Talampanel With Standard Radiation and Temozolomide in Patients With Newly Diagnosed Glioblastoma: A Multicenter Phase II Trial

Stuart A. Grossman, Xiaobu Ye, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Serena Desideri, Steven Piantadosi, Joy Fisher, and Howard A. Fine

From the New Approaches to Brain Tumor Therapy CNS Consortium, Baltimore, MD.

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Corresponding author: Stuart A. Grossman, MD, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Cancer Research Building II – Suite 1M-16, 1550 Orleans St, Baltimore, MD 21231; e-mail: grossman@jhmi.edu.

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A B S T R A C T

Purpose

Recent data suggest that the glutamatergic system is important in the proliferation and migration of glioblastoma. Talampanel is a well-tolerated, oral α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blocker that could be beneficial in this disease.

Patients and Methods

This trial was designed to estimate overall survival in adults with newly diagnosed glioblastoma treated with talampanel in addition to standard radiation (RT) and temozolomide (TMZ). A secondary purpose was to evaluate talampanel toxicity in this setting. Talampanel was initiated with RT + TMZ and discontinued for toxicity or disease progression. Survival was compared with historical controls.

Results

Seventy-two patients were enrolled from December 2005 to July 2006. Their median age was 60 years (range, 37 to 85 years, with 17% > 70 years), median Karnofsky performance score was 90 (range, 70 to 100), and 77% had a debulking procedure. With a median follow-up time of 18 months, 55 patients (76%) have died, yielding a median survival time of 18.3 months (95% CI, 14.6 to 22.5 months). When the 60 patients who were 18 to 70 years old were compared with the European Organisation for Research and Treatment of Cancer (EORTC) RT + TMZ data, the median survival (20.3 v 14.6 months, respectively) and percentage of patients surviving at 24 months (41.7% v 26.5%, respectively; $P = .02$) seemed superior. The percentage of patients methylated at O⁶-methylguanine–DNA methyltransferase was lower than on the EORTC study (29% v 43%, respectively). Talampanel was well tolerated and did not increase the known hematologic or nonhematologic toxicities of TMZ.

Conclusion

Talampanel can be added to RT + TMZ without significant additional toxicity. The encouraging survival results in methylated and unmethylated patients suggest that blocking AMPA receptors may be a useful strategy in newly diagnosed glioblastoma.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. In 2005, a prospective randomized comparison of radiation (RT) alone versus RT with daily temozolomide (TMZ) followed by 6 months of adjuvant TMZ yielded a 2.5-month improvement in median survival and an increase in 2-year survivors from 10% to 24%.¹ As a result, this has become standard therapy for patients with newly diagnosed GBM. Although this represents a substantial achievement, novel therapies are required to further improve the outcome of this devastating malignancy.

Glutamate is a major excitatory neurotransmitter in the mammalian CNS. It is stored in synaptic vesicles and released to mediate neurotransmission. Its effects are rapidly terminated by glutamate reuptake, which relies on sodium-dependent glutamate transporters located on the plasma membranes of neurons and glial cells. Glioma cells release glutamate in concentrations that are toxic to surrounding neurons and glia.²⁻⁴ In addition, glutamate reuptake seems to be reduced because high-grade gliomas have reduced glutamate transporters (EAAT2/GLT-1) and the glutamate transporters in astrocytes adjacent to gliomas are also downregulated.⁵ Recent studies suggest that

the glutamatergic system also plays a key role in the proliferation, survival, and migration of gliomas perhaps via activation of the Akt pathway.⁶⁻¹¹ Talampanel is an oral, noncompetitive antagonist of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamate excitatory amino acid receptors with excellent brain penetration.¹² Its toxicity profile in humans suggested that it could be safely combined with RT + TMZ in patients with newly diagnosed GBM.^{12,13}

PATIENTS AND METHODS

This study was conducted by the National Cancer Institute–funded New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. Participating institutions included University of Alabama at Birmingham, The Cleveland Clinic, Emory University, Henry Ford Hospital, Johns Hopkins University, Massachusetts General Hospital, The H. Lee Moffitt Cancer Center, University of Pennsylvania, and Wake Forest University. Ivax Pharmaceuticals (Miami, FL), which was acquired by Teva Pharmaceutical Industries (Petach Tikva, Israel) while this trial was accruing patients, provided talampanel and additional support for this study. This study was reviewed and approved by the National Cancer Institute and the institutional review board of each participating institution.

Overall Treatment Plan

The primary objective of this safety and activity trial was to estimate overall survival in adults with newly diagnosed GBM treated with talampanel in addition to standard RT + TMZ. The second objective was to describe the toxicity of talampanel in this setting. As illustrated in Figure 1, eligible patients received standard RT (5 days a week) as well as daily TMZ (75 mg/m²/d) for 6 weeks. One month later, adjuvant TMZ (200 mg/m²/d for 5 consecutive days each month) was commenced and continued for a total of 6 months. Talampanel was administered orally three times daily beginning on the first day of RT + TMZ and was continued until there was talampanel-related toxicity or tumor progression.

Patient Selection

Eligible patients were ≥ 18 years of age with a supratentorial GBM as confirmed histologically at the accruing institution. In addition, the following were required: Karnofsky performance score (KPS) ≥ 60 ; stable dexamethasone dose for ≥ 5 days; no prior RT or chemotherapy (including carmustine wafers [Gliadel; Eisai, Woodcliff Lake, NJ]), normal hematologic, renal, and liver function; ability to provide written informed consent and follow acceptable birth control methods; and a Mini-Mental State Examination score of ≥ 15 . Patients were excluded if they had taken valproic acid in the previous month, had a serious concurrent infection or medical illness, were pregnant or

breast-feeding, or had a prior malignancy unless it was curatively treated carcinoma in situ or basal cell carcinoma of the skin or the patient had been disease free for more than 5 years.

RT

RT consisted of 60 Gy in 30 fractions delivered with megavoltage machines to the tumor plus a generous margin. Electron, particle, implant, radiosurgery, or intensity-modulated RT techniques were not permitted. If three-dimensional treatment planning was used, the appropriate margin of coverage was defined dosimetrically. The initial target treatment volume was defined as the contrast-enhancing lesion plus edema plus a 1.0-cm margin. The cone-down target volume included the enhancing lesion plus a 1.0-cm margin.

TMZ

TMZ with RT. Daily TMZ (75 mg/m²) was administered orally 1 hour before each RT session and in the mornings on weekends. During this treatment period, all hematologic toxicities were attributed to TMZ. TMZ was held for an absolute neutrophil count (ANC) $\leq 1,500/\mu\text{L}$, platelets $\leq 100,000/\mu\text{L}$, or a Common Terminology Criteria of Adverse Events (CTCAE) nonhematologic toxicity of grade ≥ 2 (except for alopecia, nausea, and vomiting). Once toxicities resolved, TMZ was resumed without making up lost doses.

TMZ after RT. One month after completion of RT and concurrent TMZ, TMZ was administered at a dose of 200 mg/m² for 5 consecutive days every month for a total of 6 months with antiemetic prophylaxis. Dose modifications were dependant on the weekly counts and evaluations over the prior month. Hematologic and nonhematologic parameters were required to return to ANC $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, and CTCAE grade ≤ 1 (except for alopecia, nausea, and vomiting) before the post-RT TMZ could begin. Doses were reduced by one level (200, 150, and 100 mg/m²) after each cycle that was accompanied by a CTCAE grade 3 (except for alopecia, nausea, and vomiting) nonhematologic toxicity and/or a platelet count less than 50,000/ μL and/or ANC less than 1,000/ μL . Subsequent dose re-escalations were not permitted. TMZ was discontinued in patients who required dose reductions to a dose level less than 100 mg/m²/d or if any nonhematologic grade 3 toxicity recurred after reduction for that toxicity.

Talampanel

Prior studies of talampanel demonstrated that doses should be slowly escalated to reach the optimal daily dose and that enzyme-inducing antiepileptic drugs (EIASDs) increase the elimination of talampanel.¹² Therefore, talampanel 25 mg three times a day was administered during the first week of treatment. This was increased to 35 mg three times a day in the second week and to 50 mg three times a day thereafter in patients not taking EIASD. For patients on EIASD, the corresponding doses were 35 mg three times a day in week 1, 50 mg three times a day in week 2, and 75 mg three times a day thereafter. EIASDs included phenytoin, carbamazepine, phenobarbital, primidone, and oxcarbazepine. Patients receiving valproic acid were ineligible for this study.

Talampanel was administered from the first day of RT + TMZ until there was significant talampanel-related toxicity or evidence of tumor progression. Tumor progression was defined by new lesions on neuroimaging, a $\geq 25\%$ increase in contrast-enhancing dimensions, or neurologic deterioration on stable or increasing corticosteroids without another explanation. Dose-limiting toxicities (DLTs) included any possibly, probably, or definitely talampanel-related grade 3 or 4 toxicities. Patients with talampanel-related DLTs had talampanel suspended until toxicities resolved. If the toxicity resolved to $\leq$ grade 1 within 21 days, the patient was re-treated using the following dose reduction schedule: 20 mg three times a day on days 1 through 7, then 25 mg three times a day on days 8 through 14, followed by 35 mg three times a day thereafter for patients on EIASDs; for patients not on EIASDs, the corresponding doses were 10, 20, and 25 mg three times a day. If DLTs did not resolve to $\leq$ grade 1 within 3 weeks or if another talampanel-related DLT occurred at a reduced dose, the patient was removed from the study. Known TMZ hematologic toxicities were not attributed to talampanel and were not considered dose limiting.

Fig 1. Treatment plan. TMZ, temozolomide; RT, radiation; po, oral; tid, three times a day; EORTC, European Organisation for Research and Treatment of Cancer; qd, once daily.

Other Standard Medications

Corticosteroids, anticonvulsants, and antiemetics were administered as required to control brain edema, seizures, and TMZ-related nausea. *Pneumocystis carinii* prophylaxis was mandatory during RT and recommended until there was recovery from lymphocytopenia. Other investigational agents or anticancer therapies were not permitted while patients were on this study.

End Point Measurements, Statistical Considerations, and Data Analysis

The primary efficacy end point was overall survival because preclinical data suggested that glutamate receptor inhibition was more likely cytostatic than cytotoxic. The trial was designed to detect a hazard ratio (HR) of 0.53 compared with the NABTT CNS Consortium's internal historical control, where RT was combined with an experimental agent in newly diagnosed GBM, or a HR of 0.7 compared with the European Organisation for Research and Treatment of Cancer (EORTC) trial, where RT + TMZ was administered as in the talampanel trial.¹

The trial was to accrue 72 patients (four patients per month) to yield 49 death events, allowing detection of the target HRs with 85% power using a one-sided significance level of $P = .1$.¹⁴ All patients were included in the intent-to-treat analysis. Survival time was calculated from the date of initial histologic diagnosis to the date of death or censored at the time of analysis if patients were alive. Overall survival was estimated using the Kaplan-Meier method.¹⁵ The proportional hazards regression model was used to estimate unadjusted and adjusted HRs between the talampanel trial and NABTT internal historical controls.¹⁶ Published survival results from the EORTC trial were used to compare survival with the NABTT talampanel trial. For patients who were in the same age group as the EORTC trial (18 to 70 years old), Cochran-Mantel-Haenszel statistics were used to assess the relative risk of death between the NABTT talampanel trial and the EORTC trial at 0, 6, 12, 18, and 24 months of follow-up. All P values reported are two-sided. All analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

A safety interim analysis was planned after 30 patients received treatment. This required early termination if the observed rate of severe toxicity was more than 20% with 95% certainty. All toxicities were graded using the CTCAE (version 3.0).

RESULTS

Accrual and Patient Characteristics

Seventy-two patients with newly diagnosed GBM were enrolled from December 2005 to July 2006 (Figure 2). Their overall demographic and clinical characteristics are listed in Table 1. Their median age was 60 years (range, 37 to 85 years), and 17% of patients were older than age 70. The median KPS was 90 (range, 70 to 100), and 77% of patients had debulking surgery rather than just a biopsy. Data on

Fig 2. CONSORT diagram.

patients ≤ 70 years old are listed separately in Table 1 to facilitate comparison with the EORTC study, which excluded older patients.

Toxicity

The planned interim safety evaluation in October 2006 concluded that accrual should continue. Overall toxicities observed when talampanel was combined with RT + TMZ are listed in Table 2. Hematologic toxicities were ascribed to TMZ. There was one toxic death secondary to febrile neutropenia, which was seen in two patients (2.8%). Grade 3 to 4 leukopenia occurred in 12.5% of patients, and grade 3 to 4 thrombocytopenia occurred in 15.3%. The most common grade 3 to 4 nonhematologic toxicities were fatigue (4.2%) and nausea (4.2%). The expected talampanel toxicity of dizziness was reported as grade 3 in one patient (1.4%). Toxicities seemed to be evenly distributed between those patients who were and were not taking EIASD.

Survival

Survival follow-up was closed on September 15, 2008, with a median follow-up time of 18 months and with 55 deaths (76%). The number of deaths observed during the study period exceeded the design requirement, providing greater than nominal (85%) power for the planned comparisons. The Kaplan-Meier estimate of the median survival time for the 72 patients was 18.3 months (95% CI, 14.6 to 22.5 months). The average time that patients received talampanel was 9 months (range, < 1 to > 39 months). Seven patients remain on talampanel.

The first planned comparison of survival was with NABTT historical controls. This cohort contained 235 patients with newly diagnosed GBM treated on NABTT therapeutic protocols in the pre-TMZ era from 1994 to 2004. These patients were on phase II studies with RT and a novel agent (celecoxib, RSR13, penicillamine, suramin, or carboxyamido-triazole) that has subsequently been shown to be ineffective.¹⁷⁻²¹ The eligibility criteria and the treating institutions were virtually identical to the study reported here. The median age of these patients was 55 years (range, 21 to 82 years), median KPS was 90, and 84% were treated after debulking surgery (Table 1). The median survival time of these patients was 11.4 months (95% CI, 10.2 to 12.4 months). The unadjusted HR for death in patients treated with RT, TMZ, and talampanel compared with the historical control (RT plus a novel agent) was 0.42 (95% CI, 0.31 to 0.56; $P < .0001$ by the log-rank test). This represents a 58% relative reduction in the risk of death for patients who were treated with RT, TMZ, and talampanel compared with the historical controls. The median survival benefit was 6.9 months. The adjusted HR of 0.34 (95% CI, 0.24 to 0.47; $P < .0001$) was obtained by using proportional hazards regression models adjusting for age at initial diagnosis, baseline KPS, and baseline corticosteroid use. This HR indicates a 66% relative reduction in the risk of death after controlling those prognostic factors. The final model was selected using the backward selection procedure at significance level of $P = .05$.

The second planned survival comparison was with the EORTC study in which newly diagnosed GBM patients were treated with an RT + TMZ regimen identical to that used in the study reported here.¹ The comparability of the two patient populations is shown in Table 1. The primary difference between the patients in the EORTC study and the NABTT study is patient age. Whereas the EORTC study excluded patients greater than age 70 years, 17% of NABTT patients were older

Table 1. Patient Demographics and Clinical Characteristics at Baseline

Characteristic	NABTT RT + TMZ + Talampanel; Age ≥ 18 Years (n = 72)		NABTT RT + TMZ + Talampanel; Age ≤ 70 Years (n = 60)		EORTC Phase III RT + TMZ; Age ≤ 70 Years (n = 287)		NABTT Historical RT + Novel Agent; Age ≥ 18 Years (n = 235)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Median	59.5		56		56		55	
Range	37-85		37-70		19-70		21-82	
< 50	15	21	15	25	90	31	69	29
50-70	45	62	45	75	197	69	148	63
> 70	12	17					18	8
Sex								
Male	40	56	34	57	185	64	151	64
Female	32	44	26	43	102	36	84	36
Karnofsky performance status								
100	17	24	16	27	113*	39*	33	18
90	27	37	22	36	136†	47†	93	50
80	18	25	16	27			31	17
70	10	14	6	10	38‡	13‡	21	11
60							7	4
Extent of surgery								
Biopsy	16	22	16	27	48	17	29	16
Debulking	55	76	44	73	239	83	156	84
Other	1	1						
Time from diagnosis to RT, weeks								
Median	4.6		4.6		5		3.9	
Range	2.0-9.0		2.0-8.7		1.7-10.7		1.0- 9.7	
Baseline MMSE score								
30	29	40	24	40	100	35	63	27
27-29	30	42	24	40	96	33	85	36
≤ 26	13	18	12	20	81	28	35	15
Data missing					10	3	52	22
Corticosteroid therapy								
Yes	50	69	42	70	193	67	157	67
No	18	25	15	25	94	33	24	10
Data missing	4	6	3	5			54	23
Histologic diagnosis								
Glioblastoma	72	100	60	100	221	92	181	98
AA					7	3		
Inconclusive					3	1		
Other					8	3	3	2

Abbreviations: NABTT, New Approaches to Brain Tumor Therapy; RT, radiation; TMZ, temozolomide; EORTC, European Organisation for Research and Treatment of Cancer; MMSE, Mini-Mental State Examination; AA, anaplastic astrocytoma.

*WHO performance status grade 0.

†WHO performance status grade 1.

‡WHO performance status grade 2.

than age 70. The differences in overall survival time and overall survival rate at 6, 12, 18, and 24 months are listed in Table 3. The median survival time for patients 18 to 70 years of age was 20.3 months in the NABTT talampanel trial compared with 14.6 months in the EORTC trial, which suggests that the addition of talampanel to RT and TMZ may add a median of 5.7 months of survival. The difference may be slightly less given that NABTT calculates survival from date of surgery, whereas the EORTC uses date of random assignment. As shown in Table 3, there is a steady divergence of survival between this NABTT study (RT + TMZ + talampanel) and the EORTC trial (RT + TMZ) at 6, 12, 18, and 24 months. The proportion of patients alive at 24 months was significantly higher in the NABTT trial than in the EORTC trial (41.7% v 26.5%, respectively; $P = .02$). The estimated risk ratio was 0.66 (95% CI, 0.48 to 0.91; $P < .008$ by Cochran-Mantel-

Haenszel statistic). This yielded a 34% reduction in risk of death for patients ≤ 70 years of age attributable to talampanel. The relevant percent survival plot is presented in Figure 3. Table 3 lists median survival times and overall survival rates at 6, 12, 18, and 24 months for each population.

Since this study was developed, methylation of the O⁶-methylguanine–DNA methyltransferase (MGMT) promoter has been determined to have a significant impact on survival.²² As a result, formalin-fixed tissues from accrued patients were collected from institutions where surgery was performed and analyzed for promoter methylation of MGMT using methylation-specific polymerase chain reaction performed by OncoMethylome Sciences (Durham, NC). Fewer patients on the NABTT talampanel study (29%) had a methylated MGMT promoter than in the EORTC study (43%).

Table 2. Hematologic and Nonhematologic Toxicities

Adverse Event	No. of Patients			All Grades	
	Grade 3	Grade 4	Grade 5	No. of Patients	%
Hematologic					
Febrile neutropenia		1	1	2	2.8
Hemoglobin	2			2	2.8
Leukocytes	7	2		9	12.5
Neutrophils	6	2		8	11
Platelets	5	6		11	15.3
Infection (other)	1			1	1.4
Infection WNA (lung)	1	1		2	2.8
Infection WNA (mucosa)	1			1	1.4
Infection WNA (skin)	1			1	1.4
Infection WNA (urinary)	1			1	1.4
Nonhematologic					
Anorexia	1			1	1.4
Constipation	1			1	1.4
Decubitus	1			1	1.4
Dizziness	1			1	1.4
Fatigue	2	1		3	4.2
Hemorrhoids	1			1	1.4
Hypoxia	1			1	1.4
Nausea	2	1		3	4.2
Pyramidal dysfunction		1		1	1.4
Rash	1			1	1.4
Vomiting	2			2	2.8

Abbreviation: WNA, with normal absolute neutrophil count.

Fig 3. Overall survival probability in patients between 18 and 70 years old: New Approaches to Brain Tumor Therapy study (radiation [RT] + temozolomide [TMZ] + talampanel) v European Organisation for Research and Treatment of Cancer (EORTC) phase III study (RT + TMZ). RT + TMZ data are from Stupp et al.¹

Additionally, treatment with talampanel seemed to lengthen survival in both the methylated and unmethylated patient populations (Table 4).

This study was not designed to monitor therapies administered after patients experienced progression and were taken off study. However, because of concerns that the survival of these patients may have been extended as a result of postprogression therapy with bevacizumab, we retrospectively obtained information on its use in this population. Twenty (28%) of 72 patients accrued to this study received bevacizumab after progression. The time from diagnosis to treatment with bevacizumab ranged from 6 to 30 months, with a median of 11 months. Bevacizumab was initiated at ≥ 12 months in nine patients (45%) and at ≥ 20 months in five patients (25%). Patients who received bevacizumab were a select subset of the study population. None of the 12 patients older than age 70 years was treated with bevacizumab, and overall, recipients were younger, with a me-

dian age of 50 years (range, 39 to 69 years). Bevacizumab treatment also varied by institution; one center treated eight (89%) of nine accrued patients with bevacizumab, whereas four other institutions, which accrued 16 patients, treated no patients with bevacizumab.

DISCUSSION

There is strong scientific rationale to support interventions targeting the glutamatergic system in patients with GBM. Excess glutamate promotes neuronal cell death through receptor hyperactivation and excitotoxic injury and facilitates the proliferation and migration of glioma cells.^{4,5,23,24} In vitro and animal studies report that AMPA receptor inhibition can arrest glioma growth and invasion.^{3,25,26} Clinical trials targeting the glutamatergic system in glioblastoma are proposed or underway with sulfasalazine, riluzole, and a variety of other novel compounds.²⁷⁻³¹ Potential ways to interfere with these pathways include inhibiting glutamate release, upregulating EAAT1 glutamate transporters, and using glutamate receptor antagonists.^{32,33}

Our study demonstrates that talampanel can be safely combined with RT and TMZ in patients with newly diagnosed GBM. It also

Table 3. Survival Comparisons

Study Cohort	No. of Patients	Survival (months)		Overall Survival at 6 Months		Overall Survival at 12 Months		Overall Survival at 18 Months		Overall Survival at 24 Months	
		Median	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
NABTT historical data	235	11.4	10.2 to 12.4	75.7	69.7 to 81.1	46.4	39.9 to 53.0	20.0	15.1 to 25.7	7.7	4.6 to 11.8
Phase III EORTC, 2005*	287	14.6	13.2 to 16.8	86.3	82.3 to 90.3	61.1	55.4 to 66.7	39.4	33.8 to 45.1	26.5	21.2 to 31.7
Phase II NABTT, 2008	72	18.3	14.6 to 22.5	88.9	79.3 to 95.1	69.4	57.5 to 79.8	50.0	38.0 to 62.0	36.1	25.1 to 48.3
Phase II NABTT, 2008*	60	20.3	16.3 to 27.2	93.3	83.8 to 98.2	78.3	65.8 to 87.9	56.7	43.2 to 69.4	41.7	29.1 to 55.1

Abbreviations: NABTT, New Approaches to Brain Tumor Therapy; EORTC, European Organisation for Research and Treatment of Cancer.

*Limited to age ≤ 70 years.

Table 4. MGMT Methylation Status and Survival Outcome

MGMT Promoter	EORTC Phase III (n = 106; 37% of total population; age ≤ 70 years)	Talampanel (n = 24; 40% of total population; age ≤ 70 years)	Talampanel (n = 29; 40% of total population; all ages)
Methylated			
No. of patients	46	7	9
% of total patients	43	29	31
Median survival time, months	21.7	29.1	29
2-year overall survival rate, %	46	85.7	66.7
Unmethylated			
No. of patients	60	17	20
% of total patients	57	71	69
Median survival time, months	12.7	16.3	16.9
2-year overall survival rate, %	13.8	29.4	30

Abbreviations: MGMT, O⁶-methylguanine–DNA methyltransferase; EORTC, European Organisation for Research and Treatment of Cancer.

suggests that the survival of patients receiving RT, TMZ, and talampanel may be superior to that seen with RT and TMZ alone. The significant survival advantage seen in the talampanel study at 2 years cannot be attributed to the minor differences in the starting dates of the two studies. Similarly, MGMT methylation data were analyzed from a similar percentage of the talampanel (40%) and EORTC (37%) accruals.²² As shown in Table 4, fewer patients on the talampanel study were methylated than on the EORTC study (29% v 43%, respectively, for patients ≤ 70 years old); despite this, the overall survival of comparable patients receiving talampanel was superior (2-year survival of 41.7% v 26.5%, respectively). Additionally, the percentage of patients surviving at 2 years is higher on the talampanel trial than on the EORTC trial in patients who were methylated (86% v 46%, respectively) and unmethylated (29% v 14%, respectively) at MGMT.

Other potentially confounding factors must also be considered. The EORTC study accrued from 85 international sites, whereas our accrual came from nine brain tumor centers where aggressive therapy at recurrence could prolong survival. Because a select subpopulation comprised of 28% of the patients on the talampanel study received bevacizumab at tumor progression, the contribution of this drug to survival is difficult to quantify. However, it is unlikely that this agent is the primary factor contributing to the significant increase in overall survival observed on this study. A randomized, placebo-controlled trial is needed to rigorously assess the value of this promising and safe new therapeutic approach.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Stuart A. Grossman, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Howard A. Fine

Financial support: Stuart A. Grossman

Administrative support: Stuart A. Grossman, Serena Desideri, Joy Fisher

Provision of study materials or patients: Stuart A. Grossman, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Serena Desideri, Joy Fisher, Howard A. Fine

Collection and assembly of data: Stuart A. Grossman, Xiaobu Ye, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Serena Desideri, Steven Piantadosi, Joy Fisher, Howard A. Fine

Data analysis and interpretation: Stuart A. Grossman, Xiaobu Ye, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Serena Desideri, Steven Piantadosi, Joy Fisher, Howard A. Fine

Manuscript writing: Stuart A. Grossman, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Howard A. Fine

Final approval of manuscript: Stuart A. Grossman, Xiaobu Ye, Marc Chamberlain, Tom Mikkelsen, Tracy Batchelor, Serena Desideri, Steven Piantadosi, Joy Fisher, Howard A. Fine

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