Such patients have been shown to have a low response to daily temozolomide [17, 41]. Although the combination of temozolomide plus sorafenib showed encouraging activity among advanced melanoma patients without prior temozolomide treatment, the regimen showed minimal activity previously treated with temozolomide in a recently reported phase II study [48]. Second, 13 patients (41%) had previously failed either bevacizumab or an alternative VEGFR-2-targeting TKI. Recent data demonstrates that progressive disease on bevacizumab confers a particularly poor prognosis with a low likelihood of response to subsequent salvage therapy

[49, 50]. Another possible contributing factor to the poor outcome of our study was that patients were unselected for sorafenib target expression. Data from at least one study suggests that there may be subsets of patients who are more likely to respond to sorafenib therapy. Specifically, melanoma patients with high VEGF-R2 expression were more likely to respond to sorafenib plus chemotherapy, whereas those with elevated ERK1/2 levels did not respond [47].

Finally, our PK data suggest that EIAEDs, which were concurrently administered to 12 (38%) of our study patients, may have significantly induced sorafenib metabolism by day 28, leading to overall lower exposures and potentially poorer anti-tumor efficacy. Prior pharmacokinetic studies reveal that sorafenib metabolism exhibits significant interpatient variability [51], and that exposures increase by 3–4 fold over seven days, but reach steady-state at that point [52]. In vitro microsomal data indicate that sorafenib metabolism is mediated by phase I oxidation through cytochrome P450 (CYP) 3A4 and phase II conjugation via UGT1A9 [53]. Although co-administration of ketoconazole, a known CYP3A inhibitor, with low-dose sorafenib (50 mg/day) did not result in unexpected adverse events or evidence of altered sorafenib pharmacokinetics, presumably due to increased glucuronide elimination [53], the effect of CYP3A inducers on sorafenib metabolism are less clear. Recently reported data shows that co-administration of rifampin, a CYP3A4 and UGT 1A9 inducer, led to 37% reduction in sorafenib exposure [54]. In a recent phase I dose escalation study among malignant glioma patients, sorafenib exposures were comparable between patients on and not on EIAEDs on day one of cycle one [36]. Our study results support this finding. However, the phase I study did not evaluate later time point measures. Our study therefore provides the only source of data of steady-state pharmacokinetic measures of sorafenib among brain tumor patients. We demonstrate that sorafenib exposures differ significantly by day 28 between patients on and not on EIAEDs. Specifically, exposures significantly increased by 3–4 fold among patients not on EIAEDs by day 28 as expected based on time required to achieve steady state exposures as previously documented [52]. However, day 28 exposure did not increase compared to day 1 for patients on EIAEDs, presumably due to CYP3A induction. Alternatively, it is possible that continued sorafenib dosing may have led to auto-induction of metabolism. However, this effect has not been observed in other studies [52, 55], and should have been equally apparent regardless of EIAED status in the current study. Diminished exposures of several anti-tumor agents due to EIAEDs have been observed among brain tumor patients including irinotecan [56–58], imatinib [59–61] and erlotinib [62]. However, such an effect has not been previously recognized with sorafenib in this patient population, and is particularly relevant as several ongoing studies of sorafenib in both newly diagnosed and recurrent malignant glioma patients are employing uniform dosing regardless of EIAED status. Our study data suggests that patients on EIAEDs may be significantly underdosed relative to patients not on EIAEDs and that additional studies should be performed to determine optimal sorafenib dosing among patients on EIAEDs. In conclusion, our study demonstrates that the combination of sorafenib plus daily temozolomide is not active among unselected, recurrent GBM patients. Ongoing and future studies among malignant glioma patients should further define the effect of EIAEDs on sorafenib pharmacokinetics and also attempt to determine whether response to sorafenib-based therapy may be linked to tumor markers.

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Abbreviations

CR	Complete response
EIAEDs	Enzyme-inducing antieptileptic drugs
GBM	Glioblastoma multiforme
ITT	Intent-to treat
KPS	Karnofsky performance status
MAPK	Mitogen-activated protein kinase
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Table 1

Patient characteristics

	***n* = 32**
Age, median (years)	53.6
Range	30.4–72.5
Gender	
Male	23 (72)
Female	9 (28)
KPS	
90–100	15 (47)
80	12 (38)
70	5 (16)
Time from diagnosis, median (weeks)	86.3
Range	32.0–374.4
Anti-epileptic use	
EIAED	12 (38)
Non-EIAED	10 (31)
None	10 (31)
Dexamethasone at entry	
Yes	10 (31)
No	22 (69)
# Prior PDs	
1	15 (47)
2	9 (28)
3	8 (25)
Prior XRT	32 (100)
Surgery prior to enrollment	
GTR	1 (3)
STR	3 (9)
Biopsy	2 (6)
None	26 (81)
# Prior chemotherapy or investigational agents	
1	8 (25)
2	4 (13)
3	2 (6)
4	4 (13)
≥5	9 (28)
Failure on prior 5-day temozolomide	
Yes	15 (47)
No	17 (53)
Time from prior 5-day temozolomide (weeks)	
≤12	6 (40)

	***n* = 32**
12–24	3 (20)
≥24	6 (40)
Prior failure on bevacizumab or VEGFR2 TKI	
Yes	13 (41)
No	19 (59)

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Table 2

Toxicity summary: number of patients with each adverse event

Toxicity	Grade			Dose modification or discontinuation	
	2	3	4	Sorafenib	TMZ
Amylase/lipase	2 (6)	4 (13)	2 (6)	4 (13)	
Anorexia	2 (6)	1 (3)			
Constipation	2 (6)				
Diarrhea	2 (6)				
Dyspnea	2 (6)	2 (6)			
Fatigue	6 (19)	2 (6)			
Hyperbilirubinemia		1 (3)			
Hypertension		1 (3)			
Hypersensitivity	3 (9)				
Hypoalbuminemia	3 (9)				
Hypocalcemia	1 (3)				
Hypokalemia		2 (6)			
Hypomagnesemia	1 (3)				
Hypophosphatemia	2 (6)	3 (9)			
Infection	5 (16)	1 (3)			
Mucositis	1 (3)				
Nausea	3 (9)	1 (3)			
Neutropenia	4 (13)	1 (3)			
Palmer-Plantar Erythrodysesthesia	1 (3)	6 (19)		3 (9)	
Rash	7 (22)				
Thrombocytopenia	2 (6)				
Transaminase elevation		1 (3)			

Number in parentheses is the percent of study population

Table 3

Sorafenib pharmacokinetics

Patient Cohort	T max (h)		C max (μg/l)		AUC(24) (μg*h/l)	
EIAED						
Day	1	28	1	28	1	28
# Patients	9	9	9	9	9	9
Mean	NA	NA	3397.3	3813.9	45,309.7	47,148.2
Median	8.2	2.1				
CV%	NA	NA	66.8	40.7	61.8	65.7
Range	2.0–24.7	0–2.3				
Non-EIAED						
Day	1	28	1	28	1	28
# Patients	14	10	14	10	14	10
Mean	NA	NA	3155.1	8118.8	45,238.7	128,820.8
Median	24	4.2				
CV(%)	NA	NA	41.7	60.8	44.1	73.2
Range	2.0–25.5	0–8.2				

AUC(24) area under time curve of 24 h, C_{max} maximum concentration, *CV* coefficient of variation, *EIAED–CYP3A* enzyme-inducing anti-epileptic drugs (phenytoin, phenobarbital, carbamazepine, oxcarbazepine and primidone), *NA* not applicable, T_{max} median time to maximum concentration