An epidermal growth factor receptor variant III–targeted vaccine is safe and immunogenic in patients with glioblastoma multiforme

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Abstract

Conventional therapies for glioblastoma multiforme (GBM) fail to target tumor cells exclusively, such that their efficacy is ultimately limited by nonspecific toxicity. Immunologic targeting of tumor-specific gene mutations, however, may allow more precise eradication of neoplastic cells. The epidermal growth factor receptor variant III (EGFRvIII) is a consistent and tumor-specific mutation widely expressed in GBMs and other neoplasms. The safety and immunogenicity of a dendritic cell (DC)–based vaccine targeting the EGFRvIII antigen was evaluated in this study. Adults with newly diagnosed GBM, who had undergone gross-total resection and standard conformal external beam radiotherapy, received three consecutive intradermal vaccinations with autologous mature DCs pulsed with an EGFRvIII–specific peptide conjugated to keyhole limpet hemocyanin. The dose of DCs was escalated in cohorts of three patients. Patients were monitored for toxicity, immune response, radiographic and clinical progression, and death. No allergic reactions or serious adverse events were seen. Adverse events were limited to grade 2 toxicities. The maximum feasible dose of antigen-pulsed mature DCs was reached at $5.7 \times 10^7 \pm 2.9 \times 10^7$ SD without dose-limiting toxicity. EGFRvIII–specific immune responses were evident in most patients. The mean time from histologic diagnosis to vaccination was 3.6 ± 0.6 SD months. Median time to progression from vaccination was 6.8 months [95% confidence interval (C.I.95), 2.5–8.8], and median survival time from vaccination was 18.7 months (C.I.95, 14.5–25.6). Overall median survival from time of histologic diagnosis was 22.8 months (C.I.95, 17.5–29). This study establishes the EGFRvIII mutation as a safe and immunogenic tumor-specific target for immunotherapy. [Mol Cancer Ther 2009;8(10):2773–9]

Introduction

Patients with glioblastoma multiforme (GBM) live <15 months on average despite aggressive conventional therapy (1), which often results in incapacitating damage to surrounding normal brain and systemic tissues (2). Immunologic targeting of tumor-specific gene mutations, however, may allow more precise eradication of neoplastic cells. Most well-characterized tumor antigens are overexpressed normal proteins that have triggered immunologic tolerance to some degree. This compromises their effectiveness as tumor rejection antigens and poses a risk of autoimmunity if these normal proteins are effectively targeted. Conversely, tumor-specific antigens derived from mutations in somatic genes are less influenced by central tolerance and less likely to be associated with autoimmunity. Some studies also suggest that the autonomous immune response to human tumors is dominated by such neoantigens (3). These mutations, however, usually arise randomly as a result of the genetic instability of tumors (4, 5). As such, these mutations tend to be patient-specific, and many are incidental to the oncogenic process.

The epidermal growth factor receptor (EGFR) mutation EGFRvIII, however, is a consistent tumor-specific mutation frequently seen in patients with GBM (6–12) and a broad array of other common cancers (6, 11–19). The mutation consists of an in-frame deletion of 801 bp from the extracellular domain of the EGFR that splits a codon and produces a novel glycine at the fusion junction (20, 21). This mutation encodes a constitutively active tyrosine kinase (22, 23) that enhances tumorigenicity (23–26) and tumor cell migration (27, 28) and confers radiation and chemotherapeutic resistance (29–34) to tumor cells. The new glycine inserted at
the fusion junction of normally distant parts of the extracellular domain also results in a tumor-specific epitope not found in any normal adult tissues (35). Thus, several factors make EGFRvIII an ideal target for antitumor immunotherapy (6, 14, 15, 35).

On the basis of preclinical data supporting the potential efficacy of an EGFRvIII-specific immunotherapy against intracerebral tumors (36, 37), a dose escalation and toxicity study was initiated in patients with newly diagnosed GBM using mature dendritic cells (DC) pulsed with an EGFRvIII-specific peptide (PEPvIII) conjugated to keyhole limpet hemocyanin (KLH).

**Patients and Methods**

**Patient Eligibility**

Patients with histopathologically confirmed, newly diagnosed GBM were eligible for this trial if they were age ≥18 y, had a Karnofsky performance status of ≥80, and fit into groups I to IV as defined by Curran’s recursive partition analysis (38). All patients also had to complete standard external beam radiation therapy before vaccination. Other eligibility criteria included an absolute neutrophil count of ≥1,000/μL, platelet count of ≥50,000/μL, prothrombin and partial thromboplastin times of ≤1.5x normal, and for female patients, a negative pregnancy test. Patients had a Karnofsky performance status of ≥60% viable; ≤10% expression of CD3 (BD Biosciences clone SK7), CD14 (BD Biosciences clone M4P9), CD19 (BD Biosciences clone SJ25C1), and CD56 (BD Biosciences clone NCAm16.2); ≥60% expression of HLA-DR (BD Biosciences clone SJ25C1), and CD56 (BD Biosciences clone NCAm16.2); ≥60% expression of IL-1β (10 ng/mL), IL-6 (1,000 units/mL; R&D Systems) was then added for 18 h. The DCs were then washed twice with PBS and granulocyte-macrophage colony-stimulating factor (800 U/mL) and loaded into syringes for intradermal injection. DCs had to meet minimal phenotype release criteria as follows: ≥60% viable; <5% expression of CD3 (BD Biosciences clone SK7), CD14 (BD Biosciences clone M4P9), CD19 (BD Biosciences clone SJ25C1), and CD56 (BD Biosciences clone NCAm16.2); <5% expression of HLA-DR (BD Biosciences clone L243) and CD11c (BD Biosciences clone B-LY6) compared with isotype-matched control antibodies; and <5 endotoxin units/kg body weight. DC dose escalation occurred in cohorts of three patients to assess safety and toxicity until a maximally feasible dose of 1 × 108 antigen-loaded, mature DCs was reached. Subsequently, patients received one third of their total generated DCs up to 1 × 108 cells. Each patient received three vaccines in equal doses, 2 wk apart, in the upper thigh 10 cm below the inguinal ligament. Patients were followed without additional therapy until radiographic or clinical progression.

**Toxicity and Outcome Criteria**

Patients were monitored by general physical examination and a complete neurologic examination before each vaccination, 2 wk after the last vaccination, and every 2 mo thereafter. Erythrocyte sedimentation rate, antinuclear antibody titers, and rheumatoid factor levels were obtained before and after the last vaccination. Binomial proportions were used to estimate the percentage of patients likely to have increased values after vaccination. A contrast-enhanced magnetic resonance image of the brain was also obtained every 2 mo after the last vaccination.

Dose-limiting toxicity was defined according to the National Cancer Institute’s Common Toxicity Criteria (version 2.0) as any grade 4 toxicity or any grade 3 toxicity that did not improve before the next vaccination. The maximally tolerated dose was defined as the highest DC dose at which no less than two of six patients experienced dose-limiting toxicity.

Tumor progression was defined according to the Macdonald criteria (39) or by the development of a new contrast-enhancing lesion of ≥1 cm in two perpendicular measurements in two perpendicular planes. Time to progression (TTP) and survival were defined from time of vaccination and initial histologic diagnosis. The product limit estimator of Kaplan and Meier (40) was used to describe TTP and survival distribution.

**Immunologic Monitoring**

PBMCs collected before vaccination and 2 wk after the third vaccination were analyzed to assess lymphocyte proliferation in response to PEPvIII, KLH, and other control
stimuli. PBMCs were washed, resuspended at $1 \times 10^6$ viable cells/mL in assay media, and plated in wells (100 μL/well) with PEPvIII or KLH at concentrations of 0, 0.625, 1.25, 2.5, 5, and 10 μg/mL or concanavalin-A or phytohemagglutinin at concentrations of 0, 6.25, 12.5, 25, 50, and 100 μg/mL. The plates were then incubated at 37°C in a 5% CO₂ atmosphere. On day 4, the plates were pulsed with $^{3}H$-thymidine by adding 20 μL per well and were then returned to the incubator for 16 to 20 h. The assays were then harvested by placing each disc in a scintillation vial with 10 mL of scintillation fluid and counted on a β counter. Total proliferation response was measured as the mean of all net cpm for each individual sample. Changes from baseline observed 2 wk after the third vaccination were assessed by a paired t test.

Delayed-type hypersensitivity (DTH) testing for recall antigens was done before and 2 wk after the last vaccination with tetanus toxoid (Aventis Pasteur), Candida (Greer), Trichophyton (Greer), and mumps. The proportions of patients that converted from positive to negative or from negative to positive were computed. DTH testing for KLH (100 μg/0.1 mL saline) and PEPvIII (100 μg/0.1 mL saline) was also done on all patients before vaccination and 2 wk after the last vaccination. The proportion of patients that converted from negative to positive was computed. A positive skin-test was defined as ≥5 mm erythema and induration within 48 to 72 h.

Results

Fifteen patients with newly diagnosed GBM signed the Informed Consent form. Three of these patients progressed during external beam radiation therapy and were not vaccinated. Therefore, for this phase I trial, the analyses below are based only on the 12 patients that were vaccinated. A detailed summary of the patient population can be found in Table 1.

Toxicity

Toxicity was minimal, and no adverse events exceeded grade 2 toxicity at any of the DC doses tested. Therefore, a maximally tolerated dose was not established, but a practical upper limit for repeated DC vaccinations was reached at $\leq 1 \times 10^8$ antigen-pulsed, mature DCs. This dose was found to be safe in all patients treated with this dose. The mean feasible dose was found to be $5.7 \times 10^7$ (±2.9 × 10^7 SD) DCs.

After vaccination, a minority proportion of patients were found to have an increase in erythrocyte sedimentation rate and rheumatoid factor levels. Erythrocyte sedimentation rate was elevated in 33% (95% confidence interval (C.I.95), 7–70%; n = 9) of patients after vaccination (binomial proportions). Similarly, 10% (C.I.95, 0.25–44.5%; n = 10) of patients experienced an increase in rheumatoid factor levels. These increases were small and not associated with any clinical symptoms or signs. There was no significant increase in antinuclear antibody titers (C.I.95, 0–33%; n = 9) observed following vaccination.

Immune Responses

Antigen-specific T-cell proliferation in response to PEPvIII was measured in vitro with blood drawn before vaccination and again with blood drawn 2 wk after the third vaccination. A significant increase was seen in in vitro proliferation in response to PEPvIII in 10 of 12 (83.3%) and to KLH in 11 of 12 (91.7%) of the patients (Table 1). Overall, the proliferation level in response to PEPvIII at concentrations of 2.5, 5, 10 μg/mL was significantly greater post vaccination ($P < 0.042$; t test). The proliferation level after vaccination in response to KLH at 10 μg/mL was also statistically significantly greater ($P = 0.045$), whereas proliferation levels at lesser concentrations of KLH only approached statistical significance ($P > 0.061$). There were no significant differences in proliferation in the PEPvIII and KLH assays where concentrations were set at 0 μg/mL or at any concentrations of concanavalin-A or phytohemagglutinin when prevaccination and postvaccination samples were compared.

To assess patient cellular immune responses in general over time in vitro, DTH skin tests were done with the recall antigens tetanus toxoid, Candida, Trichophyton, and mumps before vaccination and after vaccination. One of the 12 patients had a DTH response that was not interpretable before or after vaccination due to an extreme reaction of one of the antigens, which obscured the injection sites of the remaining antigens. In the other 11 patients tested before vaccination, 1 of 11 (9%) was positive for 1 of 4 recall antigens, 4 of 11 (36%) were positive for 2 of 4 recall antigens, 4 of 11 (36%) were positive for 3 of 4 recall antigens, and 2 of 11 (18%) were positive for all 4 recall antigens at the time of initial vaccination. After vaccination, one additional patient was not readable due to an extreme reaction of one of the antigens, which obscured the injection sites of the remaining antigens, and another patient refused testing. After the third vaccination, 1 of 9 (11%) was positive for 2 of 4 recall antigens, 5 of 9 (56%) were positive for 3 of 4 recall antigens, and 2 of 11 (18%) were positive for all 4 recall antigens. These distributions are not significantly different ($P > 0.999$; $\chi^2$ test).

For tetanus toxoid, all patients were positive before vaccination, and all evaluable patients remained positive after vaccination. For Candida, 100% (C.I.95, 2.5–100%) of negative patients ($n = 1$) converted to positive during the vaccinations and DTH testing, whereas 0% (C.I.95, 0–47%) of positive patients converted to negative. For Trichophyton, 33% (C.I.95, 4–78%) of negative patients converted to positive during the vaccinations and DTH testing, whereas 0% (C.I.95, 0–71%) of positive patients converted to negative. For mumps, 67% (C.I.95, 9–99%) of negative patients converted to positive during the vaccinations and DTH testing, whereas 0% (C.I.95, 0–71%) of positive patients converted to negative.

All patients showed no response to KLH or PEPvIII before vaccination. Conversely, 9 of 9 (100%; C.I.95, 67–100%) showed a positive reaction to KLH, and 5 of 9 (56%; C.I.95, 21–86%) showed a positive response to PEPvIII after vaccination (Table 1).
TTP and Overall Survival

The mean time from histologic diagnosis to vaccination for the 12 vaccinated patients was 3.6 ± 0.6 (SD) months. Median TTP after vaccination was 6.8 months (C.I.95, 2.5–8.8), and the median TTP after histologic diagnosis was 10.2 months (C.I.95, 5.7–12.6; Fig. 1A). The proportion of patients without progression 6 months after vaccination was 0.58 (C.I.95, 0.27–0.80) and was 0.17 (C.I.95, 0.03–0.41) at 12 months. The proportion of patients without progression 6 months after histologic diagnosis was 0.67 (C.I.95, 0.34–0.86) and was 0.33 (C.I.95, 0.01–0.59) at 12 months. A univariate analysis and a multivariate analysis showed that age and Karnofsky performance status were not independent predictors of TTP.

Table 1. Patient summary

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>KPS</th>
<th>EGFRvIII</th>
<th>TTP (mo)</th>
<th>Survival (mo)</th>
<th>DC dose before vaccine</th>
<th>Treatment before vaccine</th>
<th>Treatment after vaccine</th>
<th>DTH</th>
<th>DTH</th>
<th>Proliferation (PEPvIII)</th>
<th>Proliferation (KLH)</th>
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<td>M</td>
<td>GBM</td>
<td>100</td>
<td>IND</td>
<td>22.4</td>
<td>41.0</td>
<td>3.0 × 10⁷ RT, TMZ</td>
<td>Lomustine, TMZ, Irinotecan, Celecoxib</td>
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<td></td>
<td></td>
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<tr>
<td>40</td>
<td>F</td>
<td>GBM</td>
<td>100</td>
<td>−</td>
<td>5.7</td>
<td>12.3</td>
<td>3.0 × 10⁷ RT, TMZ</td>
<td>Lomustine, Tamoxifen</td>
<td>− + + +</td>
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<td></td>
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<tr>
<td>50</td>
<td>M</td>
<td>GBM</td>
<td>100</td>
<td>IND</td>
<td>12.6</td>
<td>17.5</td>
<td>3.0 × 10⁷ RT, TMZ</td>
<td>Lomustine, Irinotecan, TMZ, VP-16, Tamoxifen, O⁆BG</td>
<td>− + + +</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>37</td>
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<td>GBM</td>
<td>90</td>
<td>IND</td>
<td>10.1</td>
<td>15.9</td>
<td>1.0 × 10⁸ CW, RT, TMZ</td>
<td>Lomustine, TMZ, Irinotecan, TMZ/O⁆BG, VP-16, Tamoxifen</td>
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<td></td>
</tr>
<tr>
<td>37</td>
<td>M</td>
<td>GBM</td>
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<td>−</td>
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<td>6.7</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>55</td>
<td>F</td>
<td>GBM</td>
<td>100</td>
<td>−</td>
<td>10.8</td>
<td>19.6</td>
<td>1.0 × 10⁸ RT, TMZ</td>
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<td></td>
<td></td>
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<tr>
<td>44</td>
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<td>GBM</td>
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<td>IND</td>
<td>55.4</td>
<td>65.4</td>
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<tr>
<td>55</td>
<td>M</td>
<td>GBM</td>
<td>100</td>
<td>IND</td>
<td>13.8</td>
<td>25.6</td>
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</tr>
<tr>
<td>35</td>
<td>M</td>
<td>GBM</td>
<td>100</td>
<td>NT</td>
<td>5.3</td>
<td>28.1</td>
<td>5.7 × 10⁷ RT, TMZ</td>
<td>Lomustine, Imatinib mesylate/Hydroxyurea, TMZ/Topotecan, Irinotecan, VP-16</td>
<td>NR NR + +</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>GBM</td>
<td>90</td>
<td>IND</td>
<td>26.0</td>
<td>46.2</td>
<td>7.6 × 10⁷ RT, TMZ</td>
<td>Lomustine/TMZ/VP-16, TMZ, Bevacizumab</td>
<td>NT NT − −</td>
<td></td>
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</tbody>
</table>

Abbreviations: CW, carmustine wafer; KPS, Karnofsky performance status; IND, indeterminate; NR, not readable; NT, not tested; O⁆BG, O⁆Benzylguanine; RT, radiation therapy; SRS, stereotactic radiosurgery; TMZ, temozolomide; VP-16, etoposide.

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The median survival after vaccination for the 12 vaccinated patients was 18.7 months (CI, 14.5–25.6), and the median survival after histologic diagnosis was 22.8 months (CI, 17.5–29; Fig. 1B). The proportion of patients alive was 0.92 (CI, 0.54–0.99) at 6 months after vaccination, 0.83 (CI, 0.48–0.96) at 12 months after vaccination, and 0.42 (CI, 0.15–0.67) at 24 months after vaccination. The proportion of patients alive was 1 at 6 months after histologic diagnosis, 0.92 (CI, 0.54–0.99) at 12 months after histologic diagnosis, and 0.5 (CI, 0.2–0.74) at 24 months after histologic diagnosis. A univariate analysis and a multivariate analysis showed that age and Karnofsky performance status were not independent predictors of survival.

To explore whether our vaccinated patients had better outcomes than would have been expected by chance, we compared our patients’ survival to that based on Curran’s recursive partition analysis (38). None of our patients were in groups I or II, which have the most favorable prognosis. Of our 12 vaccinated patients, 8 were in group III and 4 were in group IV. Patients in group III have an expected survival of 17.9 months, whereas patients in group IV have an expected survival of only 11.1 months. Overall, 9 of our 12 patients exceeded these expectations, but this did not reach statistical significance (P = 0.083; binomial proportions).

**Discussion**

The results of the present study show that intradermal vaccination with autologous DCs loaded with a tumor-specific, EGFRvIII-targeted peptide conjugated to KLH is feasible and safe in patients with GBM. Although there have been other clinical trials using DC-based vaccines in patients with malignant gliomas, all have used unselected antigens (41–45). As vaccine potency is enhanced in such approaches, cross-reactivity with normal brain antigens that potentially contaminate these preparations may ultimately limit their specificity. This is of concern because immunization with malignant glioma extracts has been shown to induce a lethal autoimmune encephalomyelitis in nonhuman primates (46). Although cross-reactivity to normal human antigens may do limited harm in the case of vaccines directed at nonessential tissues such as the prostate or breast, the development of strong immune responses against normal central nervous system antigens could be devastating. The data presented here, however, suggest that EGFRvIII may be a tumor-specific and immunologically relevant target in a broad array of tumors, in addition to GBM, which frequently express this mutation, including breast adenocarcinoma, non–small cell lung cancer, and head and neck squamous cell carcinoma (6, 11–19, 47).

This study also shows that a tumor-specific vaccine is capable of inducing EGFRvIII-specific immune responses in a majority of patients with GBM. Purev et al. (48) have previously shown that 3 of 16 patients with EGFRvIII-expressing breast adenocarcinomas had preexisting EGFRvIII-specific lymphoproliferative responses, demonstrating that the immune system of breast cancer patients can also specifically recognize EGFRvIII. In contrast to that study, none of our patients had detectable EGFRvIII-specific immune response before vaccination, but almost all developed significant responses after just three vaccinations. These data suggest that patients with a variety of cancers may be amenable to the induction of EGFRvIII-specific, antitumor immune responses.

Interestingly, there may be a trend toward an increase in nonspecific DTH responses in these patients after vaccination as well, although this did not reach statistical significance according to the χ² test (P > 0.999). This may be because patients regain some degree of immune competence after resection, and this may have made it easier for us to generate immune responses to the EGFRvIII vaccine.

The median survival time observed in this study is encouraging, but may not be different than an untreated population or than that reported in other recent studies using different approaches, often in larger patient populations (42–44, 49, 50). Patient selection bias can always influence such results in early phase trials. Only patients that remained stable during radiation therapy were vaccinated in this trial. As such, these patients represent a subpopulation with a favorable prognosis, and efficacy data should be

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**Figure 1.** TTP and survival of patients who remained stable after radiation and were vaccinated. A, median TTP after histologic diagnosis was 6.8 mo (CI, 2.5–8.8). B, median survival after histologic diagnosis was 22.8 mo (CI, 14.5–25.6). Dotted lines, CI.
interpreted with caution. On the other hand, because the goal of this trial was to assess the feasibility and safety of vaccination with PEPvIII-KLH in a broad group of patients newly diagnosed with GBM, tumor expression of EGFRvIII was not used as an entry criterion. Therefore, many of these patients’ tumors did not express EGFRvIII. Thus, the potential efficacy of this vaccination strategy may have been substantially underestimated in this unselected patient population. Although these data suggest that vaccination with PEPvIII-KLH may have benefit in patients with GBM, definitive evidence of its potential will require a randomized and controlled phase III study.

Although the present study shows the possible benefits of tumor-specific DC vaccination, there remain a number of issues that must be addressed to optimize this therapeutic modality. For example, in a study of 21 biopsy samples of human gliomas, only 47% of the tumors tested positive for EGFRvIII (51), and expression patterns even within these tumors are not homogeneous. As such, vaccinations that target only one antigen may not target all tumors or all cells comprised in a tumor, and these vaccinations may therefore select for the survival and proliferation of those cells that do not express the targeted antigen. Although the specificity of tumor-specific vaccination therapies may have the possible advantage of minimizing autoimmune complications, the heterogeneity of malignant brain tumors may limit the effectiveness of vaccinations targeting only one tumor-specific antigen. Furthermore, cross-presentation of nontargeted antigens could also lead to deleterious autoimmune responses. Conversely, multiantigenic vaccines in this patient population have shown robust immunologic responses and encouraging clinical results without the induction of autoimmunity, and catastrophic autoimmune responses have not been reported to date.

Disclosure of Potential Conflicts of Interest

D.D. Bigner, A.B. Heimberger, and J.H. Sampson have intellectual property, license payments (Celldex Therapeutics), stock options (Celldex Therapeutics), and consulting relationships (Celldex Therapeutics). These developed after completion of the trial. In accordance with Duke University Intellectual Property policies and procedures, we declare that Drs. Bigner, Heimberger, and Sampson and Duke University might benefit financially if such a therapy proves effective and is successful commercially. An independent and external Data Safety Monitoring Board reviewed and approved the manuscript prior to publication.

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Molecular Cancer Therapeutics

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