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CLINICAL STUDY - PATIENTS STUDY

Temozolomide single-agent chemotherapy for newly diagnosed anaplastic oligodendroglioma

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Abstract The treatment of patients with anaplastic oligodendroglioma (AO) has been significantly impacted by the molecular detection of loss of sequences on chromosomes 1p and 19q. We performed a clinical trial to prospectively evaluate the safety of treating patients with AO with temozolomide (TMZ) alone in patients with chromosome 1p/19q loss and with chemo-radiation in patients not harboring this loss. Forty-eight patients were enrolled, 36/48 (75%) with evidence of chromosome 1p/19q loss treated with TMZ alone and 12/18 (25%) without such losses, treated with pre-radiation TMZ followed by chemo-radiation. Despite more aggressive treatment, patients without 1p/19q loss had a shorter progression-free survival (PFS) of 13.5 months. With a median follow-up time of 32 months, patients with 1p/19q LOH had a median TTP of 28.7 months. Patients with AO with 1p/19q LOH can be safely treated with single-agent TMZ and do not appear to experience earlier or more frequent tumor progression. This treatment regimen should be studied as part of a formal randomized clinical trial.

Keywords Temozolomide · Single-agent chemotherapy · Anaplastic oligodendroglioma

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Introduction

Patients treated for high-grade glioma typically have a poor prognosis. Clinical observation, though, has identified a class of patients with oligodendroglioma, including anaplastic oligodendroglioma (AO) with a significantly more favorable response and prognosis. Expanding on this observation, Cairncross and Lewis first noted the association of 1p/19q chromosomal loss in these tumors with favorable outcome as a significant prognostic factor [1, 2]. Although the specific genes involved have not been identified, candidate genes are under evaluation, specifically as a result of the identification of specific translocation events in some of these tumors [3].

Favorable treatment responses of patients with AO and anaplastic oligoastrocytoma (AOA) tumors with combined procarbazine, cis-chloro nitrosurea (CCNU) and vincristine chemotherapy (PCV) have been described in 1p/19q allele-losing cases, including in large national clinical trials such

as RTOG-9402 [4] and the EORTC Adjuvant PCV trials [5]. Despite encouraging responses with PCV, though, an impact on overall survival (OS) could not be shown in either genetic subgroup, perhaps owing to the limited efficacy of this regimen overall. A study employing Intensive PCV has also recently been published, but with significant acute toxicity [6]. More recently, 1p/19q loss has been shown to portend a favorable response to initial treatment with temozolomide (TMZ) [7].

A recent clinical trial using TMZ alone in the treatment of patients with AO did not incorporate molecular 1p/19q LOH into treatment assignment [8]. Clinical improvement was observed in 60% of the patients, though, and the objective response rate was 75% and median TTP was 24 months. Fifty percent (10/20) had an antecedent history of a low-grade glioma which had progressed by the time of study entry. Maximal objective response was reached at a median of 6 months (range 3–12). The authors noted that tumors with 1p loss had longer progression-free survival (PFS) compared to tumors without deletions (PFS at 24 months: 1p LOH = 100%, 1p intact = 20%; $P = 0.057$) although this was not statistically significant. TMZ was well tolerated with only two events of grade 3/4 hematological toxicity. The authors concluded that newly diagnosed AO patients demonstrate a high rate of response to initial therapy with TMZ, similar to the response reported for PCV combination therapy, and a suggestion of improved PFS. Further studies were suggested to determine the optimal duration of treatment and whether radiotherapy should immediately follow chemotherapy.

Recently, Abrey et al. [9] presented survey data regarding current treatment practices for AO, suggesting that molecular markers are being used widely to guide treatment choice [9], but in the absence of controlled data supporting this approach. If formal randomized trials are to be performed, it is critical that the safety and potential efficacy be shown in a feasibility study, as presented in this report.

As a result, we evaluated in this study the response rate of newly diagnosed AO patients to pre-radiation TMZ therapy and assessed the safety and PFS associated with this treatment. Unlike the standard regimen of PCV, TMZ treatment is usually associated with a good safety and tolerability profile even with prolonged therapy. Therefore, we allowed for a prolonged treatment course to be given while external beam radiation therapy (EBRT) was deferred until relapse in the favorable 1p/19q LOH cases. Owing to the less favorable clinical course in patients in whom tumors did not carry the favorable LOH finding, combined chemo-radiation was employed following several pre-radiation TMZ cycles, to allow for initial response assessments. The goal was to report the safety of single-agent chemotherapy in the favorable group as well as to report initial clinical outcomes to justify this treatment as an arm in a formal randomized trial.

Materials and methods

Eligibility criteria

Adult patients with newly-diagnosed histologically proven AO or AOA according to the WHO classification were eligible. All pathology specimens were centrally reviewed by the same pathologist (JG). A Karnofsky performance status (KPS) greater than or equal to 60 was required and patients must have been on a stable or decreasing dose of corticosteroids at enrollment. A life expectancy greater than 12 weeks was required, and subjects had to be able to give written informed consent.

Treatment plan

TMZ was administered orally, in the fasting state, once a day for 5 days at a starting dose of 150 mg/m^2/day for the first 2 cycles and escalating to 200 mg/m^2/day if no myelosuppression was noted. Repeat dosing occurred every 28 days following the first daily dose for TMZ. For those patients with documented 1p/19q LOH, TMZ was continued without EBRT using established guidelines, initiating the first 2 cycles at 150 mg/m^2/d and escalating to 200 mg/m^2/d if no myelosuppression was noted. Patients who had intact chromosome 1p/19q initially had 2–4 cycles of TMZ and MRI for a comparative assessment of radiologic response to chemotherapy comparable to the 1p/19q deleted group, prior to initiating external beam radiation therapy to conventional doses (60 Gy) with concurrent TMZ at 75 mg/m2/d followed by post-RT TMZ.

Study requirements

Tumor response was assessed by MacDonald criteria [10]. Gadolinium-enhanced MRIs (Gd-MRI) were performed between 2 and 3 weeks following EBRT completion if applicable, and/or following every two cycles of TMZ. Responses in patients without residual disease were assessed by clinical neurological performance grading and other ancillary imaging techniques. Chromosome 1p/19q LOH status was determined using published methods employing CA-repeat polymerase chain reaction (PCR) [2]. This method defines LOH as complete absence or at least 70% reduction of one heterozygous allele in tumor tissues compared with normal blood as assessed by direct visualization of the trace using the CEQ^{TM} 8000 from Beckman Coulter as we have published [11].

Assessment of efficacy

Primary endpoints for the study were to evaluate the clinical efficacy and toxicity of TMZ single-agent chemotherapy in chromosome 1p/19q deleted LOH tumors and combined TMZ and EBRT for 1p tumors from patients with newly-diagnosed AO or AOA. Clinical efficacy endpoints were defined as radiographic and clinical tumor responses, including partial and complete responses as well as stable disease [10]. Toxicity end-points included grade 3 or 4 myelotoxicity and gastrointestinal toxicity using NCI Common Toxicity Criteria, v. 3.0.

Secondary endpoints were to evaluate overall OS and PFS as measures of long-term clinical efficacy and to correlate chemo-responsiveness with specific molecular genetic alterations, including 1p/19q LOH and O^6-methylguanine-DNA methyl transferase (MGMT) enzymatic activities, when available, for patients with newly-diagnosed AOs and AOAs.

Statistical methods

Study design and sample size calculations

The original design was a two-stage Phase 2 study with early (8 week) toxicity and response observations determining success. Based on a reported study with standard therapy for 24 patients, two of whom had progressed at 6 to 8 weeks, it was assumed that 92% of patients would be progression free (SD, PR, or CR) after the first cycle of standard chemotherapy [12]. A progression-free proportion of 75% or less with TMZ would be considered unacceptably low. The rate of grade 3 or 4 myelotoxicity with standard therapy was estimated at 23%. A reduction to 5% is likely with TMZ, but a rate of 10% or less would represent a clinically useful improvement.

Using the Bryant-Day approach, a total sample size of 58 patients was planned, with a first-stage sample size of 28 patients [13]. The total sample size of 58 was calculated based on a type II error rate of 0.1 (90% power), type I error rates of 0.1 for both response and myelotoxicity and the proportions given above.

Statistical analysis

Percentages were computed for the response and toxicity rates, while Kaplan-Meier estimates were used to assess PFS and OS. In addition, LOH status was determined for all 48 patients. Demographic and clinical information comparisons between patients with and without LOH were done using two-sample t-tests, chi-square tests and Wilcoxon two-sample tests. A chi-square test was used to compare the toxicity rates between the two groups of patients. Cox proportional hazards regression models were used to compare the two groups of patients for PFS and OS, after adjusting for age and initial KPS. No imputation methods were used for missing data. All analyses were performed using SAS version 9.1.

Results

Patient flow

Forty-eight patients meeting the inclusion/exclusion criteria were enrolled. The median time between diagnosis and first TMZ treatment was 37.5 days (range 12–64). Thirty patients (62.5%) completed TMZ treatment and 18 (37.5%) discontinued TMZ treatment. The median number of TMZ cycles was 12 (range 1–24). Of the 18 patients who discontinued treatment, 2 did so because of toxicities, 11 for disease progression and 5 for noncompliance. No patients were lost to follow-up. The median length of follow-up was 32 months (range 3.7–84.4)

Baseline data

The median age was 45.5 years, 60% were male and 85% were Caucasian. Of the 48 patients, over 80% had an initial diagnosis of AO and over 60% had a subtotal resection as their initial surgical procedure (Table 1). The median KPS at TMZ initiation was 90 (range 60–100).

Thirty-six (75%) of the patients had evidence of chromosome 1p/19q LOH. No differences in age, sex, race, type of initial tumor, surgical procedures and KPS at first TMZ were detected between patients with and without LOH (Table 1). No difference was detected in TMZ completion rates for the two groups (64% for patients with LOH vs. 50% for patients without LOH, $P = 0.301$). However, patients with LOH had a significantly greater number of completed TMZ cycles compared to patients without LOH (median 12 with range 2–24 vs. median 8 with range 1–12, $P = 0.013$). Of the 12 patients with LOH who discontinued treatment, 2 did so because of toxicity, 7 due to disease progression and 3 for noncompliance. In the 6 patients without LOH who discontinued treatment, 4 did so because of disease progression and 2 for noncompliance.

Response

Of the 48 patients, 45 had a documented radiographic response. The distribution of maximum response for these 45 patients was 4 (8.9%) with complete response, 22 (48.9%) with partial response, 14 (31.1%) with stable disease and 5 (11.1%) with progressive disease. The median time to radiographic response was 5.3 months (range 2–18).

Table 1 Demographic and clinical information

Variable		All patients ($n = 48$)	LOH ($n = 36$)	No LOH ($n = 12$)	P-value[a]
Age	Mean	45.1	45.1	44.8	0.959
	SD	13.8	11.7	19.5	
	Median	45.5	46.5	32	
	Range	(18,81)	(22,68)	(18,81)	
Sex	Male	29 (60.4%)	22 (61.1%)	7 (58.3%)	0.864
	Female	19 (39.6)	14 (38.9%)	5 (41.7%)	
Race	Caucasian	41 (85.4%)	28 (84.9%)	11 (91.7%)	0.492
	African American	4 (8.3%)	4 (12.1%)	0	
	Hispanic	2 (4.2%)	1 (3.0%)	1 (8.3%)	
	Asian	1 (2.1%)	0 (0.0%)	0	
Type of tumor	Anaplastic Oligoastrocytoma	8 (16.7%)	5 (13.9%)	3 (25%)	0.583
	Anaplastic Oligodendroglioma	39 (81.3%)	30 (83.3%)	9 (75%)	
	Anaplastic mixed	1 (2.1%)	1 (2.8%)	0	
Surgical procedur e(as initial treatment)	Gross total resection	11 (22.9%)	8 (22.2%)	3 (25%)	0.777
	Subtotal resection	30 (62.5%)	22 (61.1%)	8 (66.7%)	
	Biopsy	7 (14.6%)	6 (16.7%)	1 (8.3%)	
KPS at first TMZ treatment	Mean	86.7	87.2	85.0	0.593
	SD	11.9	11.9	12.4	
	Median	90	90	90	
	Range	(60–100)	(60–100)	(60–100)	

[a] Comparing LOH to no LOH

The distributions of radiographic response for patients with and without LOH were similar ($P = 0.353$). Of the patients with LOH, 3 (8.6%) had complete response, 18 (51.4%) had partial response, 12 (34.3%) had stable disease and 2 (5.7%) had progressive disease. Of the patients without LOH, 6 (60%) had partial response, 2 (20%) had stable disease and 2 (20%) had progressive disease following a single cycle of TMZ prior to radiation.

The 6- and 12-month PFS were 89.4% (95% CI, 76.3 to 95.4) and 72.0% (95% CI, 56.7 to 82.7) with a median PFS time of 28.3 months (95% CI, 14.9 to 39.9). The OS at 12 and 24 months was 95.2% (95% CI, 81.9 to 97.9) and 88.8% (95% CI, 74.9 to 95.2), respectively. The median survival time was 77.3 months.

Patients with LOH had longer PFS than patients without LOH at 6 months with 94.3% (95% CI, 79.0 to 98.6) vs. 75% (95% CI, 40.8 to 91.2) and at 12 months with 76.7% (95% CI, 58.7 to 87.6) vs. 58.3% (95% CI, 27.0 to 80.1). During follow-up, 58.3% (21/36) of the patients with LOH had a tumor progression, while 75% (9/12) of the patients without LOH did. The median PFS time was longer in patients with LOH with 28.7 months (95% CI, 25.0 to 43.6) than patients without LOH with 13.5 months (95% CI, 10.6 to 39.9); however, this difference was not statistically significant ($P = 0.206$) (Fig. 1).

Patients with LOH also had longer OS than patients without LOH at 12 months with 97.2% (95% CI, 81.9 to 99.6) vs. 83.3% (95% CI, 48.2 to 95.6) and 24 months with 90.1% (95% CI, 72.2 to 96.7) vs. 83.3% (95% CI, 48.2 to 95.6). The difference in OS was statistically significant ($P = 0.016$) (Fig. 2).

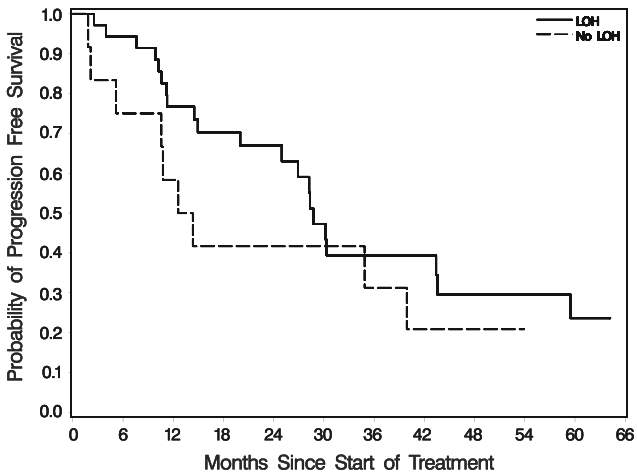

Fig. 1 Progression free survival by 1p/19q LOH status

Patients with pure AO ($n = 39$) had a median OS of 77.3 months, whereas those with mixed AOA ($n = 9$) had a median OS of only 44.6 months ($P = 0.017$). The two groups did not differ in the proportion of patients with LOH (77% for pure AO vs. 67% for mixed AOA, $P = 0.521$).

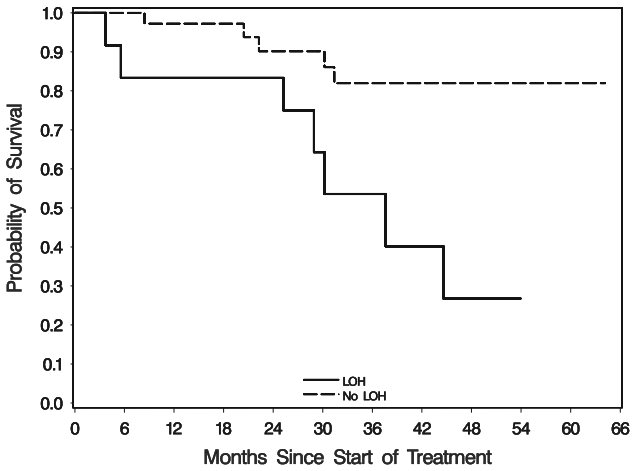

Fig. 2 Overall Survival by 1p/19q LOH status

Adverse events

Grade 3/4 toxicities were experienced by 17 (35.4%) of the 48 patients. Two patients stopped treatment due to toxicities. Of the 17 patients with grade 3/4 toxicities, 11 had at least one hematological toxicity. Eight patients had non-hematological toxicities. Table 2 displays the number of patients experiencing specific toxicities.

Grade 3/4 toxicities occurred at similar rates for patients with and without LOH (36.1% vs. 33.3%, respectively, $P = 0.861$). Of the 13 patients with LOH and grade 3/4 toxicities, 8 had at least one hematological toxicity and 7 had non-hematological toxicities. Of the 4 patients without LOH and grade 3/4 toxicities, 3 had at least one hematological toxicity and one had a non-hematological toxicity.

Treatment at progression

During follow-up, 30 (62.5%) of the patients experienced tumor progression, with 58.3% ($n = 21$) of the patients with LOH and 75% ($n = 9$) of the patients without LOH. Of the 21 patients with LOH, 16 had documented treatments at recurrence which could have impacted OS. For these 16 patients, the treatment or combination of treatments were 12 with EBRT, 6 with surgery, 8 with TMZ, 6 with other chemotherapies (i.e., PCV, irinotecan, procarbazine, CCNU, bevacizumab/irinotecan) and one with thalidomide. Of the 9 patients with no LOH, 7 had documented treatments at recurrence and one refused additional treatment. For these 7 patients, 3 were treated with EBRT, 4 with surgery, one with TMZ, 6 with other chemotherapies (i.e., PCV, irinotecan, procarbazine, CCNU, bevacizumab/irinotecan) and 5 with biological therapies (i.e., one with erlotinib, one with bortozemib and one with imatinib/hydroxyurea).

Ancillary analyses

No pharmacokinetic analyses were performed. Methylguanine methyl-transferase (MGMT) promoter methylation status was evaluated using methylation-specific polymerase chain reaction (MSPCR) [14]. In the 24 patients with MGMT promoter methylation data available [15], 13 showed evidence of methylated promoter and 11 were negative with no evidence of methylated promoter. The PFS was similar for the two groups ($P = 0.726$). The PFS at 12 months was 69.2% (95% CI, 37.3 to 87.2) for patients with methylated MGMT promoter and 63.6% (95% CI, 29.7 to 84.5) for patients with no MGMT promoter methylation.

Table 2 List of specific Grade 3/4 toxicities

Category	Adverse events	All patients N (%)	Patients with LOH N (%)	Patients w/o LOH N (%)
Blood/bone marrow	Lymphopenia	4 (8.3)	2 (5.6)	2 (16.7)
	Hemoglobin	1 (2.1)	1 (2.8)	0
	Platelets	7 (14.6)	6 (16.7)	1 (8.3)
	Neutrophils	6 (12.5)	5 (13.9)	1 (8.3)
	Leukocytes	3 (6.3)	3 (8.3)	0
	At least one of the above	11 (22.9)	8 (22.2)	3 (25)
Constitutional	Fatigue	1 (2.1)	1 (2.8)	0
Gastrointestinal	Constipation	1 (2.1)	1 (2.8)	0
	Vomiting	1 (2.1)	1 (2.8)	0
Infection	Febrile Neutropenia	2 (4.2)	2 (5.6)	0
Hepatic	GGT	1 (2.1)	1 (2.8)	0
	SGPT/SGOT	1 (2.1)	1 (2.8)	0
	Bilirubin	1 (2.1)	0	1 (8.3)

The two groups did not differ in the proportion of patients with LOH, although the rate was higher in patients with MGMT (85% for MGMT vs. 64% for no MGMT, $P = 0.237$).

Interpretation

In comparison with the trial described by Taliansky-Aronov [8], where 50% of the patients had prior diagnosis of oligodendroglioma grade 2, 85% of our cases were de novo AO and 15% had prior low-grade oligodendroglioma. OS did not appear to be impacted by treatment at progression and our data suggest that first-line chemotherapy with TMZ is safe and effective.

Expected versus observed

This study was initially designed to enroll a total of 58 patients, but was stopped after only 48 patients due to slow recruitment. As described by Abrey et al. [9], this was largely due to the fact that changes in practice since the initiation of the study resulted in the use of single-agent TMZ as per this protocol as a de facto standard.

Definitive evaluation of single-agent TMZ chemotherapy for newly diagnosed AO patients will require prospective randomized trials.

The 12-month PFS (72.6%) from this study compares favorably to those found in the combined PCV/EBRT treated groups of Cairncross et al. [4] (69%) and van den Bent et al. [5] (65%); however, the OS at 12 months (95%) was higher for this study when compared to the other two studies (85% and 81%, respectively). This difference could be attributed to the larger proportion of 1p/19q LOH AO patients (75%) in this study than in the other two studies (43% and 25%, respectively). When considering just 1p/19q LOH AO patients, the OS at 12 months in this study was similar to that found in the Cairncross study (97.5% vs. 95%, respectively). However, when considering the grade 3 and 4 toxicities, patients treated with TMZ in this study had significantly lower rates of adverse events than patients treated with PCV in the other two studies. Our overall toxicity rate (grade 3/4) was 35%, while the rates were 65% in the Cairncross [4] study and around 50% in the van den Bent [5] study. The differences are even larger when considering only hematologic toxicities (23% for this study, 56% for Cairncross and up to 46% for van den Bent), supporting the highly significant improvement in the therapeutic index of TMZ over PCV. Given the excellent outcomes reported here for single-agent TMZ use, the contribution of EBRT in the 1p/19q LOH population may be questioned.

Since a prior diagnosis of low-grade glioma could portend a more favorable long-term outcome, it is important to note the incidence of prior low-grade tumor versus de novo AO. In the trial reported by Taliansky-Aronov et al. [8], 50% (10/20) of the patients had a prior diagnosis of low-grade oligodendroglioma. In our series, the incidence was only 15% (7/48). Prior low-grade oligodendroglioma diagnosis can have an impact on outcome, although the strength of this effect is not as clear as for glioblastoma multiforme. When comparing the findings of this study to our results, the median times to maximum response were similar (6.0 vs. 5.3 months). In addition, the median PFS times were similar (24.0 vs. 28.7 months). It is difficult to compare the 1p/19q LOH results between the two studies because of the small sample sizes in the Taliansky-Aronov study. Both studies showed favorable OS for patients with 1p/19q LOH. Interestingly, PFS was not significantly different between LOH groups, possibly due to the small sample size in this group.

Overall evidence

Our intent was to describe the relative safety of treatment for the year following diagnosis and to report outcomes. Given the uniquely favorable prognosis, the time of follow-up precluded a formal survival analysis. There were 48 patients enrolled, 36 with evidence of chromosome 1p/19q LOH treated with TMZ alone and 12 without such losses, treated with pre-radiation TMZ followed by chemo-radiation. Both groups were treated for a calendar year. The incidence of adverse events in both treatment groups was low. Despite aggressive treatment, patients without 1p/19q LOH had a shorter TTP, speaking to the prognostic significance of chromosome 1p/19q status. Conversely, patients with chromosome1p/19q LOH experienced relatively few adverse events with a median follow-up time of 32 months, and the rate of tumor progression (58%) was very low.

Future directions

Patients with AO harboring chromosome 1p/19q LOH can be safely treated with single-agent TMZ and do not appear to experience earlier or more frequent tumor progression. This treatment regimen should be formally evaluated as part of a randomized clinical trial in this patient population. Patients without 1p/19q LOH, on the other hand, despite EBRT and TMZ chemotherapy, appear to have a more aggressive clinical course and earlier progression with a lower likelihood of response. Single-agent TMZ chemotherapy does not appear to be appropriate in this patient population. Chromosome 1p/19q status appears to identify a distinctly favorable subgroup of patients with AO that appear to be safely and effectively managed with TMZ alone. This treatment regimen should be formally

evaluated as part of a randomized clinical trial in this patient population. These intergroup studies are currently being planned specifically entitled; N0577 North Central Cancer Treatment Group Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with Newly Diagnosed Anaplastic Oligodendroglioma or Anaplastic Mixed Glioma with Chromosomal Co-deletions of 1p and 19q.

Conclusions

First-line TMZ in patients with high-grade oligodendrogliomas is safe and effective. The finding of chromosome 1p/19q LOH is a favorable prognostic factor and single-agent TMZ in this subpopulation is safe and effective.

Disclosure Conflicts of interest – research support was provided by Schering.

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