A Phase I Trial of a New Recombinant Human β-Interferon (BG9015) for the Treatment of Patients with Recurrent Gliomas

Howard A. Fine,† Patrick Y. Wen, Michael Robertson, Anne O’Neill, Janis Kowal, Jay S. Loeffler, and Peter M. L. Black

ABSTRACT

Primary brain tumors represent an important cause of cancer-related morbidity and mortality in the United States. Despite advances in neurosurgery and radiotherapy, the median survival of patients with malignant gliomas remains less than 1 year. A contributing factor to the poor prognoses of these patients is the diffuse, infiltrative nature of these tumors, which limits the effectiveness of focal therapies (i.e., surgery and radiation). Unfortunately, standard chemotherapy has been of limited benefit in the treatment of malignant gliomas, underlying the necessity for new drugs with novel mechanisms of action. On the basis of promising in vitro and clinical data demonstrating significant antiglioma activity of purified IFN-β and a synthetic IFN-β (Betaseron), we conducted a Phase I trial of a new, nonmutated, glycosylated recombinant human IFN-β (BG9015) in patients with recurrent, high-grade astrocytomas. In this trial, we demonstrate that the maximally tolerated dose of BG9015 is 6 million units/m² delivered by intramuscular injection three times per week. Dose-limiting neurotoxicity was seen in both patients treated at 8 million units/m². Additionally, we demonstrate that high BG9015 serum levels are associated with a fall in natural killer cell number, radiographic response, and prolonged survival. We conclude that BG9015 has activity in patients with malignant gliomas, although the therapeutic index may be narrow. Future studies will be needed to confirm the observation that natural killer cell number and activity as well as BG9015 serum levels are important markers of antitumor activity.

INTRODUCTION

Malignant gliomas are the most common primary brain tumors in adults and are an important cause of cancer-related mortality in this country (1). Despite optimal treatment with surgery, radiotherapy, and chemotherapy, the median survival of patients with glioblastoma is only 9–12 months, and survival following recurrence is short (2). The poor results of conventional therapy for patients with malignant gliomas has led to increasing interest in alternate forms of treatment.

Over the past 2 decades, there have been a number of studies evaluating the effectiveness of biological response modifiers for the treatment of malignant gliomas. Interest has focused especially on the IFNs, a family of secreted proteins with antiviral, immunomodulatory, and antiproliferative actions. Although IFN-α (3–7) and IFN-γ (8, 9) have shown only limited activity against malignant gliomas, IFN-β has produced more promising results (5, 10–14). The best results to date have been achieved with Betaseron, a nonglycosylated human recombinant IFN-β with a serine substitution in amino acid number 17 (15). A Phase I-II multicenter trial of Betaseron in children with recurrent gliomas produced a 57% overall response rate (partial response + stable disease), and a similar study in adults produced a 51% response rate, although the duration of responses in both studies was relatively short (13, 16).

Recently, a more potent IFN-β, BG9015, has been developed. This is a 166-amino acid protein with M, 22,500 that is glycosylated like the natural human IFN-β (15). In vitro studies suggest that it has approximately twice the activity (IU/mg of protein) of Betaseron. Given the narrow therapeutic ratio of many biological response modifiers and the variability of drug metabolism in patients taking anticonvulsant medications and/or glucocorticoids, we believed it was important to conduct a formal Phase I trial of BG9015 in this patient population. In addition, we believed it was important to identify potentially useful surrogate markers of IFN biological activity. Given the difficulty in evaluating radiographic “response” in patients with malignant gliomas. We now report the results of a Phase I trial of BG9015 administered i.m. three times a week in patients with recurrent malignant gliomas.

MATERIALS AND METHODS

Patient Eligibility. Patients were eligible for the study if they had a histological diagnosis of glioblastoma multiforme or anaplastic astrocytoma, and the tumor was documented on con-
The abbreviations used are: MRI, magnetic resonance imaging; EPS, Eastern Cooperative Oncology Group performance status; MU, million unit(s); MTD, maximal tolerated dose; DLT, dose-limiting toxicity; PBMC, peripheral blood mononuclear cell; NK, natural killer; TTP, time to tumor progression.

trast-enhanced MRI scans to be progressing or recurrent. All the patients were age 18 or older, had an Eastern Cooperative Oncology Group EPS of 3 or greater, had a life expectancy of greater than 2 months, and had been treated previously with external beam radiation therapy. Other inclusion criteria included no radiation therapy or chemotherapy within 4 weeks of protocol enrollment; no prior IFN therapy; no active cardiac, renal, or psychiatric disease; serum creatinine <1.5 mg/dl; total bilirubin <1.5 mg/dl; aspartate aminotransferase <1.5 × upper limit of normal; WBC >3000/mm³; platelets >100,000/mm³; and signed informed consent.

**Drug Formulation.** BG9015, a recombinant IFN-β, is a glycosylated polypeptide of 166 amino acid residues with Mr, 22,500. It was supplied by Biogen (Cambridge, MA) as a white, lyophilized powder in vials containing 1–6 × 10⁶ IU per vial and stored at 2°C–8°C until use.

**Treatment Plan.** Patients were treated three times a week (Monday, Wednesday, and Friday) with i.m. injections of BG9015. We had initially intended to analyze four dose levels. Each dose level consisted of an intrapatent dose escalation, thus attempting to exploit the observation that patients often become tolerant to the flulike side effects of IFN with successive dosing. Following are the doses of IFN for each dose level: 2 and 4 MU/m² (dose level 1); 2, 4, and 6 MU/m² (dose level 2); 4, 6, and 8 MU/m² (dose level 3); and 4, 8, and 10 MU/m² (dose level 4).

Patients were treated at the lowest dose within that dose level (i.e., 2 MU/m² for dose level 1) for 1 week before advancing to the next higher dose in that dose-level. Once the highest dose within that dose-level was reached (i.e., 4 MU/m² for dose level 1), patients were maintained at that dose until termination of treatment. Thus, for example, patients treated on dose level 2 were given BG9015 at the dose of 2 MU/m² three times per week for the 1st week of treatment, then 4 MU/m² three times per week for the 2nd week of treatment, and then 6 MU/m² three times per week for the remainder of the time on the protocol. Cycles were defined as 6 consecutive weeks of therapy. The maximal tolerated dose (MTD) was defined as the dose level below the level at which dose-limiting toxicity (DLT) was seen in two of three patients. If one DLT was seen in the first three patients on a dose level, a fourth patient was entered on that dose level, and MTD was defined as two of four patients with DLT. A DLT was defined as grade III or IV toxicity according to the National Cancer Institute Common Toxicity Criteria.

**Patient Evaluation and Supportive Care.** A detailed neurologic examination, complete blood count, electrolytes, renal and liver function tests, and a contrast-enhanced MRI scan were obtained prior to starting treatment and at six weekly intervals. A stable dose of steroids was maintained between treatment cycles unless deterioration in the patient’s condition required an increase in the steroid dose to maintain neurological function, at which time patients were removed from the protocol. Such patients were considered to have progressed.

**Pharmacokinetics.** Pharmacokinetic studies were performed following the Monday and Wednesday injections on weeks 1 and 4 of treatment. Five ml of blood were taken from each patient immediately prior to the first BG9015 injection and 2, 4, 8, 24, and 48 h thereafter. BG9015 serum levels were determined in a standard virus-mediated cytopathic serum IFN assay and reported as units of antiviral activity.

**Immunology Assays.** Approximately 60 cc of venous blood were obtained from patients prior to and 24 h after the first BG9015 injection and then prior to and 24 hours after the Monday injection at the beginning of the 4th week of therapy. PBMCs were isolated by Ficoll-diatrizoate density gradient centrifugation. Samples of freshly isolated PBMCs were stained directly with fluorochrome-conjugated murine monoclonal antibodies, washed, fixed in 1% formaldehyde, and analyzed by flow cytometry as described previously (17). CD3, CD4, CD8, CD14, and CD56 monoclonal antibodies were obtained from Coulter Immunology (Hialeah, FL).

Aliquots of patient PBMCs and of normal PBMCs obtained from cytapheresis buffy coats from healthy platelet donors were cryopreserved in liquid nitrogen for later use. For cytotoxicity assays, cryopreserved PBMCs were thawed, incubated overnight in medium at 37°C, and plated as effector cells against K562 targets in standard 4-h chromium-release assays as described previously (18). Results presented are means ± SE of the percentage specific lysis of K562 at an E:T ratio of 40:1 as calculated using a previously published formula (19).

**Study End Points.** The study end points were grade III or IV toxicity or disease progression. Radiographic response was assessed by comparing the patient’s pretreatment MRI scan with the follow-up scans on the same MRI scanner as evaluated by a single neuroradiologist. Each MRI scan study consisted of 12 or more scans at levels to encompass the intracranial contents from the cranial base to the convexity. A “high technique” that utilized overlapping 5-mm cuts through the tumor region was utilized. To ensure consistency between scans, the same volume of gadolinium contrast agent was injected at a defined rate, and at a defined time prior to initiation of MRI scanning. Additionally, each individual patient had pretreatment and posttreatment MRI scans performed on the same MRI scanner. Patients had to be neurologically stable or improved and on stable or decreasing doses of Decadron to be considered a responder. Tumor size was calculated by multiplying the largest cross-sectional diameter of enhancing tumor by the largest diameter perpendicular to it (20). Response was determined by the change in this area of enhancement as defined below.

On the basis of the realization that neoplasms in the brain often grow as irregularly shaped lesions, it has been proposed that tumor volume, rather than area, may represent a more accurate measure of growth or regression (21). In addition to evaluating changes in tumor area, we therefore chose to explore whether measurements of changes in enhancing tumor volume added any useful prognostic information. Tumor volumetric assessment was accomplished using a computer-based volumetric imaging system based on the NIH Image software and
modified by our group. Images were downloaded directly from a network connection to the actual MRI computer, or hard copies were scanned utilizing a CobraScan CX-312T transparency/X-ray scanner (Radiographical Digital Imaging, Compton, CA). The method for obtaining scans (direct downloading or scanning) was kept constant for individual patients. Analysis was performed on a Macintosh Quadra 950 computer using a modified version of the public domain NIH Image program (written by Wayne Rasband at the NIH and available from the Internet by anonymous FTP from zippy.nlm.nih.gov or on floppy disk from the National Technical Information Service, Springfield, VA, part number PB93-504868). This system allowed us to measure the volume of contrast enhancement and to assess changes in the volume of enhancement as determined by counting image pixels at high resolution.

A complete response was defined as total resolution of all contrast enhancement on MRI or computed tomography scans for at least 1 month. Partial response was defined as 50% or more reduction in the area of enhancing tumors on consecutive computed tomography/MRI scans at least 1 month apart. Minimal response was defined as >25% but <50% reduction in the area of enhancing tumor. Progressive disease was defined as greater than or equal to 25% increase in the area of enhancing tumor, new tumor, or worsening neurological symptoms requiring higher doses of steroids. Stable disease was defined as no change in the area of the tumor or less than a 50% reduction or less than a 25% increase in tumor size.

TTP was measured from initiation of BG9015 therapy until clinical or radiographic evidence of tumor progression. Survival was measured from initiation of BG9015 treatment until death.

**Statistical Considerations.** Descriptive statistics were utilized to identify trends in pre- and posttreatment laboratory variables. Fisher’s exact test and Wilcoxon’s rank-sum test were utilized to evaluate relationships between laboratory variables and various outcomes such as response, as described in the “Results” section. Time to tumor progression and survival were determined utilizing Kaplan-Meier curves. Statistical differences between time-event curves were calculated utilizing standard log-rank analyses.

**RESULTS**

A total of 16 patients were enrolled in this trial, of which 16 were evaluable for toxicity and 13 evaluable for response. Of the three patients not evaluable for response, one patient was removed from the study following an episode of diabetic nonketotic, hyperosmolar acidosis on the first day of treatment. Another patient was removed from study secondary to a grade 3 liver transaminase elevation, which returned to normal after discontinuing the BG9015. A final patient was clinically stable but refused additional scans after his first cycle of IFN. As shown in Table 1, there were 13 males and 3 females, with a median age of 42.5 years. Eight patients had anaplastic astrocytomas, whereas the remaining of the patients had glioblastoma multiforme. Four patients were treated at dose level 1 (4 total cycles of IFN), 10 patients were treated at dose level 2 (20 total cycles of IFN), and 2 patients were treated at dose level 3 (2 total cycles of IFN). In general, this population of patients was quite debilitated by their tumors, with a median EPS of 3.

Significant treatment-related toxicity was seen in this trial, as demonstrated in Table 2. Only 2 of the 16 patients (12.5%) experienced no toxicity. The most common toxicity (10 episodes) was hepatic toxicity, manifested by asymptomatic increases in the liver transaminase levels. The other toxicities most commonly observed were anemia (seven episodes), neurotoxicity (five episodes), thrombocytopenia (four episodes), and leukopenia (four episodes). Neurotoxicity was dose limiting at 8 MU/m². At this dose, two patients experienced grade 4 neurotoxicity manifested by repeated generalized seizures and encephalopathy. One of these patients, a 50-year-old male, had resolution of his encephalopathy over 2–3 weeks but succumbed to his tumor shortly thereafter. The other patient with grade 4 neurotoxicity, a 68-year-old female, experienced progressive tumor growth as her neurotoxicity appeared to be resolving. Her cognitive function remained abnormal until her death 2 months later.

In 13 evaluable patients, there was one partial response and one minor response, and 3 patients had stable disease for an overall response rate of 38% (Table 3). Four of nine evaluable patients treated at the MTD had responses or stable disease (44%). Four of the five patients who had partial responses or stable disease by standard cross-sectional diameter area measurements had a >50% decrease in enhancing tumor volumes, whereas the other patient had a <50% decrease in enhancing volume. Median TTP was 36 days for the group as a whole, 31 days for nonresponders, and 89 days for responders (P < 0.05). The median survival for the entire cohort of evaluable patients was 86 days, 60 days for nonresponders, compared to 188 days for responders (P < 0.05). Of note, no patient received any additional surgery, radiation, or chemotherapy following progression on IFN-β.

Median TTP was not significantly different when analyzed for histology, with patients diagnosed originally with anaplastic astrocytomas having a median TTP of 34 days and those with glioblastoma, 50 days. Similarly, there were no significant dif-

---

* Unpublished results.

**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Number of patients/total number of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>I 4/4</td>
</tr>
<tr>
<td></td>
<td>II 10/20</td>
</tr>
<tr>
<td></td>
<td>III 2/2</td>
</tr>
</tbody>
</table>

---

4 Unpublished results.
In an attempt to identify meaningful biological end points other than radiographic response, we examined a number of differences in survival based on original histology, with a median survival of 70 and 103 days for patients with anaplastic astrocytomas and glioblastomas, respectively \((P > 0.10)\).

In an attempt to identify meaningful biological end points other than radiographic response, we examined a number of immunological parameters prior to treatment and then after 6 weeks of therapy. Table 4 demonstrates descriptivestatistics on the available laboratory parameters of patients who consented to and were capable of completing all testing. The percentage change from pretreatment was calculated as: \(\frac{\text{posttreatment}}{\text{pretreatment}} - 1 \times 100\). Because the data for these variables are skewed, the medians and the interquartile ranges are reported. A substantial increase in the number of monocytes was seen, with a small decrease in the number of CD4 and CD8 lymphocytes following 4 weeks of treatment with IFN-\(\beta\). No substantial change was seen in the number of NK cells. Functional assays demonstrated that NK cytotoxic activity was sub-normal to killing of NK-sensitive target cells (K562 cells), with a mean percentage specific cell lysis of 15.5 \pm 14.1\% in glioma patients compared to 50.0 \pm 9.1\% in normal donors \(P < 0.002\;\text{Fig. } 1\). Glioma patients demonstrated similar defects in NK cell killing against NK-resistant targets (COLO 205) and allogeneic human anaplastic astrocytoma and glioblastoma cell lines (A172 and T98G, respectively; data not shown).

We were also interested in determining whether any of the baseline immunological parameters were associated with obtaining a radiographic response. Because the data are skewed secondary to the inability to obtain complete biological data on all patients, the four biological parameters, NK cells (8 patients), monocytes (12 patients), CD4 counts (12 patients), and CD8 counts (12 patients), were split at their pretreatment median values (see Table 4 for values). The results of the Fisher's exact tests for all patients with complete data demonstrated lack of any significant difference between responders and nonresponders with respect to baseline biological parameters (data not shown). A Fisher's exact test was chosen over the traditional \(\chi^2\) test due to the small cell sizes.

To assess whether there were any differences in the median percentage change in these baseline biological parameters following treatment with BG9015 in responding versus nonresponding patients, Wilcoxon rank-sum tests were utilized. As can be seen in Table 5, there was no significant difference in the change of CD4, CD8, and monocyte counts between responders and nonresponders. In contrast, there was a significant decrease in NK cells in patients who responded to BG9015 compared to those who did not \(P < 0.04\).

IFN levels were also measured in patients at various times in their therapy. We were interested in evaluating whether peak IFN levels correlated with any change in the measured biological parameters. In the majority of patients, low to nondetectable levels of IFN were found at all measured time points. In contrast, five patients had high IFN levels defined as \(\geq 10\) units/ml at multiple time points. Using an analysis identical to that described above, there were no significant differences between patients with high versus low IFN levels with respect to the baseline biological parameters (data not shown). As seen in Table 6, however, patients with low serum IFN levels had a significant and substantial increase in NK cells compared to patients with high IFN levels, who experienced a modest decline in NK cells. Additionally, patients who had high serum IFN levels survived significantly longer than those with low or undetectable levels (Fig. 2).
BG9015 in patients with recurrent high-grade gliomas.

The rationale for exploring the antitumor and biological activity of IFN-3 is mutated to a serine, and the molecule is not glycosylated. This molecule differs from natural IFN, in that a IFN-3 mutated in such a way as to allow correct folding in prokaryotic cells. The promising results of the Betaseron trials and the differences in structure and in vitro activity between BG9015 and Betaseron formed the rationale for exploring the antitumor and biological activity of BG9015 in patients with recurrent high-grade gliomas.

**DISCUSSION**

Early clinical trials suggested that IFN-β had clinical activity against malignant gliomas; however, the human IFN utilized for these trials was of questionable purity and specific activity (3, 6, 10). The clinical development of recombinant human IFN-β was slowed by incorrect folding of the protein when produced in bacteria. Thus, recent trials of recombinant IFN-β have utilized a drug called Betaseron, which is human IFN-β mutated in such a way as to allow correct folding in bacteria. This molecule differs from natural IFN, in that a cysteine is mutated to a serine, and the molecule is not glycosylated. To date, two large trials have demonstrated antigen glioma activity of Betaseron with neurotoxicity being dose limiting (13, 14).

BG9015 is one of several new recombinant IFN-β that maintain the natural amino acid sequence and glycosylation of the human protein. This is achieved through the production of the recombinant protein in eukaryotic cells, thus overcoming the problem of incorrect folding in prokaryotic cells. The promising results of the Betaseron trials and the differences in structure and in vitro activity between BG9015 and Betaseron formed the rationale for exploring the antitumor and biological activity of BG9015 in patients with recurrent high-grade gliomas.

**Table 4** Descriptive statistics for mononuclear cells

<table>
<thead>
<tr>
<th>Cell type per mm³</th>
<th>Pre-BG9015</th>
<th>n</th>
<th>Post-BG9015</th>
<th>n</th>
<th>Percentage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>289* (414)*</td>
<td>12</td>
<td>367 (373)</td>
<td>12</td>
<td>-6.84 (47)</td>
</tr>
<tr>
<td>CD8</td>
<td>214 (271.5)</td>
<td>12</td>
<td>181 (177)</td>
<td>12</td>
<td>-12.38 (27)</td>
</tr>
<tr>
<td>NK cells</td>
<td>142.5 (262)</td>
<td>12</td>
<td>227 (147)</td>
<td>8</td>
<td>1.3 (63.2)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>203.5 (489)</td>
<td>12</td>
<td>324 (556)</td>
<td>12</td>
<td>40.5 (253)</td>
</tr>
</tbody>
</table>

* Values are median.

**Table 5** Relationship between change in mononuclear cells and response

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Responders*</th>
<th>n</th>
<th>Nonresponders</th>
<th>n</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cells</td>
<td>-16.52</td>
<td>3</td>
<td>17.69</td>
<td>5</td>
<td>0.0369</td>
</tr>
<tr>
<td>Monocytes</td>
<td>-24.8</td>
<td>4</td>
<td>134.0</td>
<td>8</td>
<td>0.1066</td>
</tr>
<tr>
<td>CD4 lymphocytes</td>
<td>-18.56</td>
<td>4</td>
<td>4.38</td>
<td>8</td>
<td>0.1488</td>
</tr>
<tr>
<td>CD8 lymphocytes</td>
<td>-20.72</td>
<td>4</td>
<td>-9.86</td>
<td>8</td>
<td>0.6711</td>
</tr>
</tbody>
</table>

* Values represent median percentage change defined as: [(post-BG9015/pre-BG9015) - 1] × 100.

In this trial, we found that the DLT of BG9015 was neurotoxicity, similar to the experience in other trials of type I IFNs in patients with brain tumors. The reason why the incidence of neurotoxicity is so high in this patient population is unclear, but it may be related to intrinsic brain damage from the tumor, previous radiation, surgery, concurrent antiseizure medication, or some combination of all of the above. In contrast to the Betaseron trial, however, we did not observe significant flulike symptoms in our patients. We believe that the most probable explanation for this was the use of intrapatient, incremental dose escalations and i.m. dosing of the BG9015, compared to the i.v. dosing utilized in the Betaseron trials. Animal data suggest that repeated i.m. injections could avoid the characteristic high peak and low trough serum levels typically seen with i.v. administration. Additionally, i.m. dosing, with the resultant steady-state serum IFN levels, could result in greater antitumor activity given the cytostatic activity of type I IFNs on most tumor cell lines (22). Our pharmacokinetic data did, in fact, demonstrate sustained and consistent BG9015 levels within individual patients, although BG9015 levels were quite variable between patients. These sustained BG9015 levels may have not only accounted for the lack of flulike symptoms but also the significantly lower MTD than that seen with Betaseron.

There has been much recent discussion concerning the most appropriate radiographic criteria for assessing brain tumor responses to drug treatment (20, 21, 23). Although we primarily evaluated responses using standard cross-sectional diameter measurements of enhancing tumor, we were also interested in developing preliminary data relative to whether additional, prognostically important information could be obtained by utilizing a computerized system to measure a three-dimensional volume of enhancing tissue. The rationale behind this approach is that the loss of contrast enhancement in a responding tumor is generally thought to reflect regression of tumor-associated neo-vascularity and/or repair of the damaged blood-brain barrier beyond the regressing tumor, a process that may not be uniform.

**Fig. 1** NK cell cytotoxicity assay. Difference in percentage specific NK cell cytolysis against NK-sensitive K562 target cells in vitro in the study patients (glioma patients) compared to normal subjects. The difference is statistically significant (P < 0.0020). Data presented are means; bars, SD.
that patients who had radiographic responses to BG9015 also experienced an overall decrease in NK cell number and activity. Whether this decrease in NK cell activity is somehow related to the antitumor activity of BG9015 or merely is a reflection of higher IFN serum levels is uncertain.

A final observation of potential interest was that not only did high serum IFN levels correlate with changes in certain immunological parameters and radiographic response, but they also appeared to correlate with extended survival. As can be seen in Fig. 2, patients with high serum BG9015 levels survived significantly longer from the time of initiating therapy than those with low or undetectable levels ($P < 0.05$). Given the small number of patients in this trial, it is impossible to determine whether this increase in survival is related to the BG9015. Because, however, all patients in this trial received only palliative care following removal from this trial, differences in subsequent treatments cannot account for the difference in survival. Regardless of whether the higher BG9015 levels accounted for increased survival, data from this trial demonstrate significant variability in the pharmacology of BG9015 between patients and that significant biological changes are only observed in patients who achieve moderately high serum IFN levels.

In conclusion, BG9015 appears to have activity in patients with high-grade gliomas, although the therapeutic ratio appears to be narrow. Given the apparent relationship between serum BG9015 levels, biological activity, and patient outcome, the interpatient variation in IFN pharmacology may be an important variable in the design of future Phase II trials. Because determination of IFN levels requires a cumbersome assay, identifying more readily available surrogate markers of adequate IFN serum levels (i.e., change in NK cell number) may ultimately prove useful. Future Phase II trials should be designed to further elucidate the correlation between IFN serum levels, surrogate biological endpoints, and antitumor effect. Eventually, BG9015 may prove to be most useful in combination with standard cytotoxic drugs given its spectrum of nonoverlapping toxicity with these agents.
ACKNOWLEDGMENTS

We thank Keith J. Cochran and Long H. Dang for assistance with the immunology studies and Timothy Thompson for data management and study coordination.

REFERENCES

A phase I trial of a new recombinant human beta-interferon (BG9015) for the treatment of patients with recurrent gliomas.

H A Fine, P Y Wen, M Robertson, et al.