Section 2: Executive Summary

Five-year overall survival in children with high-grade glioma (HGG) and diffuse, intrinsic brainstem glioma (DIPG) are approximately 25% and 10%, respectively[1-3]. Achieving cure for all children with HGG and DIPG remains a major goal of pediatric neuro-oncology. DIPGs are infiltrative gliomas, and have typically been found to be high-grade in histology [1,3]when tissue confirmation has been available. HGGs are highly vascularized and infiltrative tumors. They are dependent on endothelial cell proliferation regulated by proangiogenic cytokines, especially vascular endothelial growth factor [VEGF]. In fact, VEGF expression has been shown to correlate with worse prognosis in patients with HGG [4,5]. Furthermore, in a xenograft model, antibodies to VEGF have inhibited the growth of GBM[6]. Recently, the targeting of VEGF signaling, with bevacizumab in patients with recurrent HGG has led to unprecedented rates of durable responses both clinically and radiographically, with a tolerable toxicity profile among recurrent malignant glioma patients[7]. We propose targeting of VEGF signaling as a potential therapeutic target for pediatric HGG and DIPG. Pre-clinical and clinical studies with VEGF targeting agents have demonstrated *in vitro* and *in vivo* activity of these agents in HGG. [8-11] The most effective and well-studied drug targeting VEGF signaling is bevacizumab, a VEGF-specific recombinant, humanized monoclonal antibody. Bevacizumab + irinotecan has led to response rates of 60% and 6 month progression-free survival rates of 46% in adults with recurrent HGG. In this application, we propose a pilot study, designed to assess feasibility, tolerability, molecular activity and therapeutic potential of bevacizumab and irinotecan±temozolomide (TEM) in children with newly diagnosed HGG and DIPG. Data from this pilot study will be used in the rational design of future studies to stratify patients for targeted therapy and improve the clinical and functional outcome in children with these poor prognosis tumors.

Hypothesis 1: The treatment regimens proposed (bevacizumab± temozolomide and concurrent radiotherapy followed by bevacizumab and irinotecan ± temozolomide) are feasible, well-tolerated and efficacious in children with newly diagnosed HGG and DIPG tumors

1.1 To determine the proposed regimen's feasibility and toxicities in patients with HGG and DIPG.

1.2 To determine the one year EFS, median PFS and median OS in newly diagnosed patients with HGG treated with radiotherapy and concurrent temozolomide, bevacizumab followed by bevacizumab, irinotecan and temozolomide for 12 courses.

1.3 To determine the 1-yr EFS, median PFS and OS in newly diagnosed patients with DIPG undergoing radiotherapy and concurrent bevacizumab followed by bevacizumab, irinotecan for 12 courses.

Hypothesis 2: Children with HGG and DIPG have characteristic molecular and radiographic features that correlate with response and PFS.

2.1 To estimate the incidence of VEGF expression and pathway activation in tumor as well as blood of patients with HGG and DIPG (blood only) and at different time points

2.2 To document changes in MR perfusion and diffusion within 24-48 hours after the 2rd dose of bevacizumab during radiotherapy and correlate functional changes in tumor with responses to treatment

2.3 To conduct gene expression profiling, CGH and SNP arrays in tumor and blood of patients

2.4 To assess telomerase activity, *hTert* expression, and telomere length in patients' blood and tumor

2.5 To correlate the results of the biology studies in serum or tumor with PFS

Hypothesis 3: The proposed treatment in children with HGG and DIPG will lead to better quality of life and functional outcomes

3.1 To assess the health related quality of life of patients by parent report, and when possible, patient report at key points in therapy

3.2 To assess functional abilities and level of independence of patients during and following treatment.

Statistical Considerations: The primary objective of the study is to assess the safety and feasibility of the study regimen. Stopping rules have been defined. We will estimate event-free-survival and overall survival for patients by each stratum using Kaplan-Meier curves. Descriptive statistics will be used to investigate the secondary objectives. We will estimate the frequency of the laboratory marker/indicator and perform exploratory analysis to correlate them with the survival outcomes