Phase I/II Trial of Erlotinib and Temozolomide With Radiation Therapy in the Treatment of Newly Diagnosed Glioblastoma Multiforme: North Central Cancer Treatment Group Study N0177

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

Epidermal growth factor receptor (*EGFR*) amplification in glioblastoma multiforme (GBM) is a common occurrence and is associated with treatment resistance. Erlotinib, a selective *EGFR* inhibitor, was combined with temozolomide (TMZ) and radiotherapy (RT) in a phase I/II trial.

Patients and Methods

Adults not taking enzyme-inducing anticonvulsants after resection or biopsy of GBM were treated with erlotinib (150 mg daily) until progression. Erlotinib was delivered alone for 1 week, then concurrently with TMZ (75 mg/m² daily) and RT (60 Gy), and finally, concurrently with up to six cycles of adjuvant TMZ (200 mg/m² daily for 5 days every 28 days). The primary end point was survival at 1 year.

Results

Ninety-seven eligible patients were accrued with a median follow-up time of 22.2 months. By definition, the primary end point was successfully met with a median survival time of 15.3 months. However, there was no sign of benefit in overall survival when comparing N0177 with the RT/TMZ arm of the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada trial 26981/22981 (recursive partitioning analysis [RPA] class III, 19 v 21 months; RPA class IV, 16 v 16 months; RPA class V, 8 v 10 months, respectively). Presence of diarrhea, rash, and *EGFRvIII*, *p53*, phosphatase and tensin homolog (*PTEN*), combination *EGFR* and *PTEN*, and *EGFR* amplification status were not predictive ($P > .05$) of survival.

Conclusion

Although the primary end point was successfully met using nitrosourea-based (pre-TMZ) chemotherapy era historic controls, there was no sign of benefit compared with TMZ era controls. Analyses of molecular subsets did not reveal cohorts of patients sensitive to erlotinib. TMZ chemotherapy combined with RT resulted in improved outcomes compared with historical controls who received nitrosourea-based chemotherapies.

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INTRODUCTION

Glioblastoma multiforme (GBM) accounts for 25% of all primary CNS tumors in adults and is associated with a uniformly dismal prognosis.¹ Unfortunately, these tumors are characterized by resistance to all therapies and frequently recur rapidly within months of aggressive treatment. Because of these poor results there is a growing interest in targeted therapies for GBM in an effort to improve outcomes.

Epidermal growth factor receptor (*EGFR*) amplification is one of the most common oncogene

alterations in GBM, with up to 40% of tumors having increased *EGFR* gene copy numbers (amplification).² Amplification of the *EGFR* gene in GBM has been shown to be the precursor step to subsequent gene rearrangements that further augments receptor signaling,³ resulting in an increase in tumor aggressiveness that is manifested by increased proliferation, motility, and survival of tumor cells.⁴⁻⁶ Preclinical and clinical studies have also suggested that *EGFR* activation may contribute to radiation resistance⁷⁻¹⁰ and that *EGFR*-mediated radiation resistance can be abrogated by inhibiting *EGFR*.¹¹⁻¹³

Erlotinib is an orally active, potent, and selective inhibitor of the EGFR tyrosine kinase that has shown clinical activity alone and in combination with temozolomide (TMZ) in the treatment of GBM.¹⁴ Therefore, N0177 was designed to determine the feasibility and efficacy of combining standard radiotherapy (RT) and TMZ with erlotinib in the treatment of newly diagnosed GBM.

PATIENTS AND METHODS

Eligibility Criteria

All patients provided institutional review board–approved, written informed consent before study enrollment. Adult patients (age ≥ 18 years) with newly diagnosed GBM were eligible. Patients were enrolled at least 1 week after but not more than 4 weeks after maximal surgical resection (biopsy, subtotal resection, or gross total resection). Tumor tissue from all patients underwent central review by a North Central Cancer Treatment Group (NCCTG) study neuropathologist before study registration. Patients taking enzyme-inducing anticonvulsants (EIAcs; eg, phenytoin) were excluded because of the ability of these medications to modulate hepatic p450 enzymes.¹⁵ The remainder of the inclusion and exclusion criteria has been described previously.¹⁶

Schema

Erlotinib was administered as a single daily oral dose of 150 mg based on a phase I trial of dose escalation of erlotinib alone with RT in patients with GBM not taking EIAcs.¹⁶ After a 1-week run-in phase with erlotinib alone, all patients received 6 weeks of three-dimensional conformal RT (60 Gy)¹⁶ and daily TMZ (75 mg/m²/d) concurrently with once-daily erlotinib (Fig 1). Daily erlotinib was continued throughout protocol treatment until progression, but the TMZ was held for 4 weeks after the RT was completed. Maintenance TMZ was then administered daily (200 mg/m²/d) for 5 days (days 1 to 5) and repeated every 28 days for six cycles. *Pneumocystis carinii* prophylaxis and antiemetics were strongly encouraged.

Patient Evaluations

Within 14 days of initial therapy, each patient had a baseline evaluation consisting of history and physical examination, neurologic examination (including the Folstein and Folstein Mini-Mental State Examination), CBC, serum chemistries, and magnetic resonance imaging. All baseline evaluations were repeated every 2 months for the first year, every 3 months for the next year, and every 6 months thereafter. CBC and serum chemistries were performed weekly during RT.

Tissue Analyses

*O*⁶-methylguanine–DNA methyltransferase promoter methylation assay. DNA was extracted from formalin-fixed, paraffin-embedded tissue sections using the EpiCentre Masterpure Complete DNA and RNA Purification kit (Epicenter Biotechnologies, Madison, WI). Isolated tumor DNA was bisulfite-treated using the EZ DNA methylation kit (Zymo Research, Orange, CA). The *O*⁶-methylguanine–DNA methyltransferase (*MGMT*) promoter methylation status was assayed by using a slightly modified nested polymerase chain reaction, as described previously.^{17,18}

Molecular analyses. *EGFR* amplification was assessed by fluorescence in situ hybridization with probes specific for *EGFR* and for chromosome 7, as described previously.¹⁹ *EGFRvIII* mutation, *p53* expression, and phosphatase and tensin homolog (*PTEN*) expression were evaluated by immunohistochemistry, as described previously.^{20–22}

Assessment of Response and Toxicity

Response was evaluated by magnetic resonance imaging, and the details have been previously outlined.¹⁶ National Cancer Institute Common Toxicity Criteria (version 2.0) were used throughout.

Statistical Considerations

The phase I part of the trial had a standard cohort-of-three design, and the primary end point for that part was maximum-tolerated dose or tolerance of clinically effective doses, as previously outlined. The phase II part of the trial had a one-stage phase II design with one interim analysis, and the primary end point for this part of the trial was survival rate at 52 weeks after treatment initiation. The baseline expected 1-year survival rate (the historical rate) of 50% was derived from an analysis of survival data from patients enrolled onto five previous NCCTG trials for newly diagnosed high-grade gliomas. The largest success proportion where the treatment regimen would be considered ineffective in this population was P_h , and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this population was set to be $P_h + 0.15$. The study was designed to detect an increase in survival at 52 weeks after date of treatment from 0.50 to 0.65 with a power of 90% and a statistical significance of $P = .10$. The total sample size required to achieve this was 84 patients, but it was planned to accrue an additional eight patients to accommodate potential losses as a result of ineligibility, cancellations, or major protocol violations. The decision rules to be used for the interim and final analyses were based on a modified Fleming design.²³

Overall survival (OS) was calculated from time of study registration until death. Progression-free survival (PFS) was measured from time of study registration until documented progression. Patients who died without documentation of disease status were considered to have disease progression at the time of their death. OS and PFS were summarized with Kaplan-Meier estimators.²⁴ Patients who were alive (progression free) at the time of our analysis were censored for PFS. Comparisons between OS and PFS were performed with a log-rank test.²⁵ All tests were two-sided, and a $P \leq .05$ was considered to be statistically significant.

RESULTS

Phase I

Between September 2004 and May 2005, seven patients who were not on EIAcs at study entry were enrolled onto the phase I trial and treated at the erlotinib dose of 150 mg/d with TMZ and RT. Dose-limiting toxicity (grade 4 neutropenia and thrombocytopenia) occurred in only one patient, and therefore, the phase II part of the study was opened. All further discussion will include the phase II patients only.

Fig 1. Schema of treatment regimen for phase I and phase II trials; TMZ, temozolomide; RT, radiotherapy.

Table 1. Baseline Patient Characteristics of Entire Cohort and Patients ≤ 70 Years Old

Characteristic	Entire Cohort (n = 97)		Patients ≤ 70 Years Old (n = 89)	
	No.	%	No.	%
Age, years				
Median	57		55	
Range	31-84		31-70	
Mean	56.1		54.3	
SD	10.6		8.9	
Female	42	43	39	44
Extent of primary resection				
Biopsy	25	26	23	26
Subtotal resection	38	39	36	40
Gross total resection	34	35	30	34
Medication at study entry				
Corticosteroid				
Yes	59	61	54	61
No	38	39	35	39
Anticonvulsant use				
Yes	75	77	68	76
No	22	23	21	24
ECOG performance score				
0	35	36	34	38
1	48	50	43	48
2	14	14	12	14
Baseline MMSE score				
7-30	76	78	68	76
≤ 26	23	22	21	24

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; MMSE, Mini-Mental State Examination.

Table 2. Biomarker Patient Characteristics of the Patients With Tissue Available for Analyses

Variable	No. of Patients (n = 81)	%
<i>EGFRvIII</i>		
Absent	51	63
Present	30	37
<i>PTEN</i>		
Deficient	25	31
Deficient small sample	1	1
Focally deficient	9	11
Intact	46	57
<i>p53</i>		
0 (< 1%)	0	0
1 (1%-10%)	12	15
2 (10%-50%)	46	59
3 (> 50%)	20	26
Missing	3	
<i>EGFR FISH</i>		
Gain whole chromosome 7	42	53
Amplified <i>EGFR</i>	3	4
Amp <i>EGFR</i> and gain 7	24	30
Duplicate <i>EGFR</i>	1	1
Duplicate <i>EGFR</i> and gain 7	2	3
Normal	7	9
Missing	2	
<i>MGMT</i>		
Methylated	17	44
Unmethylated	22	56
Missing	42	

Abbreviations: EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; FISH, fluorescent in situ hybridization; MGMT, O⁶-methylguanine-DNA methyltransferase.

Patient Characteristics

Between May 20, 2005 and July 14, 2006, 100 patients were entered onto the phase II trial; three patients were not eligible, one patient dropped out before start of study treatment, and two patients were on phenytoin at enrollment. The patient characteristics are listed in Table 1 for the entire cohort and for only those patients ≤ 70 years old because this cohort would have been eligible for European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada trial 26981/22981 (EORTC 26981/22981-NCIC).²⁶ Biomarkers were analyzed in 81 patients with tissue available and are listed in Table 2.

Treatment Delivery

Of the 97 eligible patients, 81 patients completed cycle 1 through RT, and 34 patients completed treatment through the six cycles of TMZ. On average, the 97 eligible patients completed 6.8 months of erlotinib. The main reasons for not completing treatment were disease progression (58%) and toxicity (22%).

Survival and Progression

At a median follow-up time of 22 months, 24 patients remain alive. Seventy-three patients (75%) have died. The median PFS and OS times were 7.2 and 15.3 months, respectively. The primary end point was successfully met, with more than half of the patients (61%) alive at 1 year. However, because of concerns regarding the inadequacy of the historic control of patients treated with nitrosoureas on prior

NCCTG trials (pre-TMZ era), the results of N0177 (the current trial) were compared with the TMZ/RT arm of EORTC 26981/22981-NCIC.²⁷ N0177 patients older than 70 years were excluded from these comparisons because they would not have been eligible for EORTC 26981/22981-NCIC. The median OS time was 15 months in EORTC 26981/22981-NCIC compared with 15.7 months in N0177. Comparing EORTC 26981/22981-NCIC and N0177 via respective recursive partitioning analysis (RPA) classes, there were no significant differences in OS between the two trials (Table 3). However, there were significant survival differences between the different RPA classes (Fig 2).

Regarding the eight patients older than 70 years, there was a significantly worse outcome for older patients compared with patients age ≤ 70 years. For patients older than 70 years, the median PFS time was 4.4 months ($P = .44$), and the median OS time was 4.5 months ($P = .033$). Patient characteristics were similar to those of the younger patient cohort. Six (75%) of eight elderly patients had a performance score of 0 or 1, and six (75%) had an MMSE score of ≥ 27. Four patients (50%) underwent a gross total resection, two patients (25%) had a subtotal resection, and the rest had a biopsy only.

The following factors were analyzed for relationship to response and none were significantly predictive ($P \leq .05$) of either PFS or OS: presence of grade 2 or greater diarrhea and/or rash, anticonvulsant use at baseline, gain of chromosome 7, presence of *EGFRvIII* activating mutation of *EGFR*, *EGFR* amplification, *p53* expression (reflective of *p53* mutation), and *PTEN* expression (indicative of wild-type *PTEN*). Similarly, there was no significant predictive value in a combined

Table 3. Subgroup Comparison Between EORTC 26981/22981-NCIC and N0177 Based on RTOG/EORTC RPA Class

RTOG/EORTC RPA Class	EORTC 26981/22981-NCIC				N0177			
	Patients (n = 287)		1-Year Survival Rate (%)	Median OS With RT/TMZ (months)	Patients (n = 89)		1-Year Survival Rate (%)	Median OS With RT/TMZ/Erlotinib (months)
	No.	%			No.	%		
III: age < 50 years, PS = 0	42	15	87	21	14	16	93	19
IV: age < 50 years, PS = 1-2; or age ≥ 50 years, MMSE ≥ 27	152	53	70	16	48	54	73	16
V: age ≥ 50 years, MMSE < 27, or Bx only	93	32	42	10	27	30	33	8

Abbreviations: EORTC, European Organization for the Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada; RTOG, Radiation Therapy Oncology Group; RPA, recursive partitioning analysis; OS, overall survival; RT, radiotherapy; TMZ, temozolomide; PS, performance score; MMSE, Mini-Mental State Examination; Bx, biopsy.

analysis of *PTEN* expression and either *EGFR* amplification or *EGFR*-*vIII* mutation (all $P \geq .2$). However, for patients with high-level (greater than a doubling in *EGFR* copy number) versus low-level *EGFR* amplification, there was a trend to better OS (19.4 v 14.2 months, respectively; $P = .103$) and PFS (10.1 v 5.9 months, respectively; $P = .155$).

Because 26% of patients underwent biopsy only, *MGMT* status was assessable only in a subset of patients (40% of the eligible patients). Of 51 patients for whom a block was received, there were seven patients without sufficient viable tumor left to analyze (eg, necrotic or insufficient tissue). Ultimately, 44 patients were tested for *MGMT*, and results were successfully obtained in 39 patients (89% of patients with sufficient tissue submitted). *MGMT* was not significantly predictive of OS probably because of the small sample size (19.4 v 13.4 months in patients with methylated v unmethylated *MGMT*, respectively; $P = .068$).

Toxicity

The most frequent toxicities (all grades) were rash, fatigue, thrombocytopenia, diarrhea, leukopenia, and neutropenia (Table 4). There were two grade 5 toxicities. Both patients developed non-neutropenic pneumonias either shortly after or near the end of RT

with daily TMZ. Both patients were on dexamethasone without *Pneumocystis* prophylaxis and were not lymphopenic on the blood tests preceding the development of the pneumonia.

DISCUSSION

In this phase I/II trial (N0177) of erlotinib combined with TMZ and RT, the primary end point was successfully met, with more than half of the patients (61%) alive at 1 year. In addition, the current trial's median survival time of 15 months exceeded all prior NCCTG GBM trials. However, the prior NCCTG GBM trials that served as historical controls were nitrosourea-based (pre-TMZ) studies and did not use TMZ. Because the favorable survival response in the current trial could have been a result of the TMZ, N0177 was compared with EORTC 26981/22981-NCIC, a trial of similar patients treated with RT and TMZ alone.²⁷ To account for differences in eligibility criteria, patients older than 70 years were excluded from these comparisons because they would not have been eligible for EORTC 26981/22981-NCIC. In addition, the two trials were evaluated via respective RPA prognostic classes to allow comparison of survival outcomes between more homogenous subsets of patients.²⁷ Comparing the study results by RPA classes, there were no significant differences in OS between the two trials, which suggests there is no additional benefit for erlotinib when combined with RT and TMZ. The limited efficacy of selective *EGFR* inhibition likely reflects the need to inhibit multiple signaling pathways in addition to the *EGFR* pathway.

The results of N0177 are in contrast to a single-institution phase II trial of 65 adults with newly diagnosed GBM treated with erlotinib combined with TMZ and RT. In this study from University of California, San Francisco (UCSF), patients not taking EIACs received 100 mg/d of erlotinib during RT and 150 mg/d after RT.²⁸ After RT, the dose of erlotinib was escalated until the development of tolerable grade 2 rash or the maximum allowed dose of 200 mg/d. The median survival time was 19 months and superior to previous studies performed at UCSF, although it is unclear from the reported abstract whether the historical controls were from the TMZ or pre-TMZ (ie, nitrosourea) era and whether the studies were compared using a prognostic scoring system such as RPA. The superior survival achieved in the UCSF study compared with N0177 was certainly not a result of erlotinib dosing because the dose of erlotinib during RT was

Fig 2. Kaplan-Meier estimates of overall survival according to Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer recursive partitioning analysis classes.

Table 4. Most Frequent Treatment-Related Toxicities

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Rash/desquamation	35	36.5	32	33.3	13	13.5	1	1.0			81	84.4
Fatigue	34	35.4	24	25.0	10	10.4	3	3.1			71	74.0
Thrombocytopenia	29	30.2	10	10.4	15	15.6	4	4.2			58	60.4
Nausea	40	41.7	13	13.5	3	3.1					56	58.3
Diarrhea	30	31.3	15	15.6	6	6.3					51	53.1
Leukopenia	17	17.7	11	11.5	15	15.6	7	7.3			50	52.1
Alopecia	24	25.0	12	12.5							36	37.5
Anorexia	14	14.6	15	15.6	2	2.1					31	32.3
Neutropenia	7	7.3	8	8.3	8	8.3	6	6.3			29	30.2
Anemia	12	12.5	5	5.2	5	5.2					22	22.9
Lymphopenia	1	1.0	7	7.3	11	11.5					19	19.8
AST	14	14.6	4	4.2	1	1.0					19	19.8
Stomatitis	10	10.4	6	6.3							16	16.7
ALT	8	8.3	2	2.1	4	4.2					14	14.6
Cough	10	10.4	3	3.1							13	13.5
Infection, no neutropenia			7	7.3	4	4.2			1	1.0	12	12.5
Dyspnea			6	6.3	3	3.1	2	2.1			11	11.5
Keratitis	6	6.3	1	1.0	1	1.0					8	8.3
Dry eye	4	4.2	3	3.1							7	7.3
Pneumonitis			1	1.0	4	4.2	1	1.0	1	1.0	7	7.3

actually lower in the UCSF trial and less than half of patients enrolled onto N0177 would have been able to escalate their maintenance erlotinib from 150 to 200 mg/d because half of the patients on N0177 had grade 2 or greater rash. In addition, 22% of patients enrolled onto N0177 stopped treatment as a result of toxicity; therefore, meaningful dose escalation is unlikely to have been helpful. Because the treatment regimens were so similar between the studies, it is quite likely that the differences in survival are a result of differences in patient characteristics.

Mellinghoff et al²² reported results using tumor specimens from 49 and 33 patients enrolled onto two clinical trials conducted at University of California, Los Angeles, and UCSF, respectively, using EGFR inhibitors in patients with recurrent malignant glioma. They found that patients with coexpression of *EGFRvIII* plus wild-type *PTEN* were more likely to respond favorably to erlotinib than patients whose tumors did not express this genotype. These trials had many differences from N0177 including response being the primary end point as opposed to survival, recurrent tumors treated with EGFR inhibitors alone versus newly diagnosed GBMs treated TMZ and RT concurrently with an EGFR inhibitor, and a study conducted in two academic centers compared with a community-based cooperative group trial. Because of the significant differences, it is nearly impossible to make extrapolations or correlations between these two studies. However, we found no differences in OS or PFS in patient groups characterized by *EGFRvIII* plus wild-type *PTEN* versus groups without these genotypic features. Assays for *EGFRvIII* and *PTEN* were performed in the same laboratory that conducted the studies reported by Mellinghoff et al.²²

The favorable results achieved in N0177 compared with nitrosourea-based historical controls are intriguing because some have suggested that the benefit in median survival seen with concurrent TMZ is modest and the same as seen with nitrosoureas.²⁹ However, the median survival results achieved in N0177 do suggest greater efficacy of RT combined with TMZ compared with RT combined with

nitrosourea-based chemotherapies in the treatment of newly diagnosed GBMs. This question may be more definitively answered when the results of the Radiation Therapy Oncology Group 98-13 study, a randomized trial of TMZ or carmustine combined with RT for newly diagnosed anaplastic astrocytoma, are reported.

Analyses of toxicity and molecular and genetic profiles failed to identify subsets of GBM patients who might derive a survival benefit from erlotinib concurrent with TMZ and RT. There was a trend ($P = .103$) to better survival for *EGFR*-amplified patients; however, the significance of this result is questionable given the number of tested variables and lack of Bonferroni corrections. Therefore, although the subsets of patients with molecular and genetic profiles were small, this trial does not suggest that there would be a benefit for the use of erlotinib in combination with RT and TMZ in a selected population such as those with *EGFR* amplification or mutation.

Assessment of *MGMT* status was only possible in 40% of eligible patients, but even with these small patient numbers, there was a strong trend to better survival for patients with methylated *MGMT*. The number of assessable patients was limited, in large part, by the number of patients (26%) who underwent biopsy only. This illustrates the need for more robust *MGMT* assays that can assess *MGMT* status with smaller tumor specimens.

For the small subset of patients older than 70 years, the median PFS (4.4 months) and OS (4.5 months) were exceptionally poor and much worse than what would be expected with RT alone.³⁰ These results were surprising because other prognostic variables besides age were quite similar between the elderly and younger patient cohorts. Because it is unknown whether there is a benefit for combining TMZ with RT in patients older than 70 years, combination therapy should be considered only in select elderly patients until the ongoing randomized trials that address this question are completed.³¹

The regimen of erlotinib concurrently with TMZ and RT did have significant toxicity, including two patients who developed fatal

non-neutropenic pneumonias consistent with *Pneumocystis* pneumonia either shortly after or near the end of RT with daily TMZ. Both patients were on dexamethasone and not on *Pneumocystis* prophylaxis. In the protocol, *Pneumocystis* prophylaxis was emphasized but not mandated because of differences in practice patterns across NCCTG institutions. At many NCCTG institutions, it is a common practice to only initiate *Pneumocystis* prophylaxis when a patient develops lymphopenia; this practice would have been ineffective in these patients because neither was lymphopenic on the blood tests obtained before they developed their pneumonias. Similar difficulties with *Pneumocystis* pneumonia have been seen in other protocols, including a phase II trial of concurrent daily TMZ and RT followed by maintenance TMZ, with two of the first 15 patients developing *Pneumocystis* pneumonia during the concurrent phase of TMZ and RT.³² This led to the mandating of prophylactic pentamidine inhalations for all patients, with no additional opportunistic infections on this study. In the follow-up phase III trial, prophylaxis was again mandated, and no *Pneumocystis* pneumonias were seen in 287 patients treated with TMZ concurrent with RT.²⁶ The results of N0177 and the supporting literature have changed NCCTG practice such that *Pneumocystis* prophylaxis is mandated for all studies with concurrent daily TMZ and RT.

In conclusion, N0177 found no additional benefit for erlotinib when combined with RT and TMZ. In addition, analyses of molecular subsets did not reveal biomarkers predictive of a PFS or OS benefit from erlotinib. This trial does provide evidence that suggests that TMZ concurrent with RT is superior to nitrosourea-based chemotherapy combined with RT. To further improve on TMZ and RT in the treatment of patients with newly diagnosed GBM, future trials targeting other signaling pathways or multiple different pathways are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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