Published in final edited form as:

Cancer. 2010 April 1; 116(7): 1776–1782. doi:10.1002/cncr.24957.

Phase II Trial of Talampanel, a Glutamate Receptor Inhibitor, for Adults with Recurrent Malignant Gliomas

Fabio M. Iwamoto, MD¹, Teri N. Kreisl, MD¹, Lyndon Kim, MD¹, J. Paul Duic, MD¹, John A. Butman, MD, PhD², Paul S. Albert, PhD³, and Howard A. Fine, MD¹

¹Neuro-Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

²Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD

³Biometric Research Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Abstract

Background: Glioma cells secrete glutamate and also express AMPA glutamate receptors, which contribute to proliferation, migration and neurotoxicity of malignant gliomas. Talampanel is an oral AMPA receptor inhibitor with excellent CNS penetration and good tolerability in clinical trials for epilepsy and other neurological disorders.

Methods: We conducted a phase II trial to evaluate the efficacy of talampanel in patients with recurrent malignant glioma as measured by 6-month progression free survival (PFS6).

Results: Thirty patients (22 glioblastomas [GBM], 8 anaplastic gliomas [AG]; 63% men) with median age of 51 years (range, 20 to 67) and median KPS of 80 were included. Patients tolerated treatment well and most adverse events were mild and reversible; the most common toxicities were fatigue (27%), dizziness (23%) and ataxia (17%). There was only one partial response (5%) in the GBM stratum and none among AG patients. With a median follow-up of 13 months, 28 patients (93%) had died. The PFS6 was 4.6% for the initial 22 GBM patients and the study was terminated early due to treatment futility; PFS6 was 0% for 8 AG patients. Median PFS was 5.9 weeks for GBM and 8.9 weeks for AG patients. Median overall survival was 13 weeks for GBM and 14 months for AG patients.

Conclusion: Talampanel was well tolerated but had no significant activity as a single agent in unselected recurrent malignant gliomas.

Keywords

glioma; glioblastoma; talampanel; glutamate receptors

INTRODUCTION

Malignant gliomas are the most common primary brain tumors, with an estimated incidence of 15,000 cases yearly in the United States.¹ Glioblastomas (grade 4) account for approximately 70% of malignant gliomas while anaplastic or grade 3 gliomas are less frequent and include three main subtypes: anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas.^{1, 2} Patients with malignant gliomas

almost always experience tumor progression or recurrence despite multimodal therapy with surgical resection, radiotherapy and chemotherapy.² Conventional chemotherapy has only modest benefits in patients with recurrent malignant glioma and therefore there is a great need for novel targeted therapies.

In vitro and *in vivo* experimental studies have shown that glioma cells release high levels of glutamate, the main excitatory neurotransmitter in the brain, into the extracellular space.³⁻⁵ Moreover, glioma cells lack transporters for glutamate reuptake into the intracellular space.^{6, 7} Excess glutamate is known to cause neurotoxicity and potentially neuronal death through a mechanism called excitotoxicity.⁸ Furthermore, evidence suggests that glioma-mediated glutamate release can facilitate glioma progression and invasion.³ In fact, suppression of glutamate release in an orthotopic glioma mice model decreased vasogenic edema, delayed the onset of neurological deficits and prolonged survival.⁹ In a complementary manner, restoration of excitatory transporter-2, a glutamate reuptake transporter, induced apoptosis and suppressed glioma growth *in vitro* and *in vivo*.⁶

Surgical samples of gliomas express α -amino-3-hydroxy-5methyl-4-isoxazolepropionate (AMPA)-type glutamate receptors in most glioblastomas (GBM) and anaplastic gliomas (AG).^{10, 11} One study demonstrated that intracellular calcium influx through AMPA receptors activates the protein serine-threonine kinase Akt, a key regulator of glioma survival and proliferation.¹² Conversely, inactivation of calcium-permeable AMPA glutamate receptors induces tumor cell apoptosis and suppresses mitotic activity in glioma mouse models.^{10, 11} Therefore, the calcium permeable AMPA receptor is an attractive therapeutic target for malignant gliomas as this receptor is central to a positive feedback loop whereby elevated glutamate release and decreased glutamate uptake promotes tumor proliferation and more glutamate release.

Talampanel is a potent orally available noncompetitive antagonist of AMPA receptors with excellent penetration through the blood-brain barrier.¹³ Talampanel has already undergone phase I and II trials for refractory epilepsy, amyotrophic lateral sclerosis and Parkinson's disease.¹³⁻¹⁵ Talampanel is well tolerated with the most common toxicities being dizziness, ataxia and drowsiness. Given that prior talampanel studies have tested various doses of talampanel alone and in combination with other types of anti-epileptic drugs,¹³⁻¹⁵ we used these established dosages in our phase II trial for recurrent malignant gliomas.

PATIENTS AND METHODS

Eligibility Criteria

Patients ≥ 18 years old with histologically confirmed malignant glioma and unequivocal radiographic tumor progression following prior radiation therapy were eligible. Additional eligibility criteria included Karnofsky performance scale (KPS) ≥ 60 , adequate bone marrow function (hemoglobin ≥ 10 g/dl, absolute neutrophil count $1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$), adequate liver function (bilirubin and AST $\leq$ two times the upper limit of normal), adequate renal function (creatinine < 1.5 mg/dL or measured 24-hour creatinine clearance ≥ 60 mL/minute), and life expectancy > 8 weeks. At least 4 weeks must have elapsed from radiation therapy, 4 weeks from any investigational agent or cytotoxic drugs, 6 weeks from nitrosureas, 3 weeks from procarbazine, 2 weeks from vincristine and 1 week from non-cytotoxic agents such as interferon, tamoxifen, thalidomide and cis-retinoic acid. Patients could undergo resection for recurrent disease prior to enrollment and residual disease was not required for eligibility. There were no limits on the number of prior therapies and patients had to be on a stable dose of corticosteroids for at least 5 days before obtaining their baseline magnetic resonance imaging (MRI) scan. Patients with significant cardiac, hepatic, renal or psychiatric diseases, active infection requiring intravenous

antibiotics, or another active malignancy were ineligible. Patients who were pregnant or nursing were ineligible and birth control methods were required for both men and women during and for 2 months after treatment with talampanel. All participants signed a written informed consent approved by the National Cancer Institute Institutional Review Board.

Treatment Plan

Patients were treated with talampanel orally three times daily (TID) on 6-week cycles without planned interruptions. Prior trials for refractory epilepsy had shown significantly faster talampanel metabolism in patients on concurrent use of enzyme-inducing anti-epileptic drugs (EIAEDs) while valproic acid (VPA) inhibited its metabolism. Based on these data, three different dosing schedules have been established: 1) Patients on EIAEDs but not on VPA received 35 mg TID on week 1, 50 mg TID on week 2 and 75 mg TID starting on week 3; 2) Patients not on EIAEDs or VPA received 25 mg TID on week 1, 35 mg TID on week 2 and 50 mg TID starting on week 3; 3) Patients on VPA received 10 mg TID on week 1, 25 mg TID on week 2 and 35 mg TID starting on week 3. If patients required a change in anti-epileptic drug (AED) during study, every effort was made to switch to same class of AED or adjustments in the talampanel dose were required. History, physical and neurological exam were performed every 3 weeks for the first cycle and every 6 weeks thereafter. Complete blood count and comprehensive metabolic panel were performed every 3 weeks and AED levels every 6 weeks, if applicable. Brain MRI was repeated every 6 weeks, prior to each cycle. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0. Dose reductions were allowed for patients who experienced toxicity $\geq$ grade 3 related to talampanel.

Endpoints

This study had two strata according to histological diagnosis: glioblastoma (GBM) and anaplastic glioma (AG). The primary endpoint of this single-stage phase II trial was 6-month progression-free survival (PFS6) for each stratum. Progression-free survival (PFS) was calculated from study registration until the earliest of either date of radiographic progression, date off study for clinical decline, or start date of new therapy if off study for reason other than tumor progression. All other patients were censored at date of last follow-up if they had not progressed. Overall survival (OS) was calculated from study registration until date of death or patients were censored for OS as of the last date known to be alive.¹⁶ Radiographic response was assessed with standard criteria using largest cross sectional diameters of measurable lesions,¹⁷ or scored evaluations of non-measurable but evaluable disease.¹⁸ Determinations of complete or partial response required stable or decreasing dose of corticosteroids.

Statistics

We used historical data from eight consecutive phase II clinical trials for recurrent malignant gliomas that were deemed negative and showed a PFS6 of 15% (95% confidence interval [CI], 10% to 19%) for GBM and PFS6 of 31% (95% CI, 24% to 39%) for AG.¹⁹ For the GBM stratum, the ineffective rate (P_0) was set to 20% and the targeted effective rate (P_1) was set to 35%. For the AG stratum, P_0 was set to 40% and P_1 was set to 55%. The initial plan was to accrue 41 GBM and 50 AG patients; this single stage design had a false-positive rate (α) $\leq$ 10% and a false-negative rate (β) $\leq$ 20%. Talampanel would be considered effective if more than 11 of 41 patients GBM or more than 24 of 50 AG patients had not progressed at 6 months. Confidence intervals for response rates and PFS6 using a Clopper and Pearson interval. Kaplan-Meier methodology was used to estimate the time to event distributions for PFS and OS. An early look for futility based on a conditional power calculation²⁰ was planned after half of GBM or AG patients were enrolled. Conditional power was based on simple binomial calculations. Statistical analyses were performed with

STATA version 10.0 for Macintosh (Copyright 1985-2007 Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845, USA) and SPLUS version 7.0 (Insightful Software, Seattle Washington, USA)

RESULTS

Patient Characteristics

Patients were accrued from June 2003 to January 2006 at the Brain Tumor Clinic of the National Institutes of Health Clinical Center and follow-up extended thru December 2007. Thirty patients (22 GBM and 8 AG; 63% men) with median age of 51 years and median KPS of 80 were accrued. The median time from initial malignant glioma diagnosis to enrollment was 15 months (range, 5 to 88 months) and all patients had undergone prior radiotherapy and had received a median of 2 prior chemotherapy regimens prior to enrollment. Six patients underwent resection of recurrent tumor with a median of 6 weeks (range, 3.4 to 10.6 weeks) prior to enrollment. Fifteen patients (50%) were on EIAED and one patient was on VPA (Table 1).

Toxicity—Patients tolerated treatment well and adverse events were usually mild and reversible. The most common toxicities were fatigue, dizziness and ataxia (Table 2). All patients tolerated the planned talampanel titration, except for one patient who required dose reduction for dizziness and ataxia. One patient, who was also on corticosteroids, developed hyperglycemia that was controlled with insulin.

Outcomes—All 30 patients met eligibility criteria, received at least one dose of talampanel and were included in an intent-to-treat analysis for PFS and OS. Twenty-five patients had follow-up scans and were evaluable for objective radiographic response (ORR). Twenty-five (83%) patients received $\leq$ one 6-week cycle of talampanel and 29 (97%) discontinued treatment due to progressive disease (Table 3). All 30 patients had tumor progression and 28 (93%) had died; the median follow-up of surviving patients was 13 months.

There was only one partial response (5%, 95% confidence interval [95% CI], 0.1 to 26%, Figure 1) among 19 evaluable patients in the GBM stratum and no ORR among 6 evaluable AG patients. The best ORR was progressive disease in 19 patients, while 5 patients had stable disease for a median of 6 weeks (range, 4 to 12 weeks). The PFS6 was 4.6% (95% CI, 0.1% to 23%) for the initial 22 GBM patients and the study was terminated early due to treatment futility; PFS6 was 0% for 8 AG patients. Median PFS was 5.9 weeks (95% CI, 4.6 to 6 weeks, Figure 2A) for GBM and 8.9 weeks (95% CI, 4.4 to 12.1 weeks) for AG patients. Median overall survival was 13 weeks (95% CI, 9.5 to 25.6 weeks, Figure 2B) for GBM and 14 months for AG patients.

We conducted a conditional power calculation after approximately half the targeted sample size of GBM patients met the PFS6 endpoint. For the GBM group we computed the probability of concluding that the treatment would meet the criterion for an effective therapy ($P1 = \text{PFS6 of } 35\%$), after 21 patients met the PFS6 endpoint. The conditional power was calculated as 3.5%; this low probability showed that continuing accrual to the GBM group would likely be futile. A similar conditional power calculation for the AG group showed that the conditional power for this group after only 8 patients met the PFS6 endpoint was only 0.33. This probability along with the overall low PFS6 suggested that continuing to accrual to this group would be futile.

DISCUSSION

Our phase II results show that talampanel had minimal activity as a single agent in unselected recurrent malignant gliomas, as evidenced by a PFS6 of only 4.6% in the GBM cohort and early trial termination for futility. Only one patient with recurrent GBM had a partial response and a PFS of 35 weeks compared to median historical control of 9 weeks.¹⁹ It is likely, however, that this patient did represent a true talampanel-mediated anti-tumor response since the patient was enrolled on the trial 9 months after finishing radiation therapy thereby making pseudo-progression at enrollment unlikely. Furthermore, a pre-talampanel PET scan and MR perfusion scans showed the gadolinium enhancing area on the pre-study MRI scan to be hypermetabolic and to have high cerebral blood flow, respectively, consistent with recurrent tumor. Nevertheless, despite this apparent response, the overall efficacy of talampanel in this patient population was disappointing and consistent with the results of previous negative trials for recurrent GBM that cumulatively report PFS6 of 9%²¹ to 15%.^{19,2} Prior studies in epilepsy have defined the maximum tolerated doses of talampanel used in our study. These prior studies demonstrated the need to adjust dose based on the concurrent use of EIAED and VPA.¹³⁻¹⁵ At the doses used in this study, talampanel was well tolerated in this population. The major drug-related adverse events were mild and included fatigue, dizziness and ataxia, adverse events comparable to prior talampanel studies in epilepsy and amyotrophic lateral sclerosis.¹³⁻¹⁵ Dizziness and ataxia usually resolve after a few weeks of initiating talampanel secondary to tachyphylaxis to these side effects. Only one patient required dose reduction and no patient discontinued treatment due to toxicity. We were unable to evaluate any potential long-term side effects from talampanel because the median time on treatment was short due to early tumor progression.

Our disappointing results may be due to one or more of several factors. It is possible that the relative lack of clinical benefit seen with talampanel was secondary to the fact that our patients had been moderately pre-treated (median of 2 prior treatment regimens). Nevertheless, there is no obvious biological reason to think that resistance to prior chemotherapy would predict tumor resistance to the presumptive anti-tumor mechanism of glutamate inhibition. Furthermore, it is unlikely that the overall health of these patients can explain the lack of benefit from talampanel since the overall KPS of this patient population was good and a similar group of patients (median of 2.5 prior treatments) treated with bevacizumab at our institution demonstrating that radiographic responses and prolongation of PFS6 can be seen in this general patient population when an active treatment is utilized.²²

There may be underlying biological reasons why talampanel failed to demonstrate significant anti-tumor activity in this trial. It is well known that gliomas have multiple signaling pathways, which often limits the activity of single agent targeted therapies.² Glutamate interacts with other targets not affected by talampanel, including NMDA (N-methyl-D-aspartic acid) receptors, which are present in cancer cells and may be involved in pathways that promote tumor survival.²³ Moreover, compensatory mechanisms can develop following attempts to inhibit glutamate pathways such as compensatory upregulated expression of AMPA receptors in glioma cell lines.⁹ It is also possible that glutamate inhibition alone does not have clinically significant efficacy but can improve response to standard cytotoxic therapy. Consistent with such an effect was a recently completed phase II trial of talampanel combined with standard radiotherapy and temozolomide in 72 newly diagnosed GBM patients,²⁴ which demonstrated a median survival of 20.3 months compared to a historical control of 14.6 months seen with radiotherapy and temozolomide.²⁵ Finally, it remains plausible that despite the preclinical data, human gliomas *in situ* are not inhibited by AMPA receptor blockade. Others and we have demonstrated that the traditional preclinical glioma models (i.e. glioma cell lines) utilized in many of the glutamate inhibition studies differ both genomically and biologically (i.e. relative lack of tumor infiltration of traditional

glioma cell lines) from true human primary gliomas.^{26, 27} Thus, the experimental observations made with glutamate inhibition using standard glioma preclinical models may not be relevant to primary human gliomas *in situ*.

Talampanel was well tolerated but its limited activity does not support further investigation of this drug as a single agent in unselected recurrent malignant glioma patients. Selection of patients for targeted therapies, such as glutamate inhibition, remains challenging because tumor heterogeneity and of lack of reliable biomarkers to predict response. Sulfasalazine, an approved drug for inflammatory bowel disease, is known to inhibit glutamate release by glioma cells and decrease glioma invasion and growth in orthotopic animal models.^{28, 29} Phase 1-2 clinical trials with single agent sulfasalazine are ongoing for recurrent malignant gliomas and will provide further information on the value of inhibiting the glutamate pathways in these patients.^{30, 31} Additional preclinical studies are needed to validate the glutamate pathway as a bona fide therapeutic target using more accurate preclinical models of human glioma, to identify possible molecular predictors of response to glutamate pathway inhibitors and to better understand of underlying mechanisms of treatment failure.

REFERENCES

1. CBTRUS 2008 statistical report: Primary Brain Tumors in the United States, 2000-2004 (years of data collected). Central Brain Tumor Registry of the United States. Available at <http://www.cbtrus.org>. Accessed on January 20, 2009
2. Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med*. 2008; 359:492–507. [PubMed: 18669428]
3. Takano T, Lin JH, Arcuino G, Gao Q, Yang J, Nedergaard M. Glutamate release promotes growth of malignant gliomas. *Nat Med*. 2001; 7:1010–1015. [PubMed: 11533703]
4. Ye ZC, Rothstein JD, Sontheimer H. Compromised glutamate transport in human glioma cells: reduction-mislocalization of sodium-dependent glutamate transporters and enhanced activity of cystine-glutamate exchange. *J Neurosci*. 1999; 19:10767–10777. [PubMed: 10594060]
5. Ye ZC, Sontheimer H. Glioma cells release excitotoxic concentrations of glutamate. *Cancer Res*. 1999; 59:4383–4391. [PubMed: 10485487]
6. de Groot JF, Liu TJ, Fuller G, Yung WK. The excitatory amino acid transporter-2 induces apoptosis and decreases glioma growth in vitro and in vivo. *Cancer Res*. 2005; 65:1934–1940. [PubMed: 15753393]
7. Vanhoutte N, Hermans E. Glutamate-induced glioma cell proliferation is prevented by functional expression of the glutamate transporter GLT-1. *FEBS Lett*. 2008; 582:1847–1852. [PubMed: 18474242]
8. Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron*. 1988; 1:623–634. [PubMed: 2908446]
9. Savaskan NE, Heckel A, Hahnen E, et al. Small interfering RNA-mediated xCT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. *Nat Med*. 2008; 14:629–632. [PubMed: 18469825]
10. Ishiuchi S, Tsuzuki K, Yoshida Y, et al. Blockage of Ca(2+)-permeable AMPA receptors suppresses migration and induces apoptosis in human glioblastoma cells. *Nat Med*. 2002; 8:971–978. [PubMed: 12172541]
11. de Groot JF, Piao Y, Lu L, Fuller GN, Yung WK. Knockdown of GluR1 expression by RNA interference inhibits glioma proliferation. *J Neurooncol*. 2008; 88:121–133. [PubMed: 18317690]
12. Ishiuchi S, Yoshida Y, Sugawara K, et al. Ca2+-permeable AMPA receptors regulate growth of human glioblastoma via Akt activation. *J Neurosci*. 2007; 27:7987–8001. [PubMed: 17652589]
13. Howes JF, Bell C. Talampanel. *Neurotherapeutics*. 2007; 4:126–129. [PubMed: 17199027]
14. Chappell AS, Sander JW, Brodie MJ, et al. A crossover, add-on trial of talampanel in patients with refractory partial seizures. *Neurology*. 2002; 58:1680–1682. [PubMed: 12058100]

15. Langan YM, Lucas R, Jewell H, et al. Talampanel, a new antiepileptic drug: single- and multiple-dose pharmacokinetics and initial 1-week experience in patients with chronic intractable epilepsy. *Epilepsia*. 2003; 44:46–53. [PubMed: 12581229]
16. Lamborn KR, Yung WK, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol*. 2008; 10:162–170. [PubMed: 18356283]
17. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990; 8:1277–1280. [PubMed: 2358840]
18. Levin VA, Crafts DC, Norman DM, Hoffer PB, Spire JP, Wilson CB. Criteria for evaluating patients undergoing chemotherapy for malignant brain tumors. *J Neurosurg*. 1977; 47:329–335. [PubMed: 894339]
19. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999; 17:2572–2578. [PubMed: 10561324]
20. Lan KKG, Simon R, Halperin M. Stochastically curtailed tests in long-term clinical trials. *Commun Stat*. 1982; C1:207–219.
21. Ballman KV, Buckner JC, Brown PD, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol*. 2007; 9:29–38. [PubMed: 17108063]
22. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009; 27:740–745. [PubMed: 19114704]
23. Stepulak A, Sifringer M, Rzeski W, et al. NMDA antagonist inhibits the extracellular signal-regulated kinase pathway and suppresses cancer growth. *Proc Natl Acad Sci U S A*. 2005; 102:15605–15610. [PubMed: 16230611]
24. Grossman S, Ye XB, Chamberlain M, et al. Phase II trial of talampanel in conjunction with standard radiation (RT) and temozolomide (TMZ) in patients with newly diagnosed glioblastoma. *J Clin Oncol*. 2009 in press.
25. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005; 352:987–996. [PubMed: 15758009]
26. Lee J, Kotliarova S, Kotliarov Y, et al. Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. *Cancer Cell*. 2006; 9:391–403. [PubMed: 16697959]
27. Li A, Walling J, Kotliarov Y, et al. Genomic changes and gene expression profiles reveal that established glioma cell lines are poorly representative of primary human gliomas. *Mol Cancer Res*. 2008; 6:21–30. [PubMed: 18184972]
28. Chung WJ, Lyons SA, Nelson GM, et al. Inhibition of cystine uptake disrupts the growth of primary brain tumors. *J Neurosci*. 2005; 25:7101–7110. [PubMed: 16079392]
29. Lyons SA, Chung WJ, Weaver AK, Ogunrinu T, Sontheimer H. Autocrine glutamate signaling promotes glioma cell invasion. *Cancer Res*. 2007; 67:9463–9471. [PubMed: 17909056]
30. Robe PA, Martin D, Albert A, Deprez M, Chariot A, Bours V. A phase 1-2, prospective, double blind, randomized study of the safety and efficacy of Sulfasalazine for the treatment of progressing malignant gliomas: study protocol of [ISRCTN45828668]. *BMC Cancer*. 2006; 6:29. [PubMed: 16448552]
31. Sontheimer H. A role for glutamate in growth and invasion of primary brain tumors. *J Neurochem*. 2008; 105:287–295. [PubMed: 18284616]

Figure 1.
(A) Baseline post-gadolinium T1-weighted image showing a right frontal enhancing lesion;
(B) Post-gadolinium T1-weighted image after 2 cycles of talampanel showing a partial response.

Figure 2.

(A) Progression-free survival for glioblastoma patients (n=22) with 95% confidence intervals (dashed lines). (B) Overall survival for glioblastoma patients (n=22) with 95% confidence intervals (dashed lines).

Table 1

Patient Characteristics.

Characteristic	Patients (n=30)
Gender	
Men	19 (63%)
Women	11 (37%)
Median age (range)	51 years (20 to 67)
Karnofsky performance scale	
60-80	17 (57%)
90-100	13 (43%)
Pathological diagnosis	
Glioblastoma	22 (73%)
Anaplastic astrocytoma	2 (7%)
Anaplastic oligodendroglioma	1 (3%)
Anaplastic oligoastrocytoma	5 (17%)
Prior radiotherapy	30 (100%)
Median time from end of radiotherapy to study enrollment (range)	12.9 months (3.3 to 82.3)
Median number of prior chemotherapy regimens (range)	2 (1 to 6)
Surgery for recurrence prior to study enrollment	6 (20%)
Anti-epileptic drug (AED)	
No AED or non-enzyme inducing AED	14 (47%)
Enzyme-inducing AED	15 (50%)
Valproic Acid	1 (3%)

Table 2

Talampanel toxicity in 30 patients with malignant gliomas.

Toxicity	Number of patients	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	8 (27%)	2	6		
Dizziness	7 (23%)	4	2	1	
Ataxia	5 (17%)	3	1	1	
Nausea/Vomiting	2 (7%)	2			
Headaches	1 (3%)	1			
Diarrhea	1 (3%)	1			
Thrombocytopenia	1 (3%)	1			
Increased Alkaline Phosphatase	1 (3%)	1			
Increased Aspartate Aminotransferase (AST)	1 (3%)	1			
Hyperglycemia	1 (3%)				1

Table 3

Duration and causes of treatment discontinuation.

	Number of patients (%)
Number of 6-week cycles	
< 1	11 (37)
1	14 (47)
2	3 (10)
3	1 (3)
5	1 (3)
Cause of treatment discontinuation	
Radiographic tumor progression	23 (77)
Clinical tumor progression	6 (20)
Consent withdrawal	1 (3)