Outcomes and Prognostic Factors in Recurrent Glioma Patients Enrolled Onto Phase II Clinical Trials


Purpose: To determine aggregate outcomes and prognostic covariates in patients with recurrent glioma enrolled onto phase II chemotherapy trials.

Patients and Methods: Patients from eight consecutive phase II trials included 225 with recurrent glioblastoma multiforme (GBM) and 150 with recurrent anaplastic astrocytoma (AA). Their median age was 45 years (range, 15 to 82 years) and their median Karnofsky performance score was 80 (range, 60 to 100). Prognostic covariates were analyzed with respect to tumor response, progression-free survival (PFS), and overall survival (OS) by multivariate logistic and Cox proportional hazards regression analyses.

Results: Overall, 34 (9%) had complete or partial response, whereas 80 (21%) were alive and progression-free at 6 months (APF6). The median PFS was 10 weeks and median OS was 30 weeks. Histology was a robust prognostic factor across all outcomes. GBM patients had significantly poorer outcomes than AA patients. The APF6 proportion was 15% for GBM and 31% for AA, whereas the median PFS was 9 weeks for GBM and 13 weeks for AA. Results were also significantly poorer for patients with more than two prior surgeries or chemotherapy regimens.

Conclusion: Histology is a dominant factor in determining outcome in patients with recurrent glioma enrolled onto phase II trials. Future trials should be designed with separate histology strata.


Patients with recurrent malignant gliomas, such as glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), have poor outcome. Repeat surgery may not be feasible because of tumor infiltration into eloquent areas of the brain, and additional irradiation has limited control on further tumor growth and would potentiate neurologic toxicity. Facing limited treatment options, patients are usually enrolled onto chemotherapy trials and receive investigational drugs. Published phase II trials for malignant gliomas often include a population with heterogeneous clinical characteristics. Although several prognostic factors are well established for patients newly diagnosed with malignant gliomas, those that are important at recurrence have not been extensively studied.

Age, histology, extent of surgery, and performance status are important prognostic variables for malignant gliomas at initial diagnosis. First, age significantly affects survival and strongly correlates with chemosensitivity of these tumors to nitrosourea in vitro and in clinical series. Second, histology, particularly the presence of necrosis as in GBM, is another important prognostic factor. The median survival from initial diagnosis is 11 months for GBM as compared with 27 months for AA. Third, although preoperative tumor size has no prognostic significance, a major reduction in postoperative size prolongs patient survival, particularly in those with minimal residual disease after at least two log units of tumor removal. Lastly, multiple clinical trials have found performance status, in either Karnofsky performance score (KPS) or Eastern Cooperative Oncology Group scales, to be a significant prognostic variable.

However, the prognostic factors for patients with recurrent malignant gliomas remain unclear. Because phase II trials typically enroll patients with recurrent disease after they have failed established therapies, the small number of patients in each of these studies, typically 14 to 30 subjects, precludes a robust analysis of prognostic variables because of insufficient statistical power. Eagan and Scott combined 103 patients with recurrent malignant gliomas from five chemotherapy trials and found that none of the prognostic factors correlated with response or time to progression (TTP), except for performance score, which correlated with survival. However, their study was published more than a decade ago, and improvements in neuroimaging, surgical techniques, and chemotherapy may alter the prognosis of current patients. Moreover, a recently published phase II study on 51 adults with recurrent malignant gliomas sug-
gested that histology, myelotoxicity, and prior chemotherapy had significant correlations with time to tumor progression and survival.10 We combined 375 patients from eight phase II trials for analysis of outcomes and prognostic factors associated with recurrent GBM and recurrent AA.

PATIENTS AND METHODS

Patient Inclusion

Patients were drawn from eight consecutive phase II chemotherapy trials conducted at The University of Texas M.D. Anderson Cancer Center. From 1986 to 1995, seven trials using interferon beta (IFNβ), IFNβ combined with 13-cis-retinoic acid (CRA), menogaril, carboplatin, and a combination of carboplatin, fluorouracil (5-FU), and procarbazine were carried out at M.D. Anderson Cancer Center. One trial using difluoromethylornithine (DFMO) was carried out at M.D. Anderson Cancer Center and at the University of California, San Francisco. Menogaril, carboplatin, 5-FU, and procarbazine are known cytotoxic drugs, whereas IFNβ, CRA, and DFMO are thought to be cytostatic agents that mediate antitumor effect by blocking cell growth without effecting cell kill. All trials were approved by the respective institutional review boards, and informed consent was obtained from each patient or guardian before enrollment.

Two trials administered intravenous IFNβ at a dose of 90 million IU once daily on Mondays, Wednesdays, and Fridays. Another trial used IFNβ at 6 or 18 million units daily on Mondays, Wednesdays, and Fridays, with or without CRA at 100 mg/m²/d. Menogaril was administered intravenously at a dose of 200 mg/m² initially and was increased to 225 mg/m² in subsequent cycles if tolerated; the drug was repeated every 4 weeks. DFMO was administered orally at a dose of 3.6 gm/m² on days 1 to 14, 22 to 35, and 43 to 56; the cycle was repeated on day 63. Carboplatin was given intravenously at a dose of 400 mg/m² initially and was increased to 475 and 525 mg/m² if tolerated; the drug was repeated every 4 weeks. Two trials used a combination of carboplatin, 5-FU, and procarbazine. Carboplatin and 5-FU were given by continuous intravenous infusion at a daily dose of 75 mg/m²/d and at 1,000 mg/m²/d on days 1 to 4, respectively. Oral procarbazine was administered at a dose of 75 mg/m²/d for 10 days on days 5 to 14.

Patient eligibility and response criteria were similar among the trials. Briefly, patients with histologically identified malignant gliomas at recurrence were eligible for study. All eight studies required evidence of recurrence after prior radiotherapy and all had similar age criteria (eg, age > 16 years) and performance criteria (eg, KPS > 50). Each of the eight studies had a two-stage design (the first five were Gehan designs and the last three were Simon designs).6,11 Three studies were stopped after the first stage and enrolled fewer than 15 patients. Two studies were two-arm randomized phase II trials and three studies used separate strata for patients with and without previous chemotherapy. Although five of the eight studies did not restrict entry on the basis of previous chemotherapy, one trial excluded patients with any previous chemotherapy and two trials excluded patients with more than one previous chemotherapy regimen.

Patients enrolled onto the studies were evaluated by neurologic examinations and neuroimaging studies of the brain, contrast-enhanced computed tomography, gadolinium-enhanced magnetic resonance imaging, or both.12 Evaluations were performed at 2-month intervals during the first year, at 3-month intervals during the second year, at 4-month intervals during the third year, or until disease progression. Response to chemotherapy was assessed by radiographic criteria and extent of corticosteroid use. Complete response (CR) was defined as complete resolution of tumor as determined by neuroimaging studies with the patient on a stable dose of corticosteroid. Partial response (PR) consisted of a decrease in tumor volume by 50% or greater in the product of two diameters with no increase in corticosteroid dosage. Minor response (MR) involved a decrease in tumor size by less than 50% with stable or decreasing corticosteroid dose. Stable disease (SD) referred to no change in tumor size with stable or decreasing corticosteroid dose. Progressive disease was defined as definite worsening or development of a new lesion on imaging study with stable or increasing corticosteroid dose.

Patients who experienced medical complications, refused further participation in the study, developed toxicity, or died within 3 weeks of treatment were deemed nonassessable according to study protocols. To avoid postentry exclusion bias, these patients were included in our analysis. The response of those who suffered from an event at 3 weeks or later was based on the latest clinical and neuroimaging evaluations.

Three binary outcomes were defined: (1) CR or PR; (2) CR, PR, MR, or SD; and (3) alive and progression-free at 6 months (APF6). We also defined two time-to-event end points: progression-free survival (PFS) and overall survival (OS). Both were measured from the date of enrollment. PFS measures TTP or death, whichever occurs first. PFS at 6 months is equivalent to APF6.

Statistical Analysis

To evaluate the effects of prognostic factors on outcomes, odds ratios for the three binary end points were estimated with logistic regression,13 whereas hazard ratios for the two time-to-event end points were estimated using Cox regression.14 Both univariate and multivariate analyses were performed for each end point. PFS and OS curves were constructed using the Kaplan-Meier method,15 and estimates of medians and their respective 95% confidence intervals (CIs) were calculated from the Kaplan-Meier estimates. We also performed recursive partitioning in an attempt to identify prognostic subgroups. To perform the recursive partitioning analysis for censored data, we used the null martingale-based residual as input into the S-PLUS (MathSoft, Inc, Seattle, WA) implementation of tree-based methods.16,17 The assumptions of the regression analyses were verified with residual analyses.

Patient Characteristics

The eight chemotherapy trials accounted for a total of 458 enrollments. Eighty-three patients were excluded from analysis: 60 did not have GBM or AA (histologies included 18 mixed gliomas, 14 astrocytomas, 10 anaplastic oligodendrogliomas, eight oligodendrogliomas, five unclassified gliomas, three gliosarcomas, and two ependymomas), 18 AA or GBM patients were enrolled in more than one of the eight trials and only the first enrollment was counted, four patients were retrospectively judged to be ineligible for enrollment, and one patient had a KPS of 50. The histology and KPS exclusions were performed to increase patient homogeneity. A total of 375 unique patients remain for analysis.

The histologic diagnosis at the time of registration was recurrent GBM in 225 patients (60%) and recurrent AA in 150 patients (40%). The median age at enrollment was 45 years (range, 15 to 82 years). Six patients were younger than 20 years and five patients were older than 70. The median KPS at enrollment was 80 (range, 60 to 100). Twenty-two patients had KPS of 100 and 14 had KPS of 60. Two hundred eighty-five patients (77%) had received prior chemotherapy, whereas 92 patients (25%) had received at least two prior chemotherapy regimens. The maximum extent of previous surgery was biopsy in 46
patients (12%), partial resection in 194 patients (52%), and gross total resection in 135 patients (36%). One hundred twenty-eight patients (34%) had two prior surgeries, whereas 27 patients (7%) had more than two prior surgeries. We do not have data on the number of previous recurrences (ie, progressions), but this should be reflected in the number of previous chemotherapy regimens. Furthermore, although it is straightforward to determine whether a patient had prior chemotherapy, the lack of standardized diagnostic criteria make the determination of prior progression problematic. To separate out heavily pretreated (salvage) patients, we identified 41 patients with more than two prior chemotherapies and/or more than two prior surgeries.

RESULTS

Outcomes

Among the 375 patients, 34 (9%) experienced CR (n=1) or PR (n=33), 18 (5%) experienced MR, and 94 (25%) experienced SD. Thus a total of 146 (39%) experienced CR, PR, MR, or SD. A total of 80 (21%) were alive and progression-free at 6 months (ie, the overall APF6 was 21%). The 95% CI for APF6 was 17% to 26%. A total of 343 patients experienced a progression of disease by the end of the study and a total of 298 patients had died by the end of the study. Fifty-nine patients were alive after progression and 14 patients died without radiographic evidence of progression (although most died from their brain cancer). These 14 patients constitute the difference between freedom from progression (in which case these patients are included as events) and progression-free survival (in which case these patients are included as events). Thus our results for PFS would be similar to results using freedom from progression (357 events v 343 events). Eighteen patients were alive without progression with a median follow-up of 5.1 years (range, 35 weeks to 8.1 years). Nine patients with best protocol response of CR or PR had disease progression by 6 months after enrollment.

The median OS time in the total patient group was 30 weeks, 6-month survival proportion was 55%, 1-year survival proportion was 32%, and 5-year survival proportion was 10%. The 95% CI for median OS time was 26 to 35 weeks. The median PFS time was 10 weeks, 6-month PFS proportion was 21%, 1-year PFS proportion was 12% and 5-year PFS proportion was 4%. The 95% CI for the median PFS time was 9 to 11 weeks. Figure 1 shows the OS and PFS curves for the 375 patients. Seventy-nine percent of patients had failed by 26 weeks, and 26 weeks marks the beginning of the long tail in the PFS curve shown in Fig 1. This suggests that 26 weeks would be a convenient time point to capture most of the failures (hence our use of APF6).

Prognostic Factors

Table 1 shows the five outcomes according to the levels of the four covariates (histology, age ≥ 40 years, KPS > 80, and salvage therapy). As listed in Tables 1 and 2, for all five outcomes, GBM patients had significantly poorer outcomes as compared with AA patients. APF6 was 15% for GBM
The 5-year OS proportion was 2% for GBM and 21% for AA. The median PFS time was 9 weeks for GBM (95% CI, 8 to 10 weeks) and 13 weeks for AA (95% CI, 10 to 18 weeks). The median OS time was 25 weeks for GBM (95% CI, 21 to 28 weeks) and 47 weeks for AA (95% CI, 38 to 64 weeks).

Table 3 shows the multivariate results for the five end points. Histology remains a significant predictor for all end points. Salvage treatment is significantly associated with poorer outcome for four of the five end points (the CR/PR analysis lacks adequate statistical power). KPS was significantly associated with survival only, whereas age was not related to outcome. The results for age and KPS were similar when these variables were analyzed as continuous covariates.

We decided to use a “salvage” treatment dichotomy to summarize the previous treatment data because our data indicated that patients with fewer than three prior surgeries and fewer than three prior chemotherapies had similar responses regardless of the actual number of surgeries or chemotherapies. For example, among patients with only one prior surgery, the 48 patients with no prior chemotherapy had a 29% APF6, the 121 patients with one prior chemotherapy had a 20% APF6, and the 41 patients with two prior chemotherapies had a 24% APF6. Similarly, among patients with two prior surgeries, the 31 with no prior chemotherapy had a 23% APF6, the 63 with one prior chemotherapy had a 24% APF6, and the 28 with two prior chemotherapies had a 21% APF6. Thus, the 332 patients with no more than two prior chemotherapies and no more than two prior surgeries had an aggregate 23% APF6 proportion, compared with 10% for the 41 patients with more than two prior surgeries or more than two prior chemotherapies (ie, our salvage treatment patients).

Additional analyses were performed to compare the effects of cytotoxic and cytostatic chemotherapies in our cohort. No statistical differences in outcomes were found between the patients treated with cytotoxic agents and those treated with cytostatic agents. For example, 21 (21%) of 102 patients who received cytotoxic agents were alive and progression-free at 6 months compared with 59 (22%) of the 273 patients who received cytostatic agents (odds ratio = 0.9, 95% CI, 0.5 to 1.6, P = .80).

Recursive partitioning analysis confirmed the prognostic importance of histology. Histology was the first split for all five end points. Within the AA subgroup, recursive partitioning identified 119 patients with a KPS greater than 70 as having favorable long-term outcomes: median PFS time of 15 weeks compared with 9 weeks for 31 AA patients with a KPS of less than or equal to 70 (P = .0090); median OS time of 59 weeks compared with 20 weeks (P = .0002). No further meaningful prognostic subgroups were identified. We used a KPS of greater than 80 for our analyses because the results were similar to those obtained with using a KPS more than 70, because 85 was selected by recursive partitioning as the optimal cutoff for all five endpoints, and because a KPS greater than 80 yielded a more even split of the data, thus providing more precise effect estimates. We used an age cutoff of 40 years as a compromise between the optimal cutoffs for the five end points (which ranged from 28 to 52 years). We also chose 40 because it was close to the optimal cutoff for APF6 (41.5) and to the median age (45).

### Table 1. Prognostic Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>CR/PR* (%)</th>
<th>C/P/M/S† (%)</th>
<th>APF6‡ (%)</th>
<th>PFS at 1 year§ (%)</th>
<th>OS at 1 year§ (%)</th>
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<td>14</td>
<td>48</td>
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<tr>
<td>GBM</td>
<td>225</td>
<td>6</td>
<td>33</td>
<td>15</td>
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<td>21</td>
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<td>&lt; 40 years</td>
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<td>8</td>
<td>40</td>
<td>18</td>
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<td>≤ 80</td>
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<td>7</td>
<td>36</td>
<td>18</td>
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<td>&gt; 80</td>
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<td>12</td>
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<td>No</td>
<td>332</td>
<td>10</td>
<td>41</td>
<td>23</td>
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<tr>
<td>Yes</td>
<td>41</td>
<td>5</td>
<td>20</td>
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<td>21</td>
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<tr>
<td>All patients</td>
<td>375</td>
<td>9</td>
<td>39</td>
<td>21</td>
<td>12</td>
<td>32</td>
</tr>
</tbody>
</table>

*CR/PR = CR or PR.†C/P/M/S = CR or PR or MR or SD.‡APF6 = PFS at 6 months (binary endpoint).§Kaplan-Meier estimates.

### Table 2. Outcomes: GBM v AA

<table>
<thead>
<tr>
<th></th>
<th>OR*</th>
<th>HR†</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>2.7</td>
<td>1.3</td>
<td>5.4</td>
<td>.0081</td>
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<tr>
<td>CR/PR/MR/SD</td>
<td>1.9</td>
<td>1.2</td>
<td>2.9</td>
<td>.0036</td>
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<tr>
<td>APF6</td>
<td>2.7</td>
<td>1.6</td>
<td>4.4</td>
<td>.0002</td>
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<tr>
<td>PFS</td>
<td>1.6</td>
<td>1.3</td>
<td>2.0</td>
<td>&lt;.0001</td>
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<tr>
<td>OS</td>
<td>2.0</td>
<td>1.6</td>
<td>2.6</td>
<td>&lt;.0001</td>
</tr>
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</table>

*OR = odds ratio for nonresponse; HR = hazards ratio.

### DISCUSSION

The entry criteria for these phase II studies are similar to those generally used for recurrent glioma. Thus, the results from our historical database should apply to patients eligible for such studies. The restrictions applied to histology, age, performance status, and (in some cases) prior chemotherapy should have some affect on the apparent relationships.
between these factors and prognosis. Different results might be obtained if patients with additional histologies, younger ages, and lower performance status were included. In particular, the apparent effects of age and performance status would presumably be larger in a less restricted setting. Although the entry criteria for the studies included in our analysis were similar, they were not identical and this heterogeneity is a potential weakness of our study.

Our results demonstrate the clear differences in outcomes between recurrent AA and recurrent GBM patients. Patients with GBM histology did consistently worse than patients with AA across all measures with respect to tumor response, progression, and survival. It seems clear that future trials should report results separately for AA and GBM. Ideally, future trials would be designed with separate strata for AA and GBM. Furthermore, the relevance of the overall results of this historical database depends on future trials having roughly 60% GBM.

Among prognostic factors examined in our study, histology was a highly significant prognostic variable for recurrent malignant gliomas. To a lesser extent, a KPS greater than 80 and salvage treatment were associated with poorer outcomes. A high KPS is expected to associate with a favorable outcome because it is probably a marker for overall tumor burden, cumulative treatment-related toxicity, or both.18,19

A similar study reported more than a decade ago by Eagan and Scott9 showed that none of their six factors examined, age, sex, tumor grade, performance score, TTP after irradiation, and prior chemotherapies, correlated with response or

![Fig 2. PFS according to histology in 375 patients. PFS is 31%, 20%, and 10% at 26, 52, and 104 weeks, respectively, for AA patients, and 15%, 8%, and 4% at 26, 52, and 104 weeks, respectively, for GBM patients.](image)

### Table 3. Multivariate Results

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology GBM v AA</td>
<td>2.4</td>
<td>1.1, 5.2</td>
<td>.033</td>
<td>2.3</td>
<td>1.4, 3.6</td>
<td>.0009</td>
<td>2.4</td>
<td>1.4, 4.1</td>
<td>.0022</td>
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<tr>
<td>Age, ≥ 40 v &lt; 40 years</td>
<td>1.1</td>
<td>0.5, 2.5</td>
<td>.73</td>
<td>0.6</td>
<td>0.4, 1.1</td>
<td>.094</td>
<td>1.3</td>
<td>0.7, 2.3</td>
<td>.37</td>
</tr>
<tr>
<td>KPS, &gt; 80 v ≤ 80</td>
<td>0.6</td>
<td>0.3, 1.3</td>
<td>.24</td>
<td>0.9</td>
<td>0.6, 1.3</td>
<td>.50</td>
<td>0.8</td>
<td>0.5, 1.3</td>
<td>.36</td>
</tr>
<tr>
<td>Salvage, yes v no</td>
<td>2.3</td>
<td>0.5, 10</td>
<td>.28</td>
<td>2.9</td>
<td>1.3, 6.6</td>
<td>.010</td>
<td>3.1</td>
<td>1.1, 9.3</td>
<td>.038</td>
</tr>
</tbody>
</table>

**NOTE.** Results are shown as effect measure (95% CI) P value. Effect measure is odds ratio for binary end points CR/PR, CR/PR/MR/SD, and APF6 and hazards ratio for time-to-event end points (PFS and OS). For binary end points, effects are shown for nonresponse so that the directions of the effects are consistent with those for PFS and OS (ie, progression and death).
TTP. Performance score was the only variable correlated with survival. Our study had 375 patients combined from eight phase II trials, and this number would have enough statistical power to detect small differences in our prognostic variables (except perhaps for CR/PR where only 34 events were observed). This strategy of combining data from multiple small trials is similar to a meta-analysis, as in the one that established chemotherapy efficacy in newly diagnosed GBM and AA even though multiple small trials had failed to do so previously. But unlike a typical meta-analysis, our trials were all performed at a single institution with similar entry criteria and methods of follow-up. This feature helps to minimize the extent of heterogeneity in our data. In addition, contrary to the study by Eagan and Scott, a large number of our patients had chemotherapies, and chemotherapy may accentuate small differences between GBM and AA. Nevertheless, the paucity of prognostic factors in recurrent malignant gliomas suggests that current treatments are still inadequate and much effort will be needed to develop better treatment strategies.

Because our study included trials using cytotoxic and cytostatic agents, we performed an analysis to see whether patient outcome depends on the type of agents used. We found little difference in outcome. This result provides an important basis to combine the eight phase II trials in our study, and further suggests that recurrent malignant gliomas are relatively resistant to current second-line therapies, regardless of cytotoxic or cytostatic agents.

In addition to prognostic factors, we established a set of reference outcome parameters, with respect to response, tumor progression, and survival, that can be used in future clinical trials for recurrent malignant gliomas. Although response to therapy remains a gold standard in current clinical trials for brain tumors, PFS may play an increasingly important role in future studies. This is because emerging cytostatic drugs, such as biologic response modifiers and antiangiogenic drugs, are expected to stabilize tumor growth and would not effect tumor cell kill. As a result, a large number of patients would have SD, and cytostatic drugs would make an impact on patient outcome if their tumors remain stable for a significant period of time. Likewise, although survival is a frequently used end point in clinical trials, PFS could be an alternative measure of treatment efficacy and would help validate response and survival data. APF6 is especially convenient because binary end points are easier to use for phase II trials. A major criticism for using survival as an end point is the multiplicity of treatments received by patients during the course of their illness. Separating out the effect on survival of a particular treatment in a study from other treatment effects would be difficult but not impossible. Furthermore, as evidenced by the steep slopes and long tails in the Kaplan-Meier PFS and survival curves (Fig 1), current treatments benefit only a small number of patients with recurrent malignant gliomas.

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REFERENCES