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# Phase II Evaluation of Temozolomide and 13-cis-Retinoic Acid for the Treatment of Recurrent and Progressive Malignant Glioma: A North American Brain Tumor Consortium Study

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## ► ABSTRACT

**Purpose:** Temozolomide (TMZ) and 13-*cis*-retinoic acid (cRA) have shown activity in prior single-agent trials of recurrent malignant gliomas (MG). This phase II trial evaluated efficacy and toxicity of combination temozolomide and cRA treatment in recurrent MG.

**Patients and Methods:** Adults with recurrent supratentorial MG for whom surgery, radiation, and/or chemotherapy failed were eligible. Treatment included oral TMZ 150 or 200 mg/m<sup>2</sup>/d, days 1 through 5, and cRA 100 mg/m<sup>2</sup>/d, days 1 to 21, every 28 days. Primary end point was progression-free survival at 6 months (PFS 6); secondary end points included response, survival, and PFS12.

**Results:** Eighty-eight eligible patients (glioblastoma multiforme [n = 40]; anaplastic gliomas [n = 48; astrocytoma, 28; oligodendroglioma, 14; mixed glioma, six]) received treatment. PFS 6 was 43% (95% confidence interval [CI], 33% to 54%) and PFS12 was 16% (95% CI, 10% to 26%). Median overall PFS was 19 weeks (95% CI, 16 to 27 weeks), and median overall survival (OS) was 47 weeks (95% CI, 36 to 58 weeks). OS was 46% (95% CI, 36% to 57%) at 52 weeks and 21% (95% CI, 13% to 31%) at 104 weeks. Of 84 assessable patients, there were two (3%) complete responses and eight (12%) partial responses (complete plus partial response, 15%). Among 499 treatment cycles, the most common grade 3/4 events included granulocytopenia (1.8%), thrombocytopenia (1.4%), and hypertriglyceridemia (1.2%).

**Conclusion:** TMZ and cRA were active, exceeding our 20% thresholds for PFS 6 success, assuming 20% improvement

- ▲ **TOP**
- **ABSTRACT**
- ▼ **INTRODUCTION**
- ▼ **PATIENTS AND METHODS**
- ▼ **RESULTS**
- ▼ **DISCUSSION**
- ▼ **REFERENCES**

over our previously reported database (glioblastoma multiforme: expected, 30%; observed, 32%; anaplastic glioma: expected, 40%; observed, 50%).

## ► INTRODUCTION

DESPITE OPTIMAL treatment for malignant gliomas, recurrence is common within the first 2 years. This poor outcome was underscored by a recent analysis of eight consecutive phase II trials of 375 patients with recurrent glioma treated with various chemotherapeutic regimens.<sup>1</sup> This analysis revealed a 6-month progression-free survival rate (PFS 6) of only 15% for patients with glioblastoma multiforme (GM) and 31% for patients with anaplastic glioma (AG). After recurrence, response to treatment was observed in only 9% of patients, and overall median survival was only 30 weeks. In meta-analysis studies, there seems to be modest evidence of a survival benefit when chemotherapy is added to standard surgical and radiation therapy, particularly in selected subsets of newly diagnosed glioma patients.<sup>2,3</sup> However, there is little evidence of benefit of chemotherapy after tumor recurrence or progression, and newer agents and regimens need evaluation.

▲	<b>TOP</b>
▲	<b>ABSTRACT</b>
▪	<b>INTRODUCTION</b>
▼	<b>PATIENTS AND METHODS</b>
▼	<b>RESULTS</b>
▼	<b>DISCUSSION</b>
▼	<b>REFERENCES</b>

There is preclinical and clinical evidence of activity of retinoids and/or alkylators in gliomas, either as single agents or in combination. Two such orally administered agents with different modes of action, temozolomide (TMZ) and 13-*cis*-retinoic acid (cRA), have shown activity in recurrent malignant gliomas without overlapping toxicity in phase II clinical trials.<sup>4-6</sup> Multiagent combination regimens containing both retinoids and alkylating agents have been active in malignancies of several histologic subtypes.<sup>7-10</sup> On the basis of these observations, the North American Brain Tumor Consortium (NABTC) chose to perform a prospective, phase II, single-arm trial (NABTC 98-03) of TMZ and cRA in patients with recurrent and progressive malignant gliomas.

## ► PATIENTS AND METHODS

The study was performed by the NABTC, a National Cancer Institute (NCI) consortium of 11 participating institutions (Dana-Farber Cancer Institute, University of California at San Francisco, University of Michigan Hospital, University of Pittsburgh, Children's Hospital of Pittsburgh, University of Texas Health Sciences Center at San Antonio, University of Texas M.D. Anderson Cancer Center, University of Texas Southwestern, University of Wisconsin, University of California at Los Angeles, and University of Chicago). The study was activated December 17, 1998 at the University of Texas M.D. Anderson Cancer Center, was expanded to the NABTC on April 9, 1999, and was closed to accrual on January 30, 2000. All data were collected and analyzed at the NABTC Data Management Center at the University of Texas M.D. Anderson Cancer Center. Approval of the protocol and informed consent by local human investigation committees was obtained from each institution, in accord with assurance filed with and approved by the United States Department of Health and Human Services where appropriate. Informed consent was obtained from each subject or subject's guardian.

▲	<b>TOP</b>
▲	<b>ABSTRACT</b>
▲	<b>INTRODUCTION</b>
▪	<b>PATIENTS AND METHODS</b>
▼	<b>RESULTS</b>
▼	<b>DISCUSSION</b>
▼	<b>REFERENCES</b>

### **Objectives and End Points**

The two primary objectives of this study included determination of efficacy and toxicity of the combination of TMZ and cRA in the treatment of patients with recurrent and progressive GM or AG. The primary end point was progression-free survival at 6 months (PFS 6). Secondary end points included overall survival, time to progression, and, for assessable patients, response. Toxicity was evaluated in all eligible patients receiving at least one dose of drug.

### **Patient Eligibility**

Eligibility required a prior histologic diagnosis of supratentorial GM or AG, which was defined as anaplastic astrocytoma (AA), anaplastic oligodendroglioma, or anaplastic malignant glioma (AMG). The pathologic tissue diagnosis made at the treating institution was accepted; however, the pathology reports on all patients were centrally reviewed to verify the tumor histology. Unequivocal evidence of recurrence or progression by neuroimaging procedure (computed tomography [CT] or magnetic resonance imaging [MRI]) was required, with the progression observed after surgery and radiation and  $\leq$  two prior chemotherapy regimens, either as adjuvant treatment or at recurrence. Patients more than 4 weeks from complete resection were required to have evidence of measurably enhancing disease on MRI or CT within 14 days of registration. Those with recent ( $\leq$  4 weeks) complete resection were eligible without enhancing

disease but were not assessable for response. Patients were required to be older than 18 years; have a life expectancy greater than 8 weeks; have a Karnofsky performance status greater than 60; be recovered from toxic effects of prior radiotherapy or other therapies; and be at least 2 weeks from vincristine, 6 weeks from nitrosoureas, and 3 weeks from other chemotherapy. Other eligibility factors included absolute neutrophil counts of greater than 1,500/mL, platelets  $\geq$  100,000/mL, transaminases and alkaline phosphatase less than two times the institutional upper limits of normal, bilirubin less than 1.5 mg %, blood urea nitrogen and creatinine less than 1.5 times the upper limit of institutional normal, negative beta-human chorionic gonadotropin at registration, use of effective birth control, and provision of informed, written consent.

Patients were ineligible if they had active infection, were pregnant or breast feeding, or had history of a prior cancer (unless off therapy and in complete remission for > 3 years), excepting nonmelanotic skin cancer and carcinoma-in-situ of the cervix.

### **Toxicity and Quality Assurance**

Toxicity monitoring was performed on patients, on all cycles. Safety parameters included all laboratory and hematologic abnormalities, neurologic historical and examination findings, and adverse events reported by patients. The NCI common toxicity criteria version 2.0 was used for adverse event and toxicity reporting. Data forms were submitted to the central NABTC office according to protocol guidelines and entered in the Protocol Data Management System. The study was monitored by the Clinical Data Update System Version 1.1, with cumulative Clinical Data Update System data submitted quarterly to the Cancer Treatment and Evaluation Program. Serious adverse events (AEs) or adverse drug reactions (ADRs) were reported using the NCI/Division of Cancer Treatment ADR reporting form. The process followed the NABTC and United States Food and Drug Administration guidelines for reporting of ADRs.

Quality assurance measures included ongoing (per protocol timetable) monitoring of protocol compliance and submitted case report forms, on-site audits, and response reviews.

### **Treatment**

TMZ (Schering Plough Pharmaceuticals, Kenilworth, NJ) was administered orally at a starting dose of 200 mg/m<sup>2</sup>/d for patients who had not received prior chemotherapy (150 mg/m<sup>2</sup>/d for those who had received prior chemotherapy) days 1 through 5 every 28 days. cRA (Isotretinoin; Roche Laboratories, Nutley, NJ) was administered at 100 mg/m<sup>2</sup>/d to all patients regardless of prior treatment, in two divided doses, 12 hours apart on days 1 through 21 every 28 days. A course was defined as a 28-day period of treatment. Treatment courses were repeated every 28 days from day 1, provided that all hematologic toxicity from the previous course had resolved to grade 2 or less, and all nonhematologic toxicity had recovered to either grade 0 or 1. If recovery had not occurred by day 28, the subsequent course of TMZ and cRA was delayed until these criteria were met.

No dose escalations were allowed. Dose reduction for toxicity was allowed in 25-mg reduction increments, for both TMZ and cRA. Only two dose reductions were permitted, and patients having grade 3 toxicity of any type after two dose reductions were removed from study. Patients were pretreated with oral antiemetics before each TMZ dose and as needed symptomatically. Patients were required to maintain the lowest corticosteroid dose necessary for neurologic stability.

### **Response and Toxicity**

Patients were evaluated for response using a combination of both clinical (neurologic examination) and neuroimaging (enhanced MRI or CT) procedures before every other course (eg, 3, 5, 7, and so on) as compared with baseline. Neurologic performance was assessed by the grading of symptoms and signs that were considered to be not related to a postictal state or other non-tumor-related process, as compared with the last examination. Patients were graded as either definitely better (+2), possibly better (+1), unchanged (0), possibly worse (-1), or definitely worse (-2).

Response was assessed using a modification of the MacDonald criteria.<sup>11</sup> All final response determinations required that patients had a stable or improved clinical examination as compared with baseline and were on stable or decreased doses of corticosteroids as compared with the prior evaluation. Responses (complete response [CR] or partial response [PR]) were required to be sustained on two successive scans taken 8 weeks apart to be considered valid. Independent central review was performed on all patients considered to be responding by the local investigators, and if the central reviewer was in agreement, response was designated as confirmed. If all relevant scans were not all available at the time of central review, the response was designated as unconfirmed.

Progression-free survival (PFS) and overall survival (OS) were defined as the time from the first day of treatment until progression or death. Patients were removed from study if there was progressive disease, development of unacceptable toxicity, an unacceptable status quo or patient refusal, or noncompliance with protocol requirements.

### Statistical Considerations

The primary objective was to determine whether TMZ and cRA could significantly delay progression in patients with recurrent GM and AG. Historical values were obtained from analysis of a database of 375 patients with recurrent high-grade glioma (225 GM and 150 AA) treated on eight consecutive prospective phase II trials,<sup>1</sup> in which PFS 6 was 21% (GM, 15%; AA, 31%). The hypotheses tested are H0:  $p = p_0$  versus H1:  $p > p_1$ , where  $p$  was the probability of remaining alive and progression-free at 6 months, with an alpha of 10% and beta of 5%. For GM,  $p_0$  was set at 10% and  $p_1$  at 30%, looking for improvement of 0.2. For AG,  $p_0$  was set at 20% and  $p_1$  at 40%, looking for an improvement of 0.2. A prior phase II study of TMZ in 116 recurrent AGs showed a PFS 6 of 22%.<sup>5</sup> The current study was designed to accrue 45 GM and 40 AG patients. For GM, success was defined as observing more than seven of 40 patients alive and progression-free at 6 months (yielding alpha = 4% and beta = 6%). For AG, declaring success if 13 of 45 reached 6 months progression-free would yield an alpha of 5% and beta of 8%. Kaplan-Meier estimates for PFS and OS and exact binomial confidence intervals (CIs) were computed using S-plus 2000 (MathSoft, Inc, Seattle, WA).

## ► RESULTS

Eighty-nine patients with recurrent, progressive malignant gliomas were registered. Eighty-eight were eligible; one patient without demonstrable radiographic progression at registration was found to be ineligible. Of the 88 eligible, assessable patients, there were 40 patients with GM (one had gliosarcoma) and 48 patients with AG (28 patients with AA, 13 patients with anaplastic oligodendroglioma [AO], one with oligodendroglioma, and six with AMG).

▲	<b>TOP</b>
▲	<b>ABSTRACT</b>
▲	<b>INTRODUCTION</b>
▲	<b>PATIENTS AND METHODS</b>
▪	<b>RESULTS</b>
▼	<b>DISCUSSION</b>
▼	<b>REFERENCES</b>

The clinical and demographic features of the 88 patients are listed in Table 1<sup>☐</sup>. The median age of the patients was 45 years (range, 23 to 70 years). There was a three to two male-to-female ratio. Median Karnofsky performance status (KPS) was 80, with a minimum of 60. All patients had been unsuccessfully treated with prior surgery; 41% had one prior surgery and 59% had two or more surgeries. Almost 90% of patients had a prior partial resection or gross total resection; 13% had received biopsy only. The surgical procedures performed most proximate to registration were generally biopsy or partial resection. All 88 patients had experienced treatment failure with prior radiotherapy. Most patients (69 [78%] of 88 patients) had experienced treatment failure with one to two prior chemotherapy regimens, but 19 patients (22%) were chemotherapy-naïve. All 88 patients were assessable for toxicity, and 84 were assessable for response (four patients were not assessable for response because of gross total resections without measurably enhancing disease at registration).

**View this table:** **Table 1. Temozolomide and *cis*-Retinoic Acid in Recurrent Malignant Gliomas:**

[\[in this window\]](#) **Clinical Characteristics**

[\[in a new window\]](#)

### Response

Of the 84 patients assessable for response (Table 2<sup>☐</sup>), there were two CRs (3%) and nine PRs (12%), for an overall response rate (ORR; CR + PR) of 15%. By histologic diagnosis, responses occurred as follows: CR, AA ( $n = 1$ ), AO ( $n = 1$ ); PR, GM ( $n = 2$ ), AA, ( $n = 2$ ), AMG ( $n = 3$ ), AO ( $n = 2$ ). Radiographic responses were confirmed by independent central review in all patients except one, an unconfirmed PR patient in whom the appropriate scans were unavailable at the time of central review. On review, all responding patients were on stable (four of 11) or no corticosteroids (seven of 11) at the time of the best response.

**View this table:** **Table 2. Temozolomide and *cis*-Retinoic Acid in Recurrent Malignant Gliomas:**

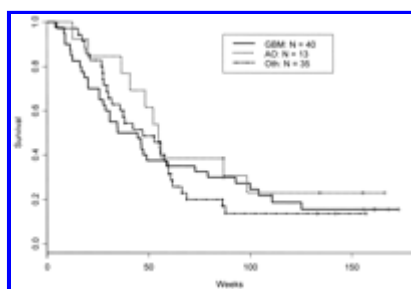
[\[in this window\]](#) **Response**

[\[in a new window\]](#)

## Survival

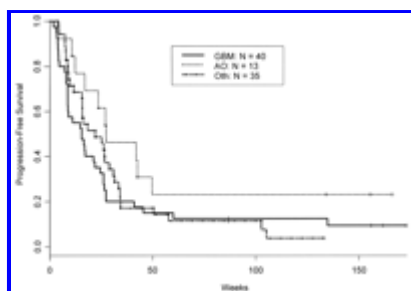
There were 88 eligible patients with recurrent supratentorial malignant gliomas (GM, n = 40; AG, n = 48) analyzed by intent to treat (Table 3<sup>+</sup>; Figs 1<sup>+</sup> and 2<sup>+</sup>). Thirty-eight patients (43%; 95% CI, 33% to 54%) were alive and progression-free at 6 months (PFS 6). The overall PFS 12 was 16% (95% CI, 10% to 26%). Median overall PFS was 19 weeks (95% CI, 16 to 27), and median OS was 47 weeks (95% CI, 36 to 58). OS was 46% (95% CI, 36% to 57%) at 52 weeks and 20% (95% CI, 13% to 31%) at 104 weeks.

**View this table:** **Table 3. Temozolomide and *cis*-Retinoic Acid in Recurrent Malignant Gliomas: Survival**  
[\[in this window\]](#) [\[in a new window\]](#)



**Fig 1. Overall survival by histologic subtype (Kaplan-Meier curve). GBM, glioblastoma multiforme; AO, anaplastic oligodendroglioma; Oth, other.**

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[\[in this window\]](#)  
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**Fig 2. Progression-free survival by histologic subtype (Kaplan-Meier curve). GBM, glioblastoma multiforme; AO, anaplastic oligodendroglioma; Oth, other.**

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Analysis by histologic strata was also performed. In the 40 patients with GM, PFS 6 was 32% (95% CI, 21% to 51%) PFS 12 was 15% (95% CI, 7% to 31%), and median PFS was 16 weeks (95% CI, 9 to 26 weeks). The OS 6 for GM was 65% (95% CI, 52% to 82%), and median OS was 35 weeks (95% CI, 28 to 79 weeks). In the 48 patients with AG (non-GM), the PFS 6 was 50% (95% CI, 38% to 66%), PFS 12 was 17% (95% CI, 9% to 31%), and median PFS was 25 weeks (95% CI, 16 to 32 weeks). The OS 6 for all patients with AG was 83% (95% CI, 73% to 95%), and median OS was 52 weeks (95% CI, 38 to 60 weeks). For the subsets of AG, end point parameters for the AO and non-AO AG subsets are provided in more detail in Table 3<sup>+</sup>. Regarding the primary end point of the study (PFS 6), the results exceeded our 20% thresholds for success, assuming a 20% improvement as compared with our previously reported database<sup>1</sup> (GM: expected, 30%; observed, 32%; AG: expected, 40%; observed, 50%).

## Treatment Intensity and Reasons for Removal From Study

The average number of 28 day cycles received was 5.7. Seventy-four patients (84%) received at least one cycle, and 70 patients (79%) completed at least two cycles. Nine patients (10%) completed at least 12 cycles (approximately 1 year of therapy), but only three (3.4%) of patients received  $\geq 24$  cycles (approximately 2 years of therapy). Five patients (6%) who did not experience disease progression refused further therapy after at least one dose, and two additional patients were noncompliant during therapy; these were included in the analysis. Sixty-six patients went off study as a result of progressive disease after one or more courses, and five additional patients died before documented radiographic progression.



## Toxicity

Toxicity was recorded for all grades for all eligible patients by type, using the NCI common toxicity criteria (version 2.0). Table 4<sup>21</sup> lists all grade 1 to 5 toxicity observed, with each figure representing the sum of the highest grade of toxicity attained, per toxicity, per course for all patients. In the total of 499 treatment courses, we observed 505 grade 1 to 4 AEs; there were no grade 5 AEs. There were 35 (7%) grade 3 AEs, and 17 (3%) grade 4 AEs. The most common grade 3 to 4 AEs were granulocytopenia (1.8%), thrombocytopenia (1.4%), and hypertriglyceridemia (1.2%). Grade 3 elevation in ALT was observed in 5.7%. No patient went off study because of toxicity, and no deaths were attributed to the drug regimen. No observable additive toxicity was observed with the combination as compared with TMZ alone, with the exception of elevated triglycerides, which was considered to be secondary to the cRA.

**View this table: Table 4. Temozolomide and *cis*-Retinoic Acid in Recurrent Malignant Gliomas:**

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## ► DISCUSSION

The prognosis of patients with recurrent malignant astrocytoma remains poor. Wong et al<sup>1</sup> published an analysis of clinical outcomes in 375 patients with recurrent malignant glioma (GM, 225; AG, 150) who received chemotherapy in eight consecutive prospective phase II trials. The overall 6-month PFS rate was only 31% and 15% for patients with recurrent AA and GBM, respectively. Because of these dismal results, there has been heightened interest in the investigation of new agents and combinations.

▲	<b>TOP</b>
▲	<b>ABSTRACT</b>
▲	<b>INTRODUCTION</b>
▲	<b>PATIENTS AND METHODS</b>
▲	<b>RESULTS</b>
■	<b>DISCUSSION</b>
▼	<b>REFERENCES</b>

TMZ is an orally bioavailable imidazotetrazine derivative of dacarbazine. TMZ undergoes chemical degradation to its active metabolite, monomethyl triazenoimidazole carboxamide, at physiologic pH.<sup>12–14</sup> Evidence to date suggests that cytotoxicity of monomethyl triazenoimidazole carboxamide is primarily due to methylation at the O<sup>6</sup> position of guanine.<sup>12–14</sup> TMZ additionally acts as an inhibitor of DNA mismatch repair and can induce apoptosis.<sup>15</sup> Additive or synergistic effects on growth inhibition have been reported in preclinical models, including cell lines and human glioma xenograft models.<sup>16–20</sup> Concentrations of TMZ in the CNS reach approximately 30% of plasma concentrations after systemic administration.<sup>21</sup> TMZ has also shown evidence of activity in clinical trials of human malignant gliomas. Yung et al<sup>5</sup> reported a CR + PR rate of 35%, a PFS 6 of 46%, and overall survival of 13.6 months in a phase II trial of TMZ in patients with recurrent AA. Another randomized study of 116 recurrent malignant glioma patients compared single-agent TMZ with procarbazine.<sup>4</sup> In that study, PFS 6 of 21% was observed with TMZ, versus 8% with procarbazine ( $P = .008$ ). Noncumulative myelosuppression, in the form of thrombocytopenia and neutropenia, was the dose-limiting toxicity in clinical studies.<sup>4,9</sup> Subsequently, TMZ was conditionally approved by the United States Food and Drug Administration for the indication of treatment of recurrent AA.

Synthetic retinoids induce apoptosis and differentiation while inhibiting cell proliferation.<sup>22</sup> Inhibition of migration and proliferation has been observed after retinoic acid treatment in primary glioma cultures but to a lesser degree in established glioma lines.<sup>23</sup> Inhibition of proliferation and induction of apoptosis in human glioma cell lines may be concentration dependent and involve signal transduction transcription factors.<sup>24</sup> *Trans*-retinoic acid has been shown to downregulate leukemia inhibitory factor and telomerase activity, resulting in inhibition of tumor growth and producing differentiation effects in medulloblastoma cells.<sup>25</sup> Retinoic acid also inhibits tenascin-C expression in C6 glioma cell lines.<sup>26</sup> cRA modulates nuclear retinoic acid receptor and the alpha and beta retinoid x-receptors in glioma cell lines.<sup>27</sup> Binding of retinoids to the nuclear retinoic acid receptor and retinoid x-receptor produces a downstream decrease in hepatocyte growth factor expression, interrupting a potential autocrine proliferative loop; hepatocyte growth factor and the related c-Met receptor is present in high levels in human gliomas.<sup>28</sup> Antitumor activity of retinoic acid has been observed in the GL-15 glioblastoma<sup>29</sup> and the U343 malignant glioma cell lines.<sup>30</sup> Pharmacokinetic studies have shown that adequate concentrations of cRA can be reached in rodent CNS after systemic administration, but with a relatively short terminal half-life in rat brain tissue (0.57 to 1.02 hours).<sup>31</sup> These data support a schedule of frequent or continuous oral dosing of cRA in human clinical trials.

A prior phase II trial (Radiation Therapy Oncology Group 91–13) of all-*trans*-retinoic acid in 30 patients with recurrent malignant glioma disclosed minor activity, with tolerable side effects; a response rate of 12% was observed, with a

median time to progression of 3.8 months and a median OS of 5.7 months.<sup>32</sup> A similar single-institution phase II trial of all-*trans*-retinoic acid in 36 patients with recurrent glioma did not show much evidence of activity, with a 3% minor response rate, and median time to progression of only 8 weeks.<sup>33</sup> A recent phase II trial of the combination of radiotherapy and cRA plus interferon alfa-2a in patients with newly diagnosed high-grade glioma did not show an improvement in survival as compared with historical controls.<sup>34</sup> Yung et al<sup>6</sup> conducted a phase II prospective study of 43 patients with recurrent malignant glioma treated with cRA as a single agent, administered at a daily oral dose of 60 to 100 mg/m<sup>2</sup>/d for 3 weeks, followed by 1 week of rest every 28 days. A response rate of 23% (PR, 7%; minor response, 16%) was observed, with median time to progression of 16 weeks and median survival of 58 weeks for GM and 34 weeks for AA.

Clinical trials of combination chemotherapy with retinoids and alkylating agents have shown activity in recurrent squamous cell carcinoma of the head and neck, non-small-cell lung carcinoma, pancreatic cancer, and childhood and acute promyelocytic leukemia.<sup>7-10</sup> It was our hypothesis that the combination of TMZ and cRA would have therapeutic potential in glioma, based on observations of preclinical and clinical activity with each agent, different mechanisms of action, and predominantly nonoverlapping toxicity profiles.

The current study was a modestly sized (N = 88) single-arm prospective trial, with separate stratification for GM and AG. The patient accrual numbers were derived from a hypothesis that a 20% improvement in PFS 6 would be observed with the combination of TMZ and cRA for both strata, based on data from the historical database.<sup>1</sup> In our study, for all patients, the PFS 6 was 43%. PFS 6 was 32% for GM and 50% for all AG combined (46% for the non-AO AG subset and 61% for pure AO subset). These results, as compared with the PFS 6 observed in the database (GM, 15%; AG, 31%), met the criteria for PFS 6 success, exceeding the 20% improvement for both the GM and AG strata. At the time of design of the current protocol, the PFS 6 for TMZ alone was not yet reported; subsequent clinical trials of single-agent TMZ reported a PFS 6 of 21% for GM and 44% for AA.<sup>4,5</sup>

An interesting aspect of this study involved the group of patients with pure AO. In this group, the PFS 6 was 62%, and OS was 55 weeks. A prior study of TMZ in treatment of 30 patients with recurrent AO showed a response rate of 30%.<sup>35</sup> Although specific survival end points were not reported, 13 (44%) of the AO patients were progression-free at 6 months. Although direct comparisons are not possible, the greater survival noted with the TMZ/cRA combination in this trial deserves further study. In addition, survival of the recurrent AO cohort was much longer than the GM and non-AO AG cohorts, raising the question of whether the AO patients should be stratified separately.

Caution is advised with regard to statistical comparisons of these uncontrolled results with the historical database<sup>1</sup> or prior TMZ trials.<sup>4,5</sup> Nevertheless, the results from the current phase II trial suggest that the combination of TMZ and cRA may be a more active regimen in recurrent malignant gliomas.

## ► NOTES

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▲ **TOP**  
▲ **ABSTRACT**  
▲ **INTRODUCTION**  
▲ **PATIENTS AND METHODS**  
▲ **RESULTS**  
▲ **DISCUSSION**  
▪ **REFERENCES**

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