

Survival of Patients with Newly Diagnosed Glioblastoma Treated with Radiation and Temozolomide in Research Studies in the United States

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Abstract

Purpose: Novel agents are currently combined with radiation and temozolomide (RT + TMZ) in newly diagnosed glioblastoma using overall survival as the primary end point. Results of these phase II studies are typically compared with the phase III European Organization for Research and Treatment of Cancer (EORTC) survival data that resulted in RT + TMZ becoming standard therapy.

Experimental Design: The New Approaches to Brain Tumor Therapy (NABTT) Consortium assigned 365 patients with glioblastoma to four single-cohort studies with similar eligibility criteria. Patients received RT + TMZ with talampanel ($n = 72$), poly-ICLC ($n = 97$), or cilengitide ($n = 112$) or RT + TMZ alone with monitoring of CD4 counts ($n = 84$). Overall survival of those ages 18 to 70 years with glioblastoma was compared with published EORTC data.

Results: NABTT and EORTC patients had comparable performance status and debulking surgery. Median, 12-month, and 24-month survival rates for the EORTC patients ($n = 287$) and the comparable NABTT patients receiving RT + TMZ and novel agents ($n = 244$) are 14.6 versus 19.6 months, 61% versus 81%, and 27% versus 37%, respectively. This represents a 37% reduction in odds of death ($P < 0.0001$) through 2 years of follow-up. NABTT and EORTC patients receiving only RT + TMZ had similar survival.

Conclusions: Newly diagnosed glioblastoma treated recently with RT + TMZ and talampanel, poly-ICLC, or cilengitide had significantly longer survival than similar patients treated with only RT + TMZ accrued internationally from 2000 to 2002. These differences could result from the novel agents or changing patterns of care. Until the reasons for these different survival rates are clarified, comparisons of outcomes from phase II studies with published RT + TMZ survival data should be interpreted with caution.

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Background

Glioblastoma multiforme remains a devastating illness that affects more than 17,000 patients in the United States each year. This tumor diffusely infiltrates the brain early in its course, making complete resections impossible. Post-operative radiation therapy prolongs survival but yields a median survival of less than 1 year, and long-term survival is extremely rare (1). Although the most promising early

results with adjuvant chemotherapy contained nitrosoureas, no single trial provided significant survival prolongation, and meta-analyses revealed a marginal benefit (2). In 2005, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada published a randomized prospective trial comparing radiation therapy with radiation and concurrent temozolomide followed by 6 months of adjuvant temozolomide (RT + TMZ) in patients with glioblastoma who were of ages 18 to 70 years (3). The RT + TMZ arm of the trial was superior, generating an improvement in median survival from 12.1 to 14.6 months and increasing the percent of patients alive at 2 years from 10% to 26%. Because this was the first study to show a chemotherapy-related survival benefit in glioblastoma, this regimen was rapidly adopted worldwide as standard therapy for patients with newly diagnosed glioblastoma. Recently updated survival data from this study reveal that 10% of patients receiving combined treatment are alive at 5 years versus 2% with radiation alone ($P < 0.0001$; ref. 4).

Two other agents are approved by the U.S. Food and Drug Administration for the treatment of glioblastoma.

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Translational Relevance

For decades, adjuvant chemotherapy provided no significant survival improvement in newly diagnosed glioblastoma. However, in 2005 the European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) documented improved survival from radiation and temozolomide (RT + TMZ) versus radiation alone. These survival results are now the standard by which single-arm phase II trials of novel agents combined with RT + TMZ are judged. We now report survival from three phase II studies of the New Approaches to Brain Tumor Therapy CNS Consortium where RT + TMZ and a novel agent were given to newly diagnosed glioblastoma. Surprisingly, the survival of patients on each study was significantly better than reported by EORTC/NCIC. Given the paucity of active agents in glioblastoma, finding three consecutive "positive" studies suggests that adding novel agents to RT + TMZ improves the efficacy of multiple novel agents or the EORTC/NCIC study is an appropriate comparison group. These issues are central to the conduct and evaluation of all phase II trials of novel agents in glioblastoma.

In September 1996, implantable 1,3-bis(2-chloroethyl)-1-nitrosourea-containing wafers (Gliadel) were approved for selected patients with localized malignant gliomas at initial surgery based on a randomized placebo controlled trial (5). Radiation and 1,3-bis(2-chloroethyl)-1-nitrosourea wafers extended the median survival of patients with glioblastoma from 11.4 to 13.1 months ($P = 0.08$). In May 2009, the Food and Drug Administration approved the use of bevacizumab for patients with recurrent glioblastoma. This approval was based on two phase II trials showing that approximately 25% of patients had clinical and radiologic improvement that lasted for about 4 months (6, 7). During the past two decades, the number of clinical trials conducted in patients with high-grade gliomas has grown with identification of important signal transduction pathways, relevant targets, and the availability of new agents directed to these pathways and targets. In addition, the continued absence of curative therapies and the maturation of multi-institutional clinical research consortia have rendered glioblastoma an attractive candidate for novel drug development.

In 2005, following the publication of the EORTC RT + TMZ survival data in newly diagnosed glioblastoma, it became apparent that novel therapies given to this patient population would need to be combined with RT + TMZ. As a result, the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium developed three trials with novel agents that could be safely combined with this new standard of care. The end point of these studies was overall survival, as treatment with RT + TMZ can increase blood-brain barrier dysfunction leading to increased con-

trast enhancement, mass effect, and peritumoral edema that may last for many months (8–11). Other radiologic techniques have been unable to reliably distinguish between tumor growth and treatment-related pseudoprogression in this clinical setting. As this presents a currently insurmountable challenge to the accurate determination of tumor response and progression in newly diagnosed glioblastoma, these NABTT trials contained preplanned comparisons of overall survival with published EORTC results. Surprisingly, the overall survival in each of the NABTT studies was prolonged as judged by this comparison. Although the improvements in survival are real and striking, these sequentially positive results are in sharp contrast to decades of disappointing clinical trial outcomes in this patient population. These survival advantages could be attributable to the novel therapies or could reflect changing patterns of care in this patient population. This report reviews these findings and considers if the published EORTC survival data should be routinely used as a comparison group to estimate the efficacy of phase II studies in patients with newly diagnosed glioblastoma.

Materials and Methods

The NABTT CNS Consortium was funded by the National Cancer Institute from 1994 to 2009 to conduct early-phase clinical trials of novel approaches to the treatment of primary brain tumors (12). Before 2005, eligible patients with newly diagnosed glioblastoma were accrued to individual trials using radiation therapy combined with novel agents. Overall survival was the primary end point and the results were compared with the NABTT historical database. After the publication of results documenting improved survival with RT + TMZ in this patient population, the NABTT CNS Consortium initiated studies of novel agents in combination with RT + TMZ in single-cohort phase II studies. A comparison of overall survival to EORTC results was formally planned.

Three studies were approved by the Cancer Therapy Evaluation Program of the National Cancer Institute and the Institutional Review Board of each participating institution. Participating institutions included University of Alabama at Birmingham, The Cleveland Clinic, Emory University, Henry Ford Hospital, Johns Hopkins University, Massachusetts General Hospital, H. Lee Moffitt Cancer Center, University of Pennsylvania, and Wake Forest University. The compounds studied were talampanel (Teva Pharmaceutical Industries), poly-ICLC (Oncovir), and cilengitide (Merck KGaA). Talampanel was provided by Teva Pharmaceutical Industries, poly-ICLC by Oncovir, and cilengitide by the National Cancer Institute. Teva Pharmaceutical Industries also provided additional funding for the trial.

The three trials were designed to enroll similar patients to enable outcome data to eventually be combined in a "post-temozolomide" survival database for the NABTT CNS Consortium. As a result, the eligibility criteria for all trials included age ≥ 18 y, newly diagnosed supratentorial

glioblastoma, no prior treatment with radiation or chemotherapy, stable glucocorticoid requirements, Karnofsky performance status rating of ≥ 60 , normal organ function (as measured by hematologic and chemistry profiles), and the ability to provide informed consent. The design of the studies was also similar. As shown in Fig. 1, the basic framework as described by the EORTC for newly diagnosed glioblastoma was used. This included 30 fractions (200 cGy/fraction) of focal radiation therapy administered 5 d per week for 6 wk to a total dose of 60 Gy. Temozolomide was administered daily beginning on the first day of radiation and ending on the last day of radiation at a dose of 75 mg/m² per day. Blood counts were checked weekly and temozolomide was held if the platelet count decreased below 100,000 or if significant leucopenia developed. Bactrim was administered prophylactically to prevent pneumocystis (jiroveci) pneumonia. After completion of the radiation therapy, the patients were given 4 wk to recover and then began receiving temozolomide at doses of 150 to 200 mg/m² for 5 consecutive days each month for a total

of 6 mo. Patients were followed with magnetic resonance or computed tomographic imaging 1 mo after completion of radiation and every 2 mo thereafter. In the talampanel and cilengitide studies, the new agents were administered beginning with the initiation of radiation therapy (13). Talampanel was administered orally every 8 h and cilengitide was given i.v. twice weekly. These agents were continued during the entire period of, the 4-wk treatment break, the 6 mo of adjuvant temozolomide, and thereafter until there was evidence of progression or toxicity. The poly-ICLC study differed in several respects. Although patients were accrued to this study before beginning RT + TMZ, the experimental agent was not initiated until after the radiation and concurrent chemotherapy and the 4 wk of recovery had been completed. At that time, adjuvant temozolomide (150-200 mg/m² daily for 5 d) was begun but the timing and duration of the temozolomide were adjusted to prevent overlapping with the poly-ICLC. Thus, it was given for 5 d every 9 wk rather than the usual every 4 wk. In an effort to adjust for the reduced temozolomide schedule, this agent was continued

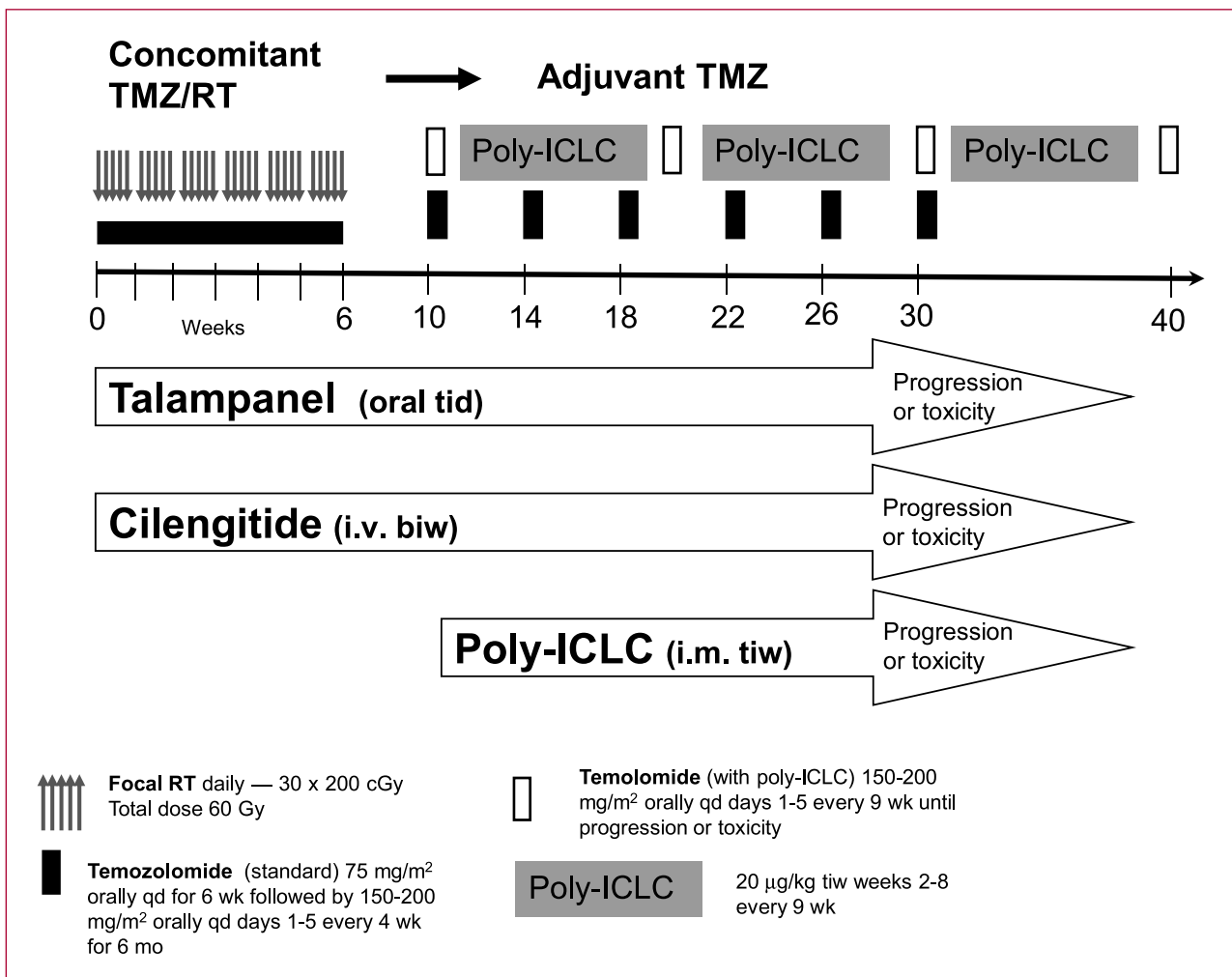


Fig. 1. Treatment strategy: EORTC and three NABTT trials.

Table 1. Patient demographics and clinical characteristics for all patients ≤ 70 y of age at baseline

Characteristics	NABTT historical: RT + non-TMZ drug (n = 217)	EORTC phase III: RT + TMZ (n = 287)	NABTT RT + TMZ: CD4 (n = 49)	NABTT RT + TMZ + new agent (n = 244)
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Age				
Median (range), y	54 (21-70)	56 (19-70)	58 (29-69)	55 (21-70)
50-70 y	148 (68)	197 (69)	38 (78)	162 (66)
Sex				
Male	140 (65)	185 (64)	28 (57)	144 (59)
KPS*				
90-100	129 (70)	249 (86)	39 (80)	180 (77)
60-80	50 (30)	38 (13)	10 (20)	64 (26)
Extent of surgery				
Biopsy	26 (12)	48 (17)	9 (18)	55 (23)
Debulking	143 (66)	239 (83)	40 (82)	186 (76)
Other or missing*	48* (22)			3 (1)
Weeks from diagnosis to treatment				
Median (range)	3.9 (1.0-9.7)	5 (1.7-10.7)	3.1 (2-7.7)	4.1 (1.9-12.7)
MMSE score				
27-30	138 (64)	196 (68)		117 (84)
≤ 26	29 (13)	81 (28)		39 (16)
Missing	50 (23)	10 (3)		
Corticosteroids				
Yes	147 (68)	193 (67)	42 (86)	179 (73)
Histologic diagnosis				
Glioblastoma	165 (98)	221 (92)	49 (100)	239 (98)

Abbreviations: KPS, Karnofsky performance status; MMSE, minimal status examination.

on an every-9-wk schedule until there was evidence of progression or toxicity. The i.m. administration of poly-ICLC (20 $\mu\text{g}/\text{kg}$) was begun 4 wk after completion of the radiation and administered three times each week from week 2 to week 8 of each 9-wk adjuvant treatment cycle. This was also continued until progression or toxicity was observed. These schedules are presented in Fig. 1.

All three trials were designed to detect 25% or larger reduction in the hazard of death per person-year of follow-up (the hazard rate) compared with the EORTC survival data. The numbers of subjects specified in each trial were 72 (talampanel), 94 (cilengitide), and 96 (poly-ICLC) with the required number of death events of 49, 63, and 64, respectively, to achieve 85% or greater power at a significant level of 0.1 using a one-sided test (13). The NABTT trial designs are conservative in that additional follow-up yields a larger than designed number of events, increasing the precision in the estimate of the hazard rate and increasing the efficiency of comparisons. The survival time was counted from the initial diagnosis of the disease to the time of death. The EORTC trial excluded patients who were over the age of 70 y, and thus all NABTT patients ages 70 y or younger were included in this comparison. The overall survival for the 244 NABTT patients ages 70 y and younger was compared

with that of the 287 patients on the EORTC study and to that of the 217 patients with comparable ages in the NABTT pre-temozolomide historical database. The effect of prognostic variables in each NABTT trial was assessed using proportional hazards regression (14). Cochran-Mantel-Haenszel statistics were used to assess the relative risk of death between the NABTT temozolomide-containing trials and the EORTC trial at 6, 12, 18, and 24 mo of follow-up. All *P* values are reported as two-sided. All analyses were done using the SAS software (version 9.1, SAS Institute).

In addition, a fourth NABTT study accrued 99 patients with newly diagnosed high-grade gliomas who were to receive standard RT + TMZ. This protocol was designed to follow monthly CD4 counts for 12 mo from the start of their RT + TMZ. Patients were accrued from the participating NABTT institutions during the same time as the talampanel, poly-ICLC, and cilengitide trials. Patients on those trials were permitted to enroll on the CD4 study as well.

Results

This analysis was done using a total of 797 patients with newly diagnosed glioblastoma who were 70 years of age or younger. The NABTT pre-temozolomide historical database

Table 2. Survival comparison

	No. of patients	Median survival (95% CI), mo	Overall survival at 6 mo, % (95% CI)	Overall survival at 12 mo, % (95% CI)	Overall survival at 18 mo, % (95% CI)	Overall survival at 24 mo, % (95% CI)
NABTT historical RT + non-TMZ drug	217	12 (10.3-12.7)	78 (72-83)	49 (42-56)	22 (16-28)	8 (5-13)
EORTC RT + TMZ	287	14.6 (13.2-16.8)	86 (82-90)*	61 (55-67) [†]	39 (34-45) [‡]	27 (21-32) [§]
NABTT RT + TMZ	49	16.2 (12.9-18.9)	88 (75-95)	65 (50-78)	41 (27-56)	20 (10-34)
NABTT RT + TMZ + new agent	244	19.6 (17.8-21.2)	94 (91-97)*	81 (75-86) [†]	55 (48-61) [‡]	37 (29-46) ^{§,}

* $P = 0.003$.[†] $P = 0.0001$ [‡] $P = 0.0003$.[§] $P = 0.02$.^{||}As only two trials of the three NABTT trials have mature 24-mo survival data, so this point contains 143 patients.

contained 217 patients who received radiation plus a novel agent, which has subsequently been found to be ineffective. The EORTC study contained 287 patients treated with RT + TMZ. The three therapeutic NABTT trials contained a total of 244 patients treated with RT + TMZ combined with talampanel, cilengitide, or poly-ICLC. In addition, there were 49 patients on the nontherapeutic NABTT study who had a diagnosis of glioblastoma and who received only RT + TMZ. At the time of analysis, the NABTT historical database contained 213 death events. The number of events in the talampanel, cilengitide, poly-ICLC, and CD4 trials was 47, 62, 62, and 44, respectively.

There are no differences in important prognostic variables in the four patient cohorts (Table 1). The recent NABTT trials had proportionately fewer patients undergoing a debulking surgical procedure and more patients with lower performance status than did the EORTC trial. The NABTT pretemozolomide historical cohort had a median survival of 12 months with a 2-year survival of 8% (Table 2; Fig. 2). The EORTC trial reported a median survival of 14.6 months and a 26.5% 2-year survival (Table 2; Fig. 2). Combined survival data from the three recent therapeutic NABTT studies show a statistically significant improved median survival compared with the EORTC trial from 14.6 months [95% confidence interval (95% CI), 13.2-16.8] to 19.6 months (95% CI, 17.8-21.2). In addition, these NABTT studies generated higher overall survival at 6, 12, 18, and 24 months compared with the EORTC trial ($P = 0.003$, $P = 0.0001$, $P = 0.0003$, and $P = 0.02$, respectively). Of note, the 24-month comparison includes data from only two of the NABTT trials; the remaining trial contains mature data to 18 months (Fig. 2, dotted line). The estimated common risk ratio was 0.63 (95% CI, 0.51-0.78; $P < 0.0001$ by Cochran-Mantel Haenszel statistics), which yields an overall 37% reduction in the risk of death for patients on recent trials compared with those in the TMZ + RT alone trial.

Forty-nine of the 99 patients on the CD4 count trial were between 18 and 70 years of age, had a histologic

diagnosis of glioblastoma, and did not receive any experimental agents with their standard RT + TMZ. These patients were accrued and treated at NABTT institutions. To the date, 44 of the 49 patients died. There was no statistical significant difference in the baseline patient characteristics and between the patients on the therapeutic NABTT trials who were treated with RT + TMZ and an experimental agent and those who received only RT + TMZ with serial CD4 measurements, with the exception of a shorter time between diagnosis and initiation of treatment in the CD4 patients (median of 3.1 versus 4.1 weeks; $P = 0.0001$; Table 1). The unadjusted hazard ratio of death between the patients on the NABTT therapeutic trials and those on the nontherapeutic CD4 study was 0.64 (95% CI, 0.45-0.89; $P = 0.008$), with a median time of survival of 19.6 months (95% CI, 17.8-21.2) and 16.2 months (95% CI, 12.9-18.9), respectively. There is a 34.4% reduction in hazard of death (hazard ratio, 0.656; 95% CI, 0.46-0.94;

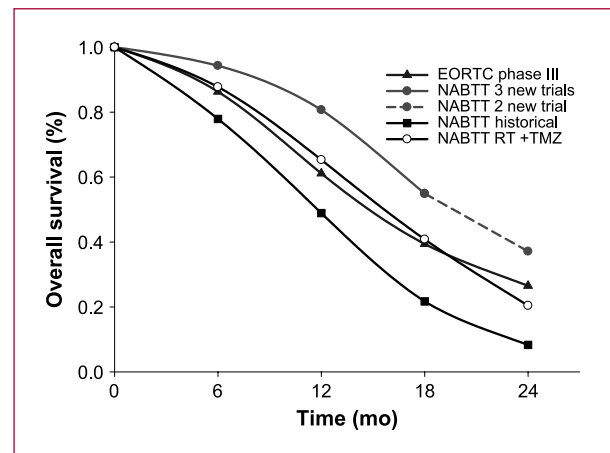


Fig. 2. Survival curves: patients ≤ 70 y of age, old NABTT, new NABTT, and EORTC.

$P = 0.02$) after adjusting for age at diagnosis, Karnofsky performance status, extent of surgery, and the time elapsed from diagnosis to the initiation of treatment.

Conclusions

The overall survival of the 244 patients with newly diagnosed glioblastoma accrued to three consecutive therapeutic trials conducted by the NABTT CNS Consortium is significantly higher than is reported with RT + TMZ alone (3). The improvement in survival was evident as early as 6 months after study initiation (94% versus 86% survival; $P < 0.003$) and continued over 2 years (37% versus 27%; $P < 0.02$). In each of these trials, a novel agent was combined with standard RT + TMZ. The experimental agents had diverse mechanisms of action and included a glutamate receptor blocker, an immunostimulatory compound, and an integrin inhibitor. Each NABTT study was designed as a single-arm phase II study and used overall survival as the primary efficacy outcome measure. The planned comparison was with published EORTC survival data where patients received only RT + TMZ.

During the past three decades, thousands of patients have been accrued to clinical trials examining the efficacy of systemically administered adjuvant chemotherapy against glioblastoma (15, 16). Only one of these trials, the EORTC study using RT + TMZ, provided a convincing survival advantage (3, 4). As a result, the improvement in survival noted in the first three NABTT glioblastoma trials where standard RT + TMZ was combined with novel agents was unanticipated and must be thoughtfully considered. One possible explanation is that baseline prognostic factors were more favorable for patients on the NABTT studies than for patients in the EORTC study. However, the baseline characteristics of patients ages 70 years or younger in all cohorts were remarkably similar. In addition, the percent of patients with MGMT promoter methylation was substantially lower in the NABTT talampanel trial than in the EORTC study (27% versus 43%), suggesting that this was in fact a higher-risk population (13).

Another potential explanation for these results is that RT + TMZ provides a treatment platform that permits improved survival with a variety of novel agents that may not be efficacious as single agents. Other studies that have combined new agents with RT + TMZ in this disease have reported varied results. For example, single-institution studies combining RT + TMZ with erlotinib reported improved survival, whereas the addition of *cis*-retinoic acid or thalidomide yielded results more consistent with the EORTC findings (17, 18).

It is also possible that survival following treatment with standard RT + TMZ has improved since 2000 when the original study was initiated. The EORTC study was conducted in 85 hospitals in Europe and Canada when experience with temozolomide was limited. Since then, clinicians have recognized that early clinical and radiologic deterioration is often treatment related ("pseudo-progression") rather than secondary to true tumor progression.

As a result, temozolomide therapy is often continued in this setting rather than aborted early. Clinicians have also become more adept and aggressive at recognizing treatment complications and treating tumor recurrences. Although bevacizumab is associated with radiologic and clinical improvements, it has not yet been shown to prolong survival (6, 7, 16, 19). In the NABTT talampanel study, bevacizumab did not seem to contribute to 42% of patients being alive at 2 years (13). The results of the NABTT CD4 trial suggest that therapy with RT + TMZ alone administered at the same institutions, during the same time calendar years, and with similar treatments available for recurrent disease generates survival results that are very similar to the EORTC data and are inferior to survival when RT + TMZ are combined with talampanel, cilengitide, or poly-ICLC.

Although the findings described above are provocative, the available data do not permit us to determine if the improvement in survival in the NABTT studies is secondary to the new agents or to an overall change in the care of patients with newly diagnosed glioblastoma. The control arms of several currently accruing large randomized trials exploring dose-intense temozolomide and the early addition of bevacizumab will provide important information to address this issue. A randomized comparison group might have helped to clarify some of the ambiguity in the present circumstance, and suggestions have been made that these should be included in every safety and activity (phase II) trial. Aside from the lack of precision in such underpowered comparisons, this would generate other significant inefficiencies. In the past 30 years, there has been only one systemic adjuvant chemotherapy trial that had positive results in patients with glioblastoma. There are now more novel agents with different mechanisms of action to test than ever before. Adding an internal control arm would significantly increase the size of all safety and activity trials and would result in fewer agents being tested. In addition, it would likely make these trials much less acceptable to patients who are not anxious to be randomized to a placebo control. Alternative end points that might speed decision making have also been proposed. However, accurately determining response and progression in newly diagnosed glioblastomas is exceedingly difficult because standard therapy is known to perturb the integrity of the blood-brain barrier and, thus, the results of neuroimaging studies.

This report documents significant improvements in the survival of patients with newly diagnosed glioblastoma. As evident from Table 2, the 2-year survival of patients placed on NABTT CNS Consortium trials was 8% before 2005 and now approaches 40% in 244 patients treated at the same participating institutions. However, it remains uncertain if these results are attributable to the novel therapies themselves or reflect evolving patterns of care in this patient population. Until this important issue is clarified, caution should be used in comparing the EORTC survival data to results of phase II studies in newly diagnosed glioblastoma. In the meantime, the priority for clinical investigations in this devastating disease must be to efficiently

screen as many novel agents with diverse mechanisms of action as possible for early evidence of activity in an effort to build on the recent progress that has been made in the treatment of this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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