Sorafenib plus Daily Low-dose Temozolomide for Relapsed Glioblastoma: A Phase II Study

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Abstract. *Background: Bevacizumab has provided encouraging results in relapsed glioblastoma multiforme (GBM). Pre-clinical and clinical investigations also showed that continuous low-dose temozolomide has some antiangiogenic activity. Based on this evidence, a phase II trial was designed to investigate an oral regimen of sorafenib, an oral multikinase inhibitor, and metronomic temozolomide for relapsed GBM. Patients and Methods: Forty-three patients (median age=60.0 years) naive for antiangiogenic agents received 400 mg sorafenib twice daily plus TMZ 40 mg/m^2/day until disease progression. Results: Toxicity, mostly grade 1-2, was manageable. Grade 3-4 toxicities were hand-foot syndrome (n=4), hypertension (n=2), and fatigue (n=3). Five patients (12%) achieved partial response, 18 (43%) stable disease, 20 (48%) showed progression. The median time-to-progression was 3.2 months, 6-month progression-free survival was 26%, and median overall survival was 7.4 months. Conclusion: This combination of sorafenib and temozolomide was feasible and safe, showing some activity in patients with relapsed GBM.*

In Europe, primary brain tumors are responsible for 2% of all cancer deaths and account for four deaths per 100,000 person-years (1, 2). Most brain tumors are glial-derived; among them, glioblastoma multiforme (GBM) has the greatest epidemiological burden in terms of incidence and aggressiveness.

The standard first-line therapeutic approach for patients with GBM is surgery followed by radiotherapy combined with temozolomide and adjuvant temozolomide (3). In patients with relapsed GBM, second-line treatment with conventional chemotherapeutic agents [*e.g.*, fotemustine, cisplatin, irinotecan, procarbazin; and procarbazine, lomustine, and vincristine (PCV)] has yielded poor results in terms of efficacy and a not negligible toxicity (4-10).

New therapeutic approaches involve the use of metronomic chemotherapy or new targeted agents (11-13). Compared with conventional chemotherapy, metronomic chemotherapy, which is based on frequent or continuous low-dose drug administration, is able to induce sustained and effective anti-angiogenic effects by targeting the endothelial cells of newly-growing tumor blood vessels. These outcomes occur without increasing the severity of side effects caused by the destruction of other cell types normally sensitive to the conventional doses of chemotherapy, thus suggesting a marked and selective sensitivity of activated endothelial cells (14).

In neuro-oncology, specifically, Kurzen *et al.* (15) carried out *in vitro* and *in vivo* studies using temozolomide at a 5-μM concentration and achieved significant inhibition of tumor angiogenesis. Metronomic TMZ showed promising results in the treatment of recurrent GBM (16-19). Among the targeted agents, sorafenib, an oral multikinase inhibitor that targets both cell surface kinase receptors [vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)] and downstream intracellular serine/threonine kinases, could represent an excellent drug for the control of tumor angiogenesis (20). The underlying rationale was based on the evaluation of the antitumor activity

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of the combination through a double mechanism: i. by inhibition of tumor growth induced by sorafenib and ii. by inhibition of the proliferation, adhesion, and migration of the endothelial cells through continuous administration of small doses of temozolomide and sorafenib. On this basis, the combination of sorafenib and temozolomide in the treatment of GBM has been already tested in the first-line setting (21) and in heavily pre-treated patients with recurrent GBM and poor performance status (22). The use of this molecule in combination with temsirolimus has also been investigated (23). Bevacizumab, another inhibitor of angiogenesis, has already been tested for the treatment of recurrent GBM (24-28) and is now approved by the Food and Drug Administration (FDA) for this indication; however, this approval was not yet completed at the time of the planning of the present study, and the clinical outcomes reported in available studies are not entirely favourable. In addition, it may be of interest to evaluate the efficacy and safety of anti-angiogenic agents other than bevacizumab for the treatment of recurrent GBM, a highly vascularizated tumor.

Based on these assumptions, a study consisting of the metronomic administration of temozolomide in combination with sorafenib in patients with relapsed GBM was designed. Among the objectives of the study was an evaluation of the safety of the combination, which theoretically was without overlapping toxicities. The combination was then expected to increase treatment compliance, since patients often exhibit poor acceptance of infusion treatments due to the peculiarity of the disease and their own neurological status.

Patients and Methods

The criteria for patient inclusion was age of 18 years or older, prior histological diagnosis of GBM (World Health Organization grade IV), documented radiological relapse during or after first-line treatment with radiotherapy plus temozolomide, the presence of evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) (29), Eastern Cooperative Oncology Group performance status (ECOG PS) 2 or less, life expectancy longer than eight weeks, adequate renal function [creatinine level less than 1.25-times normal value (NV)], adequate liver function [total bilirubin less than 1.5 the times NV, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) less than 3-times NV], adequate bone marrow reserve [white blood cell count higher than 3000/μl, platelet count higher than 100,000/μl, hemoglobin level higher than 10 g/dl, international normalized ratio less than 1.5, and activated partial thromboplastin time (aPTT) less than 1.5-times NV], and written informed consent.

Criteria for exclusion included previous treatment with antiangiogenic agents or small molecules, diagnosis of other adequately treated malignant neoplasms in the previous 3 years (except carcinoma *in situ* of the uterine cervix, basalioma or cutaneous spinocellular carcinoma, or superficial bladder carcinoma), infection from human immunodeficiency virus or hepatitis B or C virus, history of heart disease (congestive heart failure higher than New York Heart Association classification 2, active ischemic heart disease, or arrhythmia requiring the use of anti-arrhythmic therapy except digitalis and β-blockers) or uncontrolled hypertension, presence of active bacterial infection, being on dialysis, and having a history of hemorrhagic diathesis or subcutaneous bleeding.

The treatment schedule consisted of temozolomide at a dosage of 40 mg/m^2 per day and sorafenib at a dosage of 800 mg/day (two tablets twice daily), which were orally administered continuously until disease progression, unacceptable toxicity, and/or withdrawal of patient consent. Because the antiepileptic drugs that are cytochrome P-450 inducers (*e.g.*, phenobarbital and phenytoin) interfere with the metabolism of sorafenib, all enrolled patients received oxcarbazepine as an anti-convulsant agent. All patients were allowed to take cortisone throughout the entire experimental treatment. In the case of unbearable toxicity, treatment doses were reduced in a stepwise manner, by 20% at each step up to discontinuation if necessary; doses were then escalated to standard dosages again in a stepwise manner (+20% at each step) (please note that information on drug discontinuation/dose reductions were not recorded in the clinical study report).

Baseline evaluation included gathering the patient's anamnesis, performing a complete physical and neurological examination, and evaluating cortisone consumption. Hematochemical examinations included a complete blood test and an estimate of serum levels of creatinine, blood glucose, electrolytes, lactate dehydrogenase, SGOT, SGPT, γ-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, total proteins, and fibrinogen, as well as prothrombin time and aPTT evaluation. Baseline brain gadolinium-enhanced magnetic resonance imaging (MRI) was performed within a month of the start of treatment. An assessment of toxicity was undertaken every four weeks using National Cancer Institute criteria v.3.0 (30). Values of the hematochemical tests and all adverse events reported by the patient or highlighted by the investigator were recorded. A complete physical examination, neurological examination, and brain gadolinium-enhanced MRI were performed every eight weeks during treatment, this also reduces the risk of considering a pseudoprogression as a real progression, and responses were evaluated using the RECIST criteria.

The primary objective of the study was to evaluate the percentage of patients not progressing within 6 months from the start of treatment. Because second-line chemotherapy treatments are generally associated with a 10% rate of progression-free survival (PFS) at six months, the new chemotherapeutic regimen was considered promising in terms of activity if the percentage of patients not progressing at six months increased from 10% to 25%. We considered a lower rate of PFS than the 15% rate proposed by Wong *et al.* at the end of the 1990s (31): in fact, since the publication of their meta-analysis, which evaluated a more selected population, a number of new treatments have been introduced into clinical practice and therefore more treatment lines are available.

In agreement with the single-stage design described by Fleming (32), selecting 0.1 as parameter *p0* (percentage of patients not progressing at six months in the null hypothesis), 0.25 as parameter *p1* (percentage of patients not progressing at six months in the alternative hypothesis), and 0.10 as both α error and β error showed that the study required the enrollment of 40 evaluable patients. Based on this assumption, the treatment was considered worthy of further evaluation if at least seven patients were progression-free at six months. Because of the assumption that 5% of the patients would not be evaluable, 43 patients were enrolled.

Table I. *Patients' characteristics*.

Characteristic	No. of patients (n=43)
Gender	
Male	18
Female	25
Median age (range), years	60.0 (36.1;77.0)
Median ECOG PS (range)	1 (0;2)
Prior therapy	
Surgery	43
Radiotherapy and temozolomide	43
Adjuvant temozolomide	43
Second-line chemotherapy	10
Third-line chemotherapy	5

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table II. *Overall toxicity during treatment*.

Type of toxicity	Grade 1-2 n=43	Grade 3-4 n=43
Hepatic	5	1
Hand-foot syndrome	12	4
Anemia	1	0
Thrombocytopenia	3	0
Anorexia	2	0
Nausea	6	0
Vomiting	3	1
Itch	1	0
Diarrhea	3	1
Pancreatic*	0	1
Fatigue	13	3
Infection†	0	1
Hypertension	6	2
Hyperthyroidism‡	1	0

*Lipase elevation; †Necrotizing fasciitis; ‡Autoimmune thyroiditis.

Data pertaining to treatment toxicities were analyzed by descriptive analysis. The Kaplan-Meier plot model was used to analyze survival. Any correlations among pharmacokinetic parameters, biological activity, and clinical activity were evaluated using multivariate data analysis.

The study protocol was approved by the local Ethical Committee (approval no 3797/2009), in line with current regulations, and the study was conducted according to the Declaration of Helsinki. The study was registered in the EUDRACT Register (registration code 2008-001763-11).

Results

From July 2008 to October 2011, 43 patients (18 men, 25 women) were enrolled in the study. Their median age was 60.0 years (range=36.1-77.0 years), and the median ECOG PS was 1 (range=0-2). All patients had histologically proven GBM that relapsed after surgery, radiotherapy, and temozolomide after at least 6 months. Five patients had had previous second-line chemotherapy; five patients had had two prior lines of therapy. No patient had received prior antiangiogenic treatment. Table I lists the main characteristics of patients at baseline.

Treatment toxicity is reported in detail in Table II. The main grade 3-4 toxicities were hand-foot syndrome (HFS), hypertension, and fatigue in 3 patients.

Out of the 43 patients accrued, 42 patients were considered evaluable for a response; one patient had to be eliminated from the study because of venous thromboembolism that required treatment withdrawal. Five patients (12%) achieved a partial response, 18 patients (43%) had stable disease, and 20 patients (48%) disease progression. The median time-to-progression was 3.2 months [95% confidence interval (CI), 1.8-4.8 months] (Figure 1), 6-month PFS was 26%, and the median overall survival (OS) was 7.4 months (95% CI=5.6-9.0 months) (Figure 2).

Discussion

Results from this preliminary investigation seem to support the value of a combined treatment of patients with relapsed GBM consisting of the metronomic administration of temozolomide along with the targeted tyrosine kinase inhibitor sorafenib. Metronomic chemotherapy, based on the continuous administration of chemotherapeutic agents at relatively low and minimally toxic doses, has gained support following new evidence of a larger number of more effective treatment options (31). Results obtained in various tumor types have demonstrated that such an approach is able to inhibit *in vitro* proliferation, adhesion, and migration of endothelial cells, as well as *in vivo* tumor growth in heterotransplants of human carcinomas, through the inhibition of tumor angiogenesis (15, 34-39). In a phase II clinical investigation undertaken in 48 patients with relapsed high-grade glioma (GBM plus anaplastic astrocytoma plus anaplastic oligoastrocytoma), Kesari *et al*. (40), using metronomic therapy with etoposide and cyclophosphamide in combination with thalidomide and celecoxib, achieved 70% overall disease control with a 6-month PFS of approximately 15% without remarkable toxicities. In a pilot study, 12 patients with recurrent GMB received metronomic temozolomide at a daily dose of 40 mg/m^2 (17). Median OS and PFS from the initiation of metronomic treatment were 11.0 months and 6.0 months, respectively, with a PFS rate of 58.3% at 3 months, and no grade III/IV toxicities were reported. These promising results were overall confirmed in a subsequent study on 38 patients with recurrent GBM, who received metronomic temozolomide (40 mg/m^2 per day or 50 mg/m^2 per day for the initial phase of the study, and 50 mg/m^2 per day thereafter) (18). The

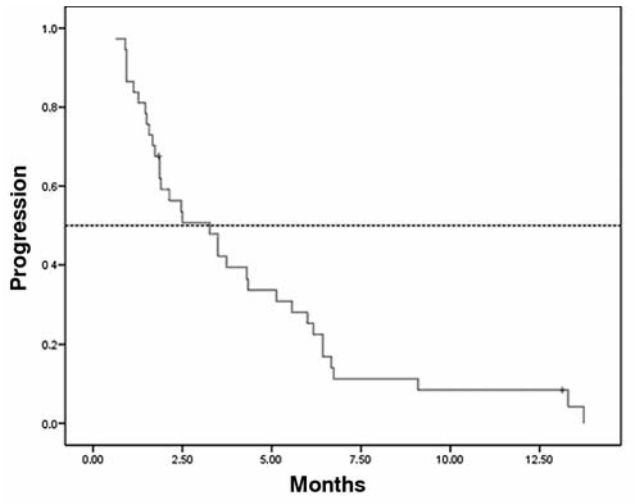

Figure 1. *Time-to-progression. Median value: 3.2 months (CI 95%: 1.8-4.8).*

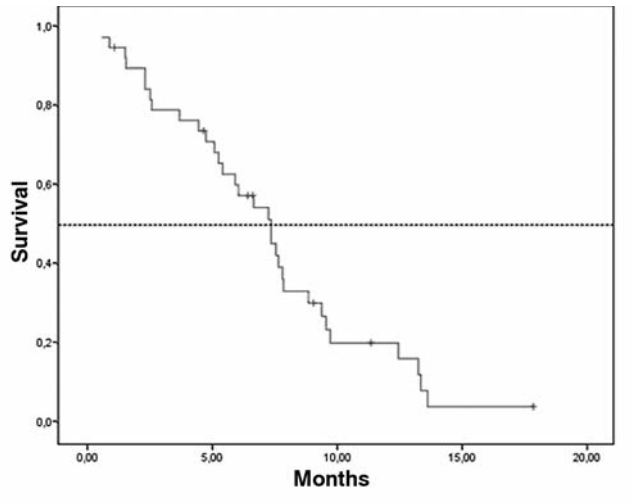

Figure 2. *Overall survival. Median value: 7.4 months (CI 95%: 5.7-9.0).*

6-month PFS rate was 32.5%, and OS rate was 56.0%. Toxicity was manageable. The landmark multicenter, phase II RESCUE trial by Perry *et al*. assessed the efficacy and safety of continuous dose-intense TMZ (50 mg/m^2 per day) in 91 patients with progression of GBM after standard temozolomide (150 to 200 mg/m^2 for 5 days in a 28-day cycle for three or more cycles) (16). Patients were divided into three groups (early, extended, and rechallenge) according to the time-of-progression during adjuvant treatment. The rate of PFS at six months was 23.9% (early: 27.3%; extended: 7.4%; rechallenge: 35.7%), while 1-year survival was 27.3% in the early group, 14.8% in the extended group, and 28.6% in the rechallenge group. The most common grade III and IV nonhematological toxicities were nausea/vomiting (6.7%) and fatigue (5.8%), while severe hematological toxicities were uncommon. Collectively, these results lend support to the efficacy and safety of metronomic temozolomide for the treatment of recurrent GBM, a hypothesis confirmed in a very recent study by Omuro *et al*., conducted in a total of 47 heavily pretreated patients with recurrent GBM, half of whom had failed bevacizumab (19).

In regard to targeted therapies, the first series of clinical investigations in patients with relapsed GBM that used these new agents either as a single agent or in combination with chemotherapy led to inconsistent results. Studies evaluating antibodies against VEGF (bevacizumab), small molecules inhibiting the intracellular tyrosine kinase moiety (gefitinib, erlotinib), c-KIT inhibitors (imatinib), mammalian target of rapamycin inhibitors (temsirolimus, everolimus), and other inhibitors of critical steps of signal transduction (24-28, 39, 40) all demonstrated good tolerance but overall moderate activity in terms of responses, with a limited impact on survival.

In particular, bevacizumab received a fast-track approval by the US FDA for the treatment of recurrent GBM. However, recent investigations in patients with recurrent GBM treated with bevacizumab, either as a single agent or in combination, resulted in disappointing time to progression and OS, with a high rate of recurrence. In light of this evidence, the European Regulatory Authority required a well-designed phase II study, currently ongoing and supported by EORTC, before a final decision on the approval of bevacizumab, in this study together with lomustine, in the European Union for the treatment of recurrent GBM (study code: NCT01290939). While waiting for the results of this study, the evaluation of other antiangiogenic agents for the treatment of recurrent GBM appears therefore of immediate importance.

The decision to test sorafenib in combination with metronomic therapy with temozolomide was based on a scientific rationale strictly related to the characteristics of this targeted agent, which inhibits cell proliferation and angiogenesis. Preliminary efficacy data from a phase I and a pharmacokinetic study carried out in patients with advanced refractory solid tumors emphasized the observation that sorafenib is associated with clinically meaningful and long-lasting stabilization of disease rather than tumor shrinkage, thus suggesting that the effect of the antiangiogenic component of this molecule could be markedly more pronounced compared to other targeted agents (20). This initial observation was subsequently substantiated by the outcomes of clinical trials in patients with advanced renal cell carcinoma and advanced hepatocellular carcinoma. In renal cell carcinoma, when the efficacy of sorafenib in terms of response rate is compared with that of sunitinib (another

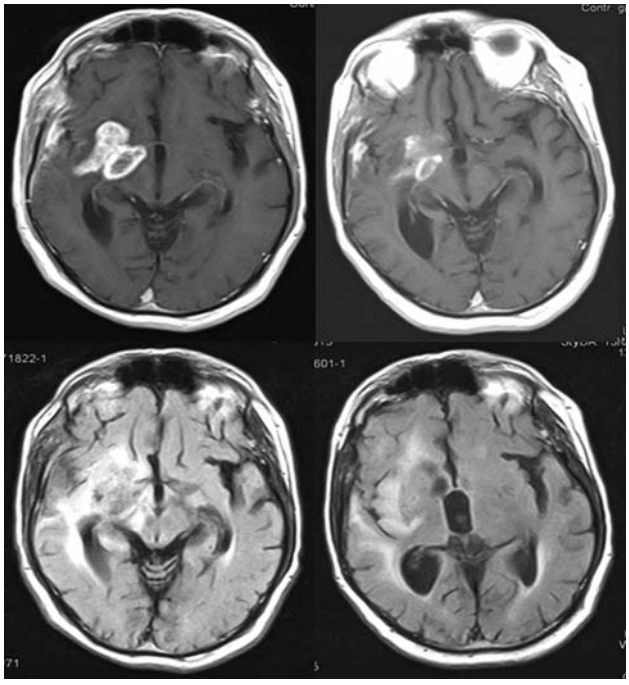

Figure 3. *Magnetic resonance imaging of a partial response: gadolinium-enhanced (top) and T2 fluid-attenuated inversion recovery (bottom).*

commonly used tyrosine kinase inhibitor), it appears that the overall disease control rates (objective responses plus stable disease) induced by the two agents are practically the same: 80% for sorafenib and 78% for sunitinib (41, 42). However, the breakdown of these figures according to the rate of objective responses and of stable disease observed in each single trial shows that compared with the 2% objective response and 78% stable disease observed with sorafenib, these figures accounted for 47% and 31%, respectively, for sunitinib. This result could further explain the idea that the sustained antiangiogenic activity of sorafenib is chiefly in control of the disease instead of tumor shrinkage. Similar observations can be made in hepatocellular carcinoma, a disease whose development depends predominantly on tumor angiogenesis. The positive results achieved in the pivotal clinical trial, which are likely due to the marked antiangiogenic activity of sorafenib, represent an important step leading to the approval of this agent as the only drug effective in the treatment of advanced hepatocellular carcinoma (43).

Overall, the results obtained in the present study appear encouraging and worthy of thoughtful consideration. In a cohort of 43 patients with relapsed GBM, the metronomic administration of temozolomide in combination with sorafenib yielded a 55% overall disease control rate (partial response plus stable disease using the RECIST criteria) and a median OS of 7.4 months. Figure 3 clearly shows evidence of a response. In addition, the primary end-point of the study (6-month PFS) was achieved: 26% of the patients were progression-free at six months. It could be argued that when using antiangiogenic drugs, an overestimate of the response due to the antivascular effect of the drugs detected on gadolinium-enhanced MRI is possible and could bias the evaluation of PFS based on this method of assessment. In addition, the reported time-to-progression (3.2 months) was overall short. Toxicity was overall manageable and in line with expectation: most adverse events were of grade 1-2, but 32% of patients experienced severe adverse events, although most of these events were of grade III severity.

This study is not without limitations. Firstly, dosages were selected without relying on the results of any phase I dose-escalation trial aimed at evaluating combined toxicity of temozolomide and sorafenib. However, the toxicity reported in the present study is in line with the expectations, and the results are positive in consideration of the pre-defined primary endpoint. Of note, all patients received oxcarbazepine as their antiepileptic agent. However, it has been suggested that oxcarbazepine, as a hepatic CYP3A inducer, may significantly reduce the exposure of sorafenib (22); therefore, patients included in the present study, who all received oxcarbazepine, could have been exposed to inadequate doses of sorafenib. Another major limitation of the study is the use of the RECIST criteria to assess response instead of the more specific MacDonald or Revised Assessment in Neuro-Oncology (RANO) criteria: the use of the RECIST criteria do not allow for any definite conclusion to be drawn from comparison with patients assessed with the more specific criteria used in neuro-oncology. We must however point out the RANO criteria were not yet published at the time of the planning of the present study; in addition, the MacDonald criteria take into account factors other than morphological response. At the time of the study planning, we therefore preferred to use the RECIST criteria, in order to focus only on the pure morphological response (and we were not fully aware of the risk of response overestimation due to gadolinium-enhanced MRI). Other important limitations of the study include the overall low number of patients evaluated, the lack of an active comparator, the lack of information on treatments following progression, and the monocentric design. In addition, the presence of a mixed population of patients with either second- or third-line therapy can reduce the robustness of the results.

Despite these limitations, we believe that the present study gains particular clinical significance thanks to the heterogeneous population accrued. In addition to patients who experienced relapse after primary treatment, the population also included five patients who had previously undergone two lines of treatment and another 5 patients who had undergone 3 lines of treatment. This heterogeneous population can better-mirror clinical practice than a rigorously-selected

cohort of patients. The outcome of the present study seems to compare favorably with other recent retrospective analyses in case series of patients with recurrent GBM treated with both bevacizumab as a single-agent or in combination (irinotecan, cyclofosphamide, PCV); these analyses report a 42% response rate and 8.5-month OS in one case (44), along with a 28% response rate and 4.5-month OS in a second case (45). However, the PFS rates reported in our study are somehow lower than those shown in the study by Perry *et al.* on temozolomide rechallenge (16); however, the different administration schemes used for temozolomide do not allow for any reliable comparison to be made.

Other studies have evaluated sorafenib in the treatment of GBM, and led to results somewhat conflicting with those documented in our cohort. Hainsworth *et al.* conducted a study on patients with newly diagnosed GMB who, after surgical resection received, concurrent radiotherapy (total dose, 60 Gy) and temozolomide (75 mg/m^2 per day), followed by six months of maintenance therapy with temozolomide (150 mg/m^2 on days 1-5 every 28 days) and sorafenib 400 mg twice daily (21). In total, 28 patients received four months of maintenance therapy, and nine patients completed the planned six months of treatment. The median PFS was 6 months, with a rate of PFS at one year equal to 16%; median OS was 12 months, and no grade III/IV toxicities were reported. Another study addressed the combination of temozolomide (50 mg/m^2 per day) plus sorafenib 400 mg twice daily in the setting of recurrent GBM (22). In total, 32 patients, 17 of whom with two or more previous progressions of disease and 12 with failure on bevacizumab, were evaluated. While no new safety concerns were reported, the efficacy results, expressed in terms of PFS, were not entirely satisfactorily: PFS at six months was 9.4% and a partial response was documented only in one patient. However, the findings reported in the above-described studies are not immediately comparable to those shown by our study, due to the different setting [*e.g.*, first-line setting for the study by Hainsworth *et al.* (21)] and populations evaluated. We cannot rule out that the more favorable results reported in our cohort can be attributed, at least in part, to the better clinical status of the enrolled patients. We believe that our findings lend support to the feasibility and safety of a combination of metronomic temozolomide and sorafenib, which showed some activity in patients with relapsed GBM. Although the results of the present study are overall promising, larger trials are definitely required to further investigate the use of sorafenib and metronomic temozolomide in the treatment of relapsed GBM.

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