Section 2: Executive Summary

Scientific Merit: The prognosis of diffuse intrinsic pontine gliomas (DIPGs) has not improved significantly over the last 40 years. A major reason for this limitation is the lack of an understanding of the underlying biology of these tumors, as well as the absence of appropriate targets for therapeutic intervention. The biologic material for DIPGs that is available consists predominantly of autopsy specimens. While the analysis of these samples will provide important clues about the disease, the lack of material at the time of diagnosis continues to hamper significant progress. With dramatic advances in neurosurgical techniques that now permit the safe biopsy within the brainstem, coupled with dramatic advances in molecular profiling of very small quantities of tumor material, we can now move forward towards a direct examination of these tumors prior to the influence of radiation and chemotherapy. In collaboration with the Dana-Farber/Harvard Cancer Center, the Dana-Farber Center for Cancer Genome Discovery and the Broad Institute, as well as the active participation of approximately 20 of the largest pediatric neuro-oncology programs in the country, we are ready to embark on a new direction in the treatment of DIPG.

Disease Impact: Our approach to DIPG over the last 40 years speaks for itself. Not only do the innumerable negative clinical trials speak about our failure to change the course of this disease after all of this time, but also, we are no further ahead in terms of our understanding of these tumors or their treatment. As such, bold steps are needed to change our current approach and this proposal addresses this issue head on.

Innovation: The current clinical trial proposal is innovative in multiple ways. It builds on our improved neurosurgical expertise, thus allowing us to obtain tissue from newly diagnosed patients with the classical clinical and radiographic criteria of DIPG. We will then treat patients based on components of the individual analysis of their tumor for expression of EGFR and MGMT. This will be the first major effort of this kind and will provide important answers to the role of MGMT and EGFR for patients with newly diagnosed DIPG. While any therapy combination can be criticized and replaced by different combinations, the 4 agents selected for this trial meet the following important principles. First, radiation therapy is the standard of care and provides important effects on the tumor. We have also included bevacizumab for all patients based on the expression of VEGF in all malignant gliomas (recall that vascular proliferation is one of the diagnostic criteria of these tumors). While the presence of vascular proliferation is largely based on autopsy cases in DIPG patients, the rational for this approach is justified in newly diagnosed patients as well. The use of temozolomide is only appropriate in the absence of MGMT expression and this protocol will avoid this agent in patients unlikely to benefit, while allowing those that are MGMT negative (even if this is a small subset of patients) the opportunity to receive the drug and evaluate its potential activity. Finally, EGFR has been demonstrated in a number of DIPG autopsy cases, and this protocol will allow us to settle the relevance of this pathway in these tumors. Most importantly, all samples will undergo extensive molecular profiling to identify new pathways and targets for potential intervention in future studies.

Feasibility: The ability of the French group at Institut Gustave Roussy to complete more than 120 consecutive biopsies without mortality or prolonged morbidity demonstrates that biopsy of the pons can be performed. We have now performed 15 biopsies through this effort without significant morbidity and no mortality. We have already demonstrated the validity of all of the molecular techniques proposed in this protocol using samples from pediatric low-grade gliomas.

Expertise: We have been able to bring together approximately 20 major pediatric neurosurgical programs in the United States to obtain samples, which can then undergo molecular profiling through the Dana-Farber/Harvard Cancer Center, Dana-Farber Center for Cancer Genome Discovery and the Broad Institute. We have clinical pediatric oncologists with experience in the administration of the agents being proposed and have included significant oversight to ensure that all patients receive the same high standard of care.