Aflac Cancer and Blood Disorders Center

Children's Health Care of Atlanta

Emory University

A Phase II Study Of Pegylated Interferon ALFA-2b in Children with

Recurrent or Refractory and Radiographically or Clinically Progressive Juvenile Pilocytic

Astrocytomas and Optic Pathway Gliomas

NCT Number: NCT02343224

Protocol Version Date: December 14, 2018

Principal Investigator:

Dolly Aguilera MD

Co-Principal Investigator:

Tobey MacDonald MD.

Study Committee

Claire Mazewski MD

Anna Janss MD, PhD.

Robert Craig Castellino MD.

Radiology: Judith Gadde MD.

Pathology: Matthew Schniederjan MD

Neuro-Opthalmology: Jason Peragallo MD

Neurology: David Wolf MD

Statistics: Zhengjia Chen PhD.

Research Pharmacist: Jane Chen, Pharm D

Coordinator Research Coordinator: Karen Jacobs

Clinical Trials Coordinator- Shelley Mays

Table of Contents

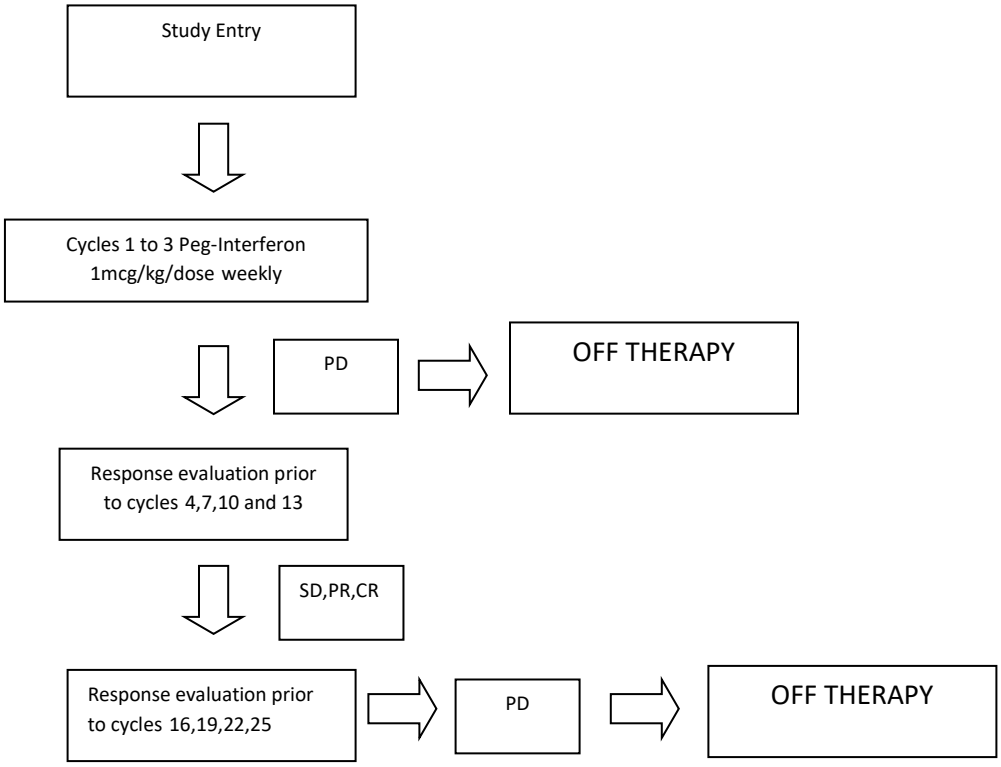
ABSTRACT

Low grade gliomas are the most common pediatric central nervous system malignancies and can occur in different parts of the brain. Patients who undergo gross total resection, usually those with hemispheric tumors, have an excellent prognosis with surgical resection alone. Patients for whom gross total resection is not achievable have a significant risk of disease progression. Therefore, these patients benefit from adjuvant therapy. Multiple chemotherapy regimens have shown some efficacy in residual tumor, but more than 50% of patients experience recurrences. Radiation has been shown to be an effective therapy in the treatment of these tumors. Because of concerns regarding radiation toxicity especially in young children, and progression despite chemotherapy, novel approaches are needed. This protocol represents an attempt to measure the efficacy and safety of use of pegylated interferon for patients with recurrent, refractory Juvenile Pilocytic Astrocytomas (JPA) or optic pathway gliomas. It provides a different approach to the commonly used treatment modalities. Patients with progressive, refractory or symptomatic JPA who have received radiation and who have received at least one prior course of chemotherapy will be eligible for this study. All patients on the study will receive a course of pegylated interferon 1 mcg/kg/dose weekly lasting for up to 2 years. Response will be evaluated with MRI every 12 weeks. The objectives of this study are to determine the response of children with chemotherapy-refractory progressive JPA or optic pathway gliomas (OPG) to weekly pegylated interferon alpha-2b. The secondary objectives include to better identify the toxicities of weekly pegylated interferon alpha-2b in pediatric patients with unresectable, refractory, recurrent JPAs or optic pathway gliomas, to evaluate various magnetic resonance imaging techniques for noninvasive monitoring of metabolic and biologic changes in the tumors and to evaluate the quality of life for patients with recurrent, refractory JPAs who receive therapy with pegylated interferon alpha-2b The primary end point is to determine the response rate. The secondary end point is to determine the Event Free survival. A two-stage design has been selected to evaluate the response rate. If the treatment demonstrates at least a 25% response rate, we would consider it a promising regimen for further study. A response rate less than 5% is considered evidence of unpromising regimen. Seventeen evaluable pediatric patients with JPA or OPG will be accrued. If at least 3 responders are seen among the 17 patients, this will be considered evidence of a promising response rate for further evaluation.

EXPERIMENTAL DESIGN SCHEMA:

Cycle# 1	Day0	Day7	Day 14	Day 21	Day28	
PEG-Interferon (1 mcg/kg/week)	X	X	X	X	X	
MRI imaging						EVERY 12 WEEKS.

EXPERIMENTAL DESIGN SCHEMA:



Note: Each cycle is 28 days
PD = Progressive Disease
SD = Stable Disease
PR = Partial Response
CR = Complete Response

1.0 OBJECTIVES

1.1 PRIMARY STUDY OBJECTIVES

To determine the objective response of children with recurrent or Refractory and radiographically or clinically progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas who are treated with pegylated interferon alpha-2b Response will be determined as complete response or partial response.

1.2 SECONDARY STUDY OBJECTIVES

1.2.1

To estimate event free survival (EFS) (based on standard two or three-dimensional tumor measurements) for children with recurrent, refractory or progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas who are treated with Peginterferon.

1.2.2

To define the toxicities of long term weekly pegylated interferon alpha-2b in pediatric patients with refractory, recurrent and progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas.

1.2.3

To compare response categories and EFS across the 3 MR sequences (T2-weighted, FLAIR, T1-weighted post-contrast).

1.2.4

To evaluate the quality of life for patients with recurrent, refractory and progressive Juvenile Pilocytic Astrocytomas and Optic Pathway Gliomas who receive therapy with pegylated interferon alpha-2b

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Low-grade gliomas (LGGs) represent the most common pediatric central nervous system (CNS) malignancy, accounting for more than half of all such tumors. The most common locations are the cerebellum, followed by the cerebral hemispheres and by the deep midline structures such as the hypothalamus, thalamus, lateral and 3rd ventricles, and the corpus callosum. These tumors are also found along the visual pathways and in the brainstem and in the spinal cord.

Pediatric LGGs include pilocytic, fibrillary, protoplasmic, gemistocytic, giant-cell astrocytomas, or pleomorphic xanthoastrocytoma, oligodendrogliomas and oligoastrocytomas. They belong to the WHO classification as grade I and II. Juvenile Pilocytic Astrocytomas (JPAs) occur predominantly in young children and make up the majority of LGGs found along the optic pathway, as dorsally exophytic brain stem tumors, and in the cerebellum. Grossly, they appear well circumscribed, and in the cerebellum are often cystic, with a mural nodule. They typically, but not always, enhance on MR imaging. JPAs have been particularly associated with neurofibromatosis type 1 (NF-1), in this population lesions are mostly incidental findings and some of them can have indolent courses and close monitoring with imaging studies is recommended.

Patients with JPA patients who have gross total resection, especially those with tumors located in the cerebellar and cerebral hemispheres, have excellent survival at 8 years 99% +/- 0.8% as well as excellent event free survival (EFS). From CCG9891 and POG9130, the results of 518 pediatric patients with low grade gliomas that only underwent surgical resection and no other treatment modality, which had evidence of residual disease, the EFS at 5 years was 56%. Patients younger than 5 years of age had worse EFS than the older counterpart; however this difference does not translate into worse overall survival. [1] JPAs that cannot be completely resected, mostly due to location in or near important structures, are likely to progress and will require additional therapy. Effective treatment modalities include radiation and chemotherapy.

Radiation therapy, while effective, has long term effects that can be minimized if the modality can be delayed or avoided.

Merchant conducted a phase II study that included 78 pediatric patients with unresectable low grade gliomas who received radiation therapy. The 5 year EFS was 87% +/- 4.4 and 10 year EFS was 74.3% +/- 15.4%. The mean and standard error cumulative incidence of vasculopathy was 4.79% +/- 2.73 at 6 years and it was higher for patients younger than 5 years of age at the time of radiation. The main reason to the delay in radiation in young patients with LGG is to reduce their risk of vasculopathy [2]. Additionally, patients with LGG after radiation treatment experienced some adverse endocrine events that were limited. The 3 more common hormone replacements were: growth hormone, thyroid and glucocorticoid. The 5- and 10-year confident intervals for growth hormone replacement were 46.0% +/- 7.2% and 48.9% +/- 7.4%. The thyroid hormone replacement, 61.4% +/-7.5% and 64.0% +/-7.5%. The glucocorticoid replacement was 19.2% +/-5.8% and 19.2% +/-5.8%. Additionally, in the CBCL activities scores, for patients with neurofibromatosis -1 who underwent treatment with radiation have a decrease in the score from 44.2 to 36.8 after 5 years of treatment, while the average score of a patient without NF-1 remained unchanged at 44.2806 despite radiation therapy. [2]

2.2 Chemotherapy for pediatric low grade gliomas:

COG 9952 was the first randomized upfront clinical trial for low grade gliomas. It investigated two chemotherapy regimens for children less than 10 years with unresected LGGs. Regimen A included carboplatin and vincristine (CV). Regimen B included thioguanine, procarbazine, lomustine and vincristine (TPCV). Only regimen A included patients with neurofibromatosis-1. Of 274 randomly assigned between both regimens, 137 received regimen A and 137 received regimen B. The 5-year EFS and overall survival (OS) rates were 45% ± 3.2% and 86% ± 2.2%, respectively. The 5-year EFS rates were 39% ± 4% for CV and 52% ± 5% for TPCV (P = 0.10). Independent factors by multivariate analysis that were predictive of worse EFS and OS are younger age and tumor size greater than 3 cm. Additionally, the location of the tumor in the thalamic region was also associated with poor survival. [3]

Boufet et al conducted a phase II trial with vinblastine for recurrent or refractory pediatric low grade glioma dose of 6mg/m2/dose. 36% of patients had complete, partial or minor response. 23/51 patients have not had progression. 5 year OS was 93.2% +/- 3/8% and 5 year PFS was 42.3% +/- 7.2%. Vinblastine as a weekly regimen was comparable to first line COG 9952. [4]

The experience of bevacizumab for low grade gliomas is limited to case series. Ten children heavily treated for multiply recurrent LGG received the combination of bevacizumab and irinotecan for a median of 5.2 years of age, range 1.5-11.1 years. 70% patients had an objective radiographic response (1 CR, 3 PR and 3 minor Responses). Other clinical improvements were: improved visual acuity, improved

motor function, weight gain in patients with a diencephalic syndrome, and reversal of psychomotor retardation. Dose-limiting toxicities included transient leukoencephalopathy and grade 3 proteinuria. The majority of patients had durable responses. Six patients remained on treatment for almost 2 years. Multiply recurrent low-grade gliomas in children demonstrated responses to the combination of bevacizumab and irinotecan.[5, 6]

A second series reported 7 children who received bevacizumab with irinotecan. Tumor reduction could be observed in 6/7 (85%) patients with recurrent low-grade gliomas. Bevacizumab-related acute toxicity appears to be low in children, even in combination with irinotecan. [7]

Finally, 14 pediatric patients with multiply recurrent low-grade gliomas were treated with bevacizumab and irinotecan for at least twelve months of follow-up after completion of initial therapy. Median treatment duration was 12 months (range, 1 - 24 months). 12/14 patients had an objective response; two had stable disease, and no progressions. 13/14 patients progressed after stopping bevacizumab at a median of four months. Four patients were retreated with bevacizumab alone and all responded or stabilized on treatment. Bevacizumab-based therapy is successful at inducing LGG regression and stabilization after initial therapy or with repeated treatment, although nearly all patients' tumors will progress off-therapy. Toxicities are not insignificant but usually reversible (6). A subsequent report, gave additional details of responses after progression of LGG when retreated with bevacizumab in 4/4 patients, however alternative dose strategies such as bevacizumab as a single agent and interval does every 3 weeks were evaluated. [8]

Therashima et al evaluated pediatric patients with centrally located LGG who received either chemo or radiation to better understanding the risk factors along with the effects of interventions on long-term outcome through a retrospective chart review. Forty-seven patients with a median follow-up of 79 months were included in the analysis. The 5-year EFS and OS were 53% and 96%. The 5-year PFS for those that received radiation upfront was 76% vs. those who received chemotherapy as a first line 37%. p=0.02. The 5-year PFS after salvage RT was 55% for those who progressed after chemotherapy. [9]

Pilocytic astrocytomas often have a solid and cystic component at presentation or recurrence. The management of the cystic component of the tumor can be difficult when gross total resection is not possible. Multiple treatment options are available, including additional resection, fenestration of the cyst, and placement of an Ommaya reservoir for intermittent aspiration, systemic chemotherapy, and radiation therapy. In a retrospective analysis, the cases of children with pathology confirmed WHO grade 1 astrocytomas and identified patients with complications arising from the cystic portion of the tumor were reported. 54 patients with tumors with a cystic component. In 31.4% there was progression of the cystic portion of the tumor. The optic pathway/hypothalamus was the most common location for progressive tumor cysts. Surgical resection was attempted in all cases at least once; a total of 39 surgical procedures were performed. Cyst fenestration was attempted in 35.2%. Ommaya reservoir was placed in 47%. 9 patients got external beam radiation and 5/9 (56%) had stabilization of cyst growth with no additional therapies. Intra-cystic administration of P32 was given to only one patient. Chemotherapy was used in 65% of cases. 7 of the 11 children who received chemotherapy required more than one regimen. This retrospective study shows that management of tumor-associated cysts in low grade gliomas remains challenging. (Wolf D, Cohen KJ, Neuro-oncology vol 14, 2012, issue suppl i69-i81, abstract LG-35)

2.3 Interferon Alpha

Mechanism of Action: The interferons (IFN) are a family of glycoproteins with antiproliferative, antiviral, and immune-modulating capabilities. Studies have shown that they are involved in control of cell function and replication, but their mechanisms of action are not fully known. They bind to cell surface receptors, resulting in a signal transduction that induces or suppresses gene expression.

The interferons induce protein synthesis, inhibit mitotic activity, modify cell membranes and regulate immune effector cells. They block cell transition from G0/G1 into the S phase of the cell cycle. They are known to suppress the expression of the c-myc and c-fos proto-oncogenes, and receptors for certain growth factors. Other effects of peg interferon alpha-2b include inhibition of viral replication in virus-infected cells, the suppression of cell cycle progression/cell proliferation, induction of apoptosis, anti-angiogenic activities, and numerous immunomodulating activities, such as enhancement of the phagocytic activity of macrophages, activation of NK cells, stimulation of cytotoxic T-lymphocytes, and the upregulation of the Th1 T-helper cell subset.
Peginterferon raises concentrations of effector proteins such as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and causes reversible decrease in leukocyte and platelet counts.

The type I interferons (IFN-alpha and IFN-beta) are also negative regulators of cell growth and can modify cell differentiation. Interferon-alpha can be induced by foreign cells, tumor cells, and virus-infected cells that stimulate B- lymphocytes, null lymphocytes and macrophages.

Numerous clinical trials have been performed investigating the utility of interferons for viral diseases and cancer. The interferons have been approved by the FDA for several clinical indications, including hairy cell leukemia, chronic myelogenous leukemia and melanoma.

Interferon therapy has been associated with a variety of side effects including an acute flu-like syndrome with malaise, fever and chills, irritability, fatigue and musculoskeletal pain. Longer-term effects include depression, anorexia, headache and cognitive impairment. At least some of these effects are felt to be dose-related.

Clinical studies using alpha, beta and gamma interferons have been performed on patients with malignant brain tumors using different methods of administration, including intravenous, subcutaneous, intramuscular, intrathecal and intracavitary. The results have been mixed.

2.4 Peg-interferon:

There are 2 brand names of peginterferon alpha 2b on the market, both from the same manufacture.

-PEG-Intron™(SCHERING-PLOUGH/MERCK) PEG-Intron™is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol (PEG), that was FDA-approved in January, 2001 for use in patients with Hepatitis C.**-Sylatron (SCHERING-PLOUGH/MERCK)** is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The average molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the SYLATRON molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alfa-2b is approximately 0.7 x 10^8 international units/mg protein. Initial approval for the adjuvant treatment of melanoma.

Interferon alfa-2b is a water-soluble protein produced by recombinant DNA techniques from the bacterial fermentation of an E. Coli strain with a genetically engineered plasmid containing an interferon gene from human leukocytes. (package insert)

Pegylation increases the biologic half-life of the compound, enabling it to be administered once weekly, and also reduces the peaks and troughs in blood levels. Pegylated interferon uses a 12 kilodalton PEG that is attached to interferon in a linear fashion. Maximal serum concentrations occur between 15-44 hours after dosing, and are sustained for up to 72 hours. The mean elimination half-life is 22-60 hours in patients with Hepatitis C virus infection. Renal elimination accounts for 30% of the clearance. Although there is extensive data on the use of Pegylated interferon in adults with hepatitis C and melanoma, there is limited data on its use in children or in patients with other cancers.

2.5 Clinical Data of Interferon in Cancer

2.5.1 Interferon and Gliomas: In gliomas, Nagai et al reported a partial response in 2 / 9 patients with glioblastoma treated with rIFN-alpha A, and 40% response rate (1 complete response, 7 partial responses) in 20 patients with glioblastoma treated with human fibroblast interferon-beta. [10]

Two phase II trials of temozolomide with interferon alpha-2b (pegylated and non-pegylated) in patients with recurrent glioblastoma multiforme demonstrated PFS at 6months was 31% for 29 evaluable patients in the IFN study and 38% for 26 evaluable patients in the PEG group. In recurrent GBM patients, in combination with both studies of standard dose TMZ with either IFN or PEG showed improved efficacy when compared to reports using TMZ alone. The grade 3 or 4 toxicities more common were leucopenia and thrombocytopenia. Grade 3 or 4 fatigue occurred in 18% of patients on both studies. Lymphopenia was not seen frequently. [11]

In a pediatric study involving children with recurrent malignant tumors treated with recombinant interferon-ß, 2 of 9 children with brainstem gliomas had a partial response (>50% reduction in tumor size) and 2 children had prolonged disease stabilization (1 child for 3.5 years).[12]

In a follow-up study of pediatric patients with brainstem gliomas treated with IV recombinant ß-interferon during hyperfractionated radiation therapy, 13 of 32 patients required dose modifications due to hepatic or hematologic toxicity. [13]

The optimal dosing for interferon alpha has not yet been established, although it has been used to treat a variety of neoplasms. It has traditionally been administered in high doses = 3,000,000 U/m2, 2-3x/week. Significant side effects have limited its use.

In one study in which interferon alpha-2a was administered to pediatric patients with recurrent or progressive craniopharyngiomas at a dose of 8,000,000 U/m2 daily for 16 weeks, followed by the same dose 3 times a week for an additional 32 weeks, the need for radiation therapy was significantly delayed in 6 of 15 patients, but more than 50% of the patients experienced significant toxicity requiring intervention or dose reduction within the first 8 weeks of therapy. [14]

2.6 Pegylated interferon in Clinical Studies and Case Series

-Pegylated interferon in Children with Diffuse Intrinsic Pontine Gliomas: Warren et al conducted phase II trial of Pegylated interferon for children with diffuse intrinsic pontine glioma (DIPG). Pegylated interferon was administered as a low-dose of 0.3 μg/kg continuous exposure beginning 2 to 10 weeks after the completion of radiation therapy until they developed disease progression. Thirty-two patients (median age, 5.3 years; range, 1.8-14.8 years) received a median of 7 cycles of therapy. PEGylated interferon was well tolerated. The 2-year survival rate was not significantly improved compared with the historic cohort. The median time to progression was 7.8 months. DIPG compared with an historic control population, it did delay the time to progression. The scientific reason for the low dose of interferon was the anti-angiogenic affect seen in animal models. [15]

-Pegylated interferon in Children with Cystic Craniopharyngiomas:

In a different type of brain tumor, however it carries similarities to LGG since both can have cystic components, the use of Pegylated interferon has been described. Recently, a case series of 5 children with recurrent craniopharyngiomas treated with Pegylated interferon-alpha-2b was published. Their age ranged from 9 to 15 years treated for up to 2 years with subcutaneous injections of Pegylated interferon at a dose of 1-3 μg/kg/week. Tumor response was assessed using MRIs. All 5 patients had stable disease or responses to the Pegylater interferon. One patient experienced increase in the predominantly cystic tumor after 3 months of treatment, followed by a complete response with no recurrence for greater than 10 years. Another patient had complete disappearance of the predominantly cystic component after 4 months of treatment, and a small residual calcified mass remains 5 years later. The third patient experienced a complete response after 7 months of treatment and remains without disease 19 months after starting treatment. The fourth patient experienced a 30% decrease in tumor size after 4 months of treatment, which was maintained for 12 months at which point the cyst began to increase in size. The final patient had stable disease 6 months after starting treatment. These case series are the basis for a clinical trial for recurrent craniopharyngiomas to evaluate the response to Pegylated interferon. Based on the responses, it could be possible to potentially delay or avoid the need for radiation therapy in the future. [16]

-Pegylated interferon in Children with Progressive Neurofibromas: The safety and tolerability of pegylated interferon was evaluated in a phase I trial in patients unresectable progressive or symptomatic plexiform neurofibromas (PN).Thirty patients (median age 9.3 years) were treated. All 5 patients at the 4.5 μg/kg DL came off study or required dose reductions for behavioral toxicity or fatigue. During the first 4 weeks, no dose-limiting toxicity (DLT) was seen in patients treated at the 3 μg/kg dose level (DL), however similar DLT on the 3 μg/kg DL became apparent over time. At the 1.0 μg/kg DL, there was 1 DLT (myoclonus) in 12 patients enrolled. 11/16 patients had pain improvement and 13/14 patients had a decrease in size of a palpable mass. Volumetric analysis had a 15%-22% decrease in volume in 5/ 17 patients (29%). The dose recommended for phase II of pegylated interferon for pediatric patients is 1 μg/kg/wk. This trial is currently ongoing.[17] (www.clinicaltrials.gov)

2.7 Dose and Schedule

The type I interferons down-regulate the expression of pro-angiogenic molecules, including bFGF, IL-8, MMP-2 and MMP-9. Systemic chronic administration of IFN-a or IFN-ß has been shown to produce regression of vascular tumors by down-regulation of mRNA expression and protein production of the angiogenic factor, bFGF23.

This effect requires long term exposure to IFNs, as has been demonstrated clinically and in vitro. Through in vitro and animal model, Slaton et.al have demonstrated that daily administration of interferon alpha-2a, at doses far below maximally tolerated doses, produced the most significant inhibition of tumor growth, tumor vascularization, and maximal inhibition of angiogenesis-regulating genes. His experiments demonstrated that when human bladder cancer cell lines were implanted into the bladder of mice and the mice were injected subcutaneously daily, 1x/ week or 2x/ week for 4 weeks with interferon alfa-2a. Examination and evaluation after 4 weeks demonstrated that interferon alfa-2a administered daily produced superior anti-proliferative and anti-angiogenic activities compared to an equivalent weekly dose administered 1, 2 or 3 X/week.

In a comparison of escalating daily doses of interferon alfa-2-a (2500-50,000 units/dose), maximal inhibition occurred at a dose of 5000 or 10,000 units/day. Administration of higher doses failed to produce significant anti-angiogenic effects. [18]

2.7.1 Doses for Pegylated interferon

-For patients with chronic hepatitis as a monotherapy the dose is 1 mcg/kg/Week SC x1 year.

-For patients with melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy, the doses used are 6mcg/kg/week subcutaneous for 8 doses, then 3 mcg/kg/week SC for up to 5 yr. Rotating the injection sites.

-Phase I study in patients with neurofibromatosis related plexiform neurofibromas had a recommended dose for phase II of 1mcg/kg/week. [17]

-The doses used for the patients treated in the series with recurrent craniopharyngioma ranged from 1 to 3 mcg/kg/dose.

-For this trial, **the dose is 1 mcg/kg/dose**. There are specific criteria for reduction of the dose based on toxicity. Two dose modifications have been permitted.

2.8 Imaging

Imaging of the tumor will be assessed with MRI of brain and /or spine with and without contrast performed on a 1.5 or 3T scanner. Progressive disease will be defined on the basis of a comparison of the baseline scan to the scan demonstrating best response. All axial images should be obtained in a plane parallel to a line intersecting the bottom of the genu and of the splenium of the corpus callosum to assure consistency of imaging plane. Coronal images should be obtained in a plane perpendicular to the axial images.

1) Axial diffusion tensor imaging whole brain

2) Sagittal, volumetric T1-weighted, gradient echo whole head

3) Axial T2-weighted fast spin echo (FSE) whole head

4) 3D Coronal FLAIR.

5) Coronal T2-weighted fast spin echo (FSE), fat saturated through the orbits and chiasm.

6) Axial T2-weighted fast spin echo (FSE), fat saturated through the orbits and chiasm.

7) Axial volumetric T1-weighted gradient echo post contrast whole brain.

8) Axial Oblique T1-weighted Fat Suppressed gradient echo post contrast, optic nerves and chiasm.

9) Coronal T1-weighted Fat suppressed gradient echo post contrast, optic nerves and chiasm. If imaging of the spine is needed, axial and sagittal T2 and post contrast T1 weighted images will be acquired. Diffusion images of the spine will be obtained if clinically indicated. Volumetric studies for MRI of the brain will be obtain to better evaluate the cystic component of the
Low grade gliomas and be able to evaluate responses to the therapy.
These sequences are the minimum required to evaluate the response to the treatment. Additional sequences such as MR spectroscopy can be obtained if clinically indicated per institutional protocols.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient registration

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. A registration packet is available from the study coordinator to assist with registration requirements for this protocol. The Aflac Cancer Center CRO will provide electronic confirmation of registration and a study number will be assigned to the patient prior to begin treatment. The study number will be used to identify the patient in all future communications/interactions. An email confirming eligibility will be sent to the Study PI, and Co-PI. The date protocol therapy is projected to start must be no later than 14 calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.1.2 IRB Approval

Emory IRB approval of this study is to be provided to the Aflac CRO prior to any patient enrollment.

3.1.3 Reservation and Contact Requirements

Investigators should refer to the Emory IRB website to determine if the study is currently open for accrual and listed as active. Before enrolling a patient on study, a reservation must be made at the Aflac CRO.

Patients must be enrolled within 14 calendar days of making a reservation.

Eligible patients can make a reservation by contacting the Clinical Research Office, Monday through Friday, 8:00 am-4:30 pm Eastern Standard Time at (404) 824-2778 (phone) except holidays. Calls will be returned within one business day. The appropriate research coordinator will review preliminary eligibility by phone before forwarding a registration packet. The information requested in the registration packet must be completed. The signed informed consent statement along with the documentation confirming eligibility must be faxed to (404) 785-9248. Upon receipt of the completed registration packet, the research coordinator at Children's Healthcare of Atlanta will assign a unique study subject number.

3.1.4 Timelines Summary

All pre-treatment evaluations should be performed within **14 days** prior to enrollment and **30 days** for baseline MRI brain and/or spine. From the reservation to enrollment a maximum of 14 calendar days. From enrollment to start therapy maximum 14 calendar days. Patients must not receive any protocol therapy prior to enrollment.

3.1.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient’s parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.1.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.1.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be faxed immediately following enrollment to the Aflac Cancer Center CRO at 404-785-9248.

3.2 Eligibility Criteria

All clinical and laboratory studies to determine eligibility must be performed within **14 days** prior to enrollment, except MRI brain and/or spine within **30 days** prior to enrollment. If more than 14 calendar days elapse between the date eligibility studies were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility (labs may again be repeated within 48-72 hours), then the patient is off protocol therapy. Imaging studies are required within **30 days** prior to enrollment.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

3.2 INCLUSION CRITERIA

3.2.1 Age

Patients must be older than 3 years and less than or equal to 25 years of age at the time of enrollment

3.2.2 Neurofibromatosis

Patients with neurofibromatosis are eligible.

3.2.3 Diagnosis

Histologic confirmation is not required for this if the patient has NF-1 with MRI findings consistent with optic pathway glioma or JPA. Any other tumors will need histological confirmation, either at the time of diagnosis or at the time of recurrence. The histological diagnosis includes WHO grade I JPA.

3.2.4 Measurable Disease

Patients must have measurable residual disease, defined as tumor that is measurable in two or three perpendicular diameters on MRI. For a lesion to be considered measurable, it must be at least twice the slice thickness on MRI (i.e visible on more than one slice)

3.2.5 Brain and/or Spine MRI

All patients must have a brain MRI with and without contrast (gadolinium) within **30 days** prior to study enrollment. All patients with history of spinal or leptomeningeal disease and those patients with symptoms suspicious of spinal disease, must have a spine MRI with contrast (gadollinium) performed within **30 days** prior to study enrollment. Lumbar Puncture is necessary if there is evidence of tumor dissemination on the MRI of spine.

3.2.6 Performance status

Performance Level: Karnofsky >or equal to 50% for patients > 10 years of age or Lansky > or equal to 50 for patients < 10 years of age (Appendix I). Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.2.7 Prior therapy

- 3.2.7.1 No limit in the number of previous surgical resections.
- 3.2.7.2 No limit to number of prior anti-cancer regimens, including chemotherapy, biologic agents, immunotherapy, vaccines, monoclonal antibodies or radiation therapy. Patients who have received prior radiation therapy for this tumor are eligible. There should be at least 2 yearstime since the completion of radiation therapy.

3.2.8
Patients must have recovered (to CTC v.5.0 ≤ Grade 1 unless indicated below) from the acute toxic effects of all prior chemotherapy, immunotherapy prior to entering this study, with the exception of alopecia, weight changes and Grade I or II lymphopenia.

a -Myelosuppressive chemotherapy: Must not have received within 3 weeks of enrollment onto this study (6 weeks if prior nitrosourea).

B -Biologic (anti-neoplastic agent): At least 7 days must have elapsed since the completion of therapy with other biologic agents. For other biologic agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. **The duration of this interval must be discussed with the study chair.**

c-Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. Specifically for bevacizumab 36 days after the last dose.

d -Resection: At least 3 weeks from the last surgical resection, prior to start study drug.

e- Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.

g- Radiation therapy (RT): Patients must have had their last fraction of cranial or craniospinal Radiation ≥ 24 months prior to study entry.

f. Study specific limitations on prior therapy:
1) Patients who have received Poly-ICLC are eligible for this trial if all acute Poly-ICLC -related toxicity has resolved.

2) Patients must not have received Pegylated interferon previously.

3.2.9 Concomitant Medications Restrictions

a. Growth factor(s): Must not have received within 2 weeks of entry onto this study.
b. Steroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior enrollment in the study.

3.2.10 Organ Function Requirements

- Hepatic function: Patients must have adequate liver function, defined as
    - Total bilirubin <2.0x the upper limit of normal and
    - Direct bilirubin within normal limits and
    - SGPT (ALT) <2.5 x the upper limit of normal.
    - Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin but they must have an indirect bilirubin of <6mg/dl, and a direct bilirubin of <0.5mg/dl in order to be eligible. (Gilbert syndrome is found in 3-10% of the general population and is characterized by mild, chronic hyperbilirubinemia in the absence of liver disease or overt hemolysis).

- Hematological function: Patients must have adequate bone marrow function defined as:
    - peripheral absolute granulocyte count of >1000/mm3,
    - hemoglobin >8 gm/dL, Patients may be transfused with RBC's
    - platelet count >100,000/mm3. Independent of transfusion.

- Renal function: Patients must have an age-adjusted normal serum creatinine (see below) OR a creatinine clearance or GFR >/= or more than 60 mL/min/1.73 m2.

Age (years)	Maximum Serum Creatinine (mg/dl)
<5	0.8
5<age<10	1.0
10<age<15	1.2
>15	1.5

- Adequate Pulmonary function defined as:
    - no evidence of dyspnea at rest and pulse oxymetry >94% .

3.2.11 If history of depression or psychiatric illness, has to be well controlled with antidepressants and/or under psychiatrist/ psychologist care.

3.3 EXCLUSION CRITERIA

3.3.1

Patients who are receiving concurrent chemotherapy, or who are currently receiving other investigational chemotherapeutic agents or concurrently receiving radiation.

3.3.2

Patients with a known hypersensitivity to interferon-alpha.

3.3.3

Prior use of Pegylated interferon or interferon.

3.3.4

Less than 2 years since completion of radiation therapy.

3.3.5

Pregnant or breast-feeding females are excluded because the effects of pegylated interferon alfa-2b on the unborn fetus are unknown

3.3.6

Patients with clinically significant unrelated systemic illness (including autoimmune disease, serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) which in the judgment of the Principal or Associate Investigators would compromise the patient's ability to tolerate this therapy or are likely to interfere with the study procedures or results.

3.3.7

Dental braces or prosthesis that interferes with MR imaging.

3.3.8

History of noncompliance to medical regimens.

3.3.9

Patients unwilling to or unable to comply with the protocol.

3.3.10

Patients with a positive history of Hepatitis B or Hepatitis C.

3.3.11

Male patient whose sexual partner(s) are women of childbearing potential who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment.

3.3.12

Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period. Close contact with those who have received attenuated live vaccines should be avoided during treatment with pegylated interferon. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

3.3.13

Patient with diagnosis of Diffuse Intrinsic Pontine Glioma.

3.4 Regulatory

3.4.1
All patients and/or their parents or legal guardians must sign a written informed consent.
The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and benefits, and potential alternative therapies will be carefully explained to the patient, the patient's parents or guardian if he/she is a child, or previously assigned DPA and a signed informed consent document will be obtained prior to entry onto the study.

The PI or an associate investigator on the trial will obtain consent. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and verbal assent will be obtained. The parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent.

3.4.2
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures **(+/- up to 5 days**) from protocol directed therapy (and up to 1 week for surgery) and/or disease evaluations for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable. If an unavoidable departure occurs, patients should continue to follow the roadmap and diary and get assessments **within the 5 day** period, with the exception of course 1.

4.1 **Overview of the treatment plan**

Treatment with pegylated interferon alpha-2b must begin within 14 days of patient enrollment. Patients may be pre-medicated as needed with acetaminophen 10-15 mg/kg (maximum 650 mg per dose) or ibuprofen 10 mg/kg within 1 hour of receiving Pegylated interferon. The patients can continue on either acetaminophen or ibuprofen for up to 48 hours after Pegylated interferon injection. The maximum dose of ibuprofen in a 24-hour period will be 40 mg/kg. Ibuprofen for Adolescents and Adults the maximum daily dose: 2.4 grams in 24 hours. Premedication is optional.

Each cycle of therapy will consist of pegylated interferon alfa-2b administered subcutaneously once weekly **(+/- 5days**) for 4 weeks for up to 2 years. Each dose should be administered on the same day

each week. There will be no breaks between cycles. Total number of cycles 26. Each dose is 1µg/kg subcutaneously. Nursing staff will instruct the patients or their caregivers regarding sites of injection and injection technique. Teaching needs to be documented. Rotating the sites of injection is strongly recommended.

Patients and/or their caregivers will be asked to maintain a diary (Appendix 5) documenting the dose of pegylated interferon alpha-2b given, site of administration and any side effects. This diary will be reviewed at each clinic visit. Patients will return to the Aflac clinic prior to start next cycles.

Doses could be rounded up to the nearest upper 5mcg for easier administration. For patients whose weight is greater than 150kg the maximum dose of Pegylated interferon to be administered is 150mcg/dose/ week.

MRI brain and /or spine will be performed as a baseline within **30 days** of enrollment and subsequently every 3 cycles.

See section 7.1 for required observations prior to start therapy.

4.2 **Concomitant therapy restrictions**

4.2.1
Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy can **NOT** be administered to patients while on this study. The use of alternative or complementary therapies is discouraged.

4.2.2
Radiotherapy is not permitted.

4.2.3
Filgrastim (G-CSF) may be used at the treating physician's discretion in patients with severe neutropenia (i.e. ANC <500/µL) to enhance neutrophil recovery when clinically indicated (for culture proven bacteremia or invasive fungal infections). Prophylactic or routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

4.2.4
Corticosteroid therapy is permissible only for the treatment of increased intracranial pressure or physiologic replacement. The lowest dose consistent with good medical management should be used. Corticosteroids should **NOT** be used as an antiemetic due to their effect on the blood brain barrier.
Patients on steroids who require an increase in steroid dose for worsening neurologic symptoms should have an MRI performed within **5 days** to rule out tumor progression.

4.2.5
Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary. PCP prophylaxis is recommended following the institutional guidelines when absolute lymphocyte count is below 1200.

4.2.6

Anticonvulsants may be administered as clinically indicated. However, it is recommended to avoid enzyme inducing anticonvulsants.

For Supportive Care Guidelines use Children's Oncology group guidelines, see: https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.3 **Pegylated interferon Administration**

Pegylated interferon will be administered weekly **(+/- 5 days**) at a dose of 1mcg/kg/dose via subcutaneous injection, approximately at the same time every week.
It is important to rotate the injection sites. Teaching will be done to the parents/guardian/patient in the first and/or second injection so the family will learn the technique and can continue to do it at home. Family/guardian will be provided with diaries to document compliance and side effects.
Patients may be pre-medicated with acetaminophen or ibuprofen. Specifically, patients can receive acetaminophen 10-15 mg/kg (maximum 650 mg per dose, maximum dose 4 grams/24 hours) or ibuprofen 10 mg/kg within 1 hour prior to receiving PEPegylated interferon. The patients can continue on either acetaminophen or ibuprofen for up to 48 hours after the pegylated interferon injection as needed. The maximum dose of ibuprofen in a 24-hour period will be 40 mg/kg or patients with weight for more than 45 kg is 2.4 grams/24 hours. Premedication is optional.

Pegylated interferon will begin a Cycle on Day 1 if **ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL** (transfusion independent).
Dose calculations should be based on actual weight and adjusted as necessary prior to each cycle.
The maximum dose is 150 mcg.
Note: The calculated dose should be rounded to the nearest highest 5mcg of the prescribed dose for convenience of administration. Each cycle is 28 days. The total duration of the trial is 2 years a total of 26 cycles.
See Section 5.0 for Dose Modifications Based on Toxicities.

The therapy delivery maps (TDMs) for this cycle are on the next pages

Following completion of the first cycle, the Pegylated interferon cycle is repeated weekly for up to a total of 26 cycles, as tolerated and in the absence of disease progression (see Section 10.4 for Response Evaluation). If disease progression occurs, the patient will be taken off protocol therapy.
Subsequent Pegylated interferon cycles should begin on Day 29 or when ANC ≥ 1,000/µL, platelet count ≥ 100,000/µL (transfusion independent), whichever occurs later.

Therapy Delivery Plan

Pegylated interferon Dose 1mcg/kg/dose 4 consecutive weeks (28 days) will constitute one cycle. This therapy delivery map relates to all cycles of Pegylated interferon	Patient Name:_____ DOB_____

Criteria to start a cycle: ANC ≥ 1,000/µL and platelet count ≥ 100,000/µL (transfusion independent). This cycle lasts 28 days.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Pegylated interferon	SQ	1 mcg/kg/dose Max dose is 150 mcg/dose	weekly **(+/-5 days)**	Premed with Tylenol or ibuprofen as needed.	a. CBC with differential b. CMP, Magnesium, Phosphorous, Calcium, Uric Acid. c. PT/PTT d. Urinalysis e. Performance Score f. Hx, PE, Neuro Exam, Wt, Ht, VS. g. pregnancy test h. Assessment of clinical toxicity/ adverse events i. QOL questionnaire j. MRI of brain and/or spine k. Am Cortisol, Free T4, TSH. l. Ophthalmology Evaluation m. Pegylated interferon Diary n. lumbar puncture (See section 7.1) OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Cycle- 28 Days (+/- 5)	**Date Due**	**Date Given**	**Chemotherapy Dose**	**Studies**
1				**a-i, k, l, o**
				a, b, e, f, h, m
2				**a, b, e, f, h, m**

Cycle- 28 Days (+/- 5)	Date Due	Date Given	Chemotherapy Dose	Studies
3				**a, b, e, f, h, m**
4				**a, b, d, e, f, h, i, j, m, n**
5				**a, b, e, f, h, m**
6				**a, b, e, f, h, l, k, m**
7				**a, b, d, e, f, h-j, m, n**
8				**a, b, e, f, h, m**
9				**a, b, d, e, f, h, m**
10				**a, b, d, e, f, h-j ,m, n**
11				**a, b, e, f, h, m**
12				**a, b, e, f, h, k, l, m**

Cycle- 28 Days (+/- 5)	Date Due	Date Given	Chemotherapy Dose	Studies
13				**a, b, d, e, f, i, j, m, n**
14				**a, b, e, f, h, m**
15				**a, b, d ,e, f, h, m**
16				**a, b, d, e, f, h-j, m, n**
17				**a, b, e, f, h, m**
18				**a, b, e, f, h, l, k, m**
19				**a, b, d, e, f, h-j, m, n**
20				**a, b, e, f, h, m**
21				**a, b, d, e, f, h, m**
22				**a, b, d, e, f, h-j, m, n**

Cycle- 28 Days (+/- 5)	Date Due	Date Given	Chemotherapy Dose	Studies
23				**a, b, e, f, h, m**
24				**a, b, d, e, f, h, i, k, l, m**
25				**a, b, d e, f, h- j, m, n**
26				**a, b, e, f, h, m**
END of therapy				

a- Obtain weekly. If patient develops grade 4 neutropenia, CBCs should be checked **every 3 to 4 days** until recovery to grade 3.

n-Obtain prior to starting cycle one only for females of childbearing potential. For the rest of the protocol follow institutional policies about pregnancy testing.

j-Obtain after every third cycle and as clinically indicated. MRI of spine obtain at same time points as brain MRI, for patients with known or suspected spinal disease.

See Section 5.0 for Dose Modifications for Toxicities

For supportive care guidelines see:

http://members.childrensoncologygroup.org/prot/reference_material.asp

4.4 **Criteria for Starting Subsequent Courses of Treatment**
A course may be repeated every 28 days, up to a total of 2 years if the patient has at least stable disease and has again met laboratory parameters.
Patients who complete a treatment cycle may receive another cycle if:

- Disease Status: the patient has no evidence of progressive disease or in the opinion of the investigator, the patient is benefiting from the therapy with pegylated interferon alfa-2b) as evidenced by a decrease in tumor-related symptoms.
- Toxicity: the patient has not experienced any toxicity that meets off-study criteria as described in Section 5.0
- Patients will not be allowed to have a dose escalation after dose reduction due to toxicity.

5.0 DOSE MODIFICATIONS FOR TOXICITY

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of Pegylated interferon must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described below. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Pegylated interferon dose level modification guidelines

Patients who experience significant toxicity as listed in section 5.0 will have the dose reduced by 25% of the dose on subsequent cycles. Two dose reductions are allowed, as long as there is no evidence of progressive disease (see section 10.4) Patients who again experience dose modifying toxicity after 2 dose reductions will be taken off protocol therapy.

Dose Modification for Toxicity	**Dose and schedule**
Standard dose	1mcg/kg/dose
Dose Modifications	First Dose Modification: reduction by 25% of dose
	Second Dose Modification: reduction by 50% of dose
	Permanently discontinue if unable to tolerate second dose modification

*For patients whose weight is greater than 150kg, the maximum dose of Pegylated interferon to be administered is 150mcg/dose/week. (See table above)

5.1 **Non-hematological Toxicities**

The dose of Pegylated interferon will be reduced for any of the following toxicities at least possibly attributed to Pegylated interferon
• Any Grade 4 non-hematological toxicity
• Any Grade 3 non-hematological toxicity with the specific exclusion of:

- Grade 3 nausea and vomiting controlled by antiemetics
- Grade 3 fever or infection
- Grade 3 fever, myalgias, arthralgias, and rigors.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.

• Any Grade 2 non-hematologic toxicity that persists for > 3 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption

• Any other adverse event attributed to Pegylated interferon that requires treatment interruption for > 3 days or which recurs upon drug re-challenge and requires treatment interruption.

• Non-hematological toxicity that causes a delay of more than 14 days between treatment cycles.

Patients who experience non-hematologic toxicity should have appropriate laboratory testing at least weekly until the toxicity has resolved.

If the toxicity does not return to less or equal than Grade 1 within **14** days, the patient will no longer be eligible to receive treatment on this study.

If the toxicity returns to less or equal to Grade 1 within 14 days, the patient may restart the study drug at initial dose modification once weekly and remain at that dose.

If the same Grade 3 or 4 non-hematologic toxicity recurs, hold drug and wait until toxicity returns to less or equal to Grade 1. If toxicity returns to less or equal to grade 1 within 14 days, the patient may restart the study drug at second dose modification and remain at that dose. If the toxicity does not return to less than Grade 1 within **14** days, the patient will no longer be eligible to receive treatment on this study.

If the same Grade 3 or 4 non-hematological toxicity recurs and it is felt to be due to the study drug, the patient will no longer be eligible to receive pegylated interferon alfa-2b.

5.2 **Hematologic Toxicity**

The dose of Pegylated interferon will be reduced for any of the following toxicities:
• Grade 4 decreased neutrophil count (neutropenia) > 5 days duration
• Grade 4 decreased platelet count (thrombocytopenia) > 5 days duration
• ≥ 2 platelet transfusions per cycle for platelet counts < 30,000/µL
• ≥ 14 day delay in starting subsequent cycles due to low ANC (< 1,000/µL or low platelet count (less than 100,000/µL.)
Patients who experience hematologic toxicity should have appropriate laboratory testing at least weekly until the toxicity has resolved.

6.0 DRUG INFORMATION

6.1 Pegylated Interferon (Pharmaceutical Information PEG-Intron™ , Other Names: peg-interferon alfa-2b)

Chemical Structure: PEG-INTRON™is a covalent conjugate of recombinant interferon alfa-2b with polyethylene glycol (PEG). It is derived using recombinant DNA technology on a genetically engineered Escherichia coli bacterium that contains an interferon gene from human leukocytes.

Molecular weight: 31,000 daltons

Manufactured by: Schering-Plough/ MERCK

How supplied: PEG-INTRON™is a lyophilized powder supplied in 2 ml vials for subcutaneous use. Each vial contains 74 µg, 118.4 µg, 177.6 µg, or 222 µg of PEG-INTRON™, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose and 0.074 mg polysorbate 80. Following reconstitution with 0.7 ml of supplied diluent (Sterile water for injection, USP), each vial contains PEG-INTRON™at strengths of 100 µg/ml, 160 µg/ml, 240 µg/ml, or 300 µg/ml, respectively.

SYLATRON:

Manufactured by: Schering-Plough/MERCK

Preparation and Administration

Reconstitute SYLATRON with 0.7 mL of Sterile Water for Injection, USP.

Reconstitution of SYLATRON Single-Use Vials		**Diluent (Sterile Water for Injection, USP)**	**Deliverable Product and Volume**		**Final Concentration**
SYLATRON Single-Use Vial					
200 mcg*	add	0.7 mL	=	200 mcg in 0.5 mL	40 mcg/0.1 mL
300 mcg†	add	0.7 mL	=	300 mcg in 0.5 mL	60 mcg/0.1 mL
600 mcg‡	add	0.7 mL	=	600 mcg in 0.5 mL	120 mcg/0.1 mL

*Total vial content of SYLATRON is 296 mcg.
†Total vial content of SYLATRON is 444 mcg.
‡Total vial content of SYLATRON is 888 mcg.

Swirl gently to dissolve the lyophilized powder. **DO NOT SHAKE.**

- Visually inspect the solution for particulate matter and discoloration prior to administration. Discard if solution is discolored, cloudy, or if particulates are present.
- Do not withdraw more than 0.5 mL of reconstituted solution from each vial.
- Administer SYLATRON subcutaneously. Rotate injection sites.
- If reconstituted solution is not used immediately, store at 2°-8°C (36°-46°F) for no more than 24 hours. Discard reconstituted solution after 24 hours. **DO NOT FREEZE.**

Storage and Stability:

The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2-8° C. The reconstituted solution contains no preservative, is clear and colorless**.** Do not freeze.

Administration: Pegylated interferon will be administered subcutaneously once weekly, on the same day each week. Rotating sites. **Guidelines for administration:**

Education to the parents/patient and or caregivers will be provided on how to measure and draw the adequate amount of medication and subcutaneous administration will be taught to the family. Keep refrigerated. Procedures for proper handling and disposal of hazardous/anticancer drugs should be considered.

Adverse reactions reported with INTERFERON ALFA (Package insert)

CNS: neurologic deficits, headache, decreased mental status, dizziness, impaired memory, impaired concentration, paresthesia, confusion, change in taste or smell, irritability, insomnia, anxiety, change in behavior, visual disturbance, seizures, gait disturbances, hallucinations, encephalopathy, psychomotor retardation, coma, stroke, transient ischemic attacks

Psychiatric: agitation, manic behavior, psychotic reactions, depression, suicidal ideationFlu-like symptoms: fatigue, myalgia, arthralgia, fever, chills, asthenia, sweating, leg cramps, malaise

Gastrointestinal: nausea, vomiting, diarrhea, anorexia, abdominal pain, flatulence, impaired digestion, gingival bleeding, pancreatitis, colitis, gastrointestinal hemorrhage, stomatitis, abdominal fullness, hypermotility, hepatitis, dysphasia

Skin: injection site reaction, alopecia, hair change, rash, dry skin, pruritus, hematoma, psoriasis, eczema, seborrhea, bruising

Pulmonary: dryness or inflammation of the oropharynx, epistaxis, rhinitis, sinusitis, coughing, dyspnea, pneumonitis

Cardiovascular: rhythm disturbances, chest pain, hypotension, hypertension

Laboratory: neutropenia, thrombocytopenia, anemia, elevated liver function tests, proteinuria.

Other: conjunctivitis, menstrual irregularity, syncope, sexual dysfunction, coagulopathy, weight loss, night sweats, thyroid dysfunction, diabetes

Frequency of Side Effects of Pegylated Interferon

Likely or Common Happens to 21 to 100 children out of every 100	Less Likely or Occasional Happens to 5 to 20 children out of every 100	Rare but Serious, Happens to less than 5 children out of every 100.
• Injection site inflammation and reaction (bruise, itchiness, irritation) • flu-like syndrome (headache, malaise,	• dry skin • pharyngitis • impaired concentration • confusion • dizziness • decrease neutrophil • decrease in platelet	• dry mouth • sweating excessively • blurred vision/conjunctivitis • neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, aggressive behavior

fatigue, myalgia) • fever • alopecia • depression • anxiety/emotional lability/irrritability • joint pain • nausea/vomiting • muscle pain • insomnia • rigors • irritation of the liver • anorexia/decrease in appetite •	counts • hypothyroidism • hyperthyroidism • Hyperglycemia • abdominal pain • bloody diarrhea • chest pain • weight loss • gingival bleeding • proteinuria • flushing	• psychotic reactions • agitation/nervousness • hypotension, arrhythmia, tachycardia, • cardiomyopathy, angina pectoris, myocardial infarction • Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis • pancreatitis • Development or exacerbation of autoimmune disorders (e.g. thyroiditis, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, psoriasis) • hypersensitivity reactions/ allergic reactions • rash • may impair human fertility • menstrual disorder • ischemic colitis

Drug Interactions (Package Insert).

Drugs Metabolized by Cytochrome P-450**:** When administering Pegylated interferon with medications metabolized by CYP2C8/9 (e.g., warfarin and phenytoin) or CYP2D6 (e.g., ondansetron, flecainide), the therapeutic effect of these substrates may be decreased.

Methadone: Pegylated interferon may increase methadone concentrations. The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased narcotic effect.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 96 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable.

7.1 **Required Clinical, laboratory and Disease Evaluations**

All baseline studies must be performed within **14 days** prior to enrollment and MRI of brain and/or spine within **30 days** prior to enrollment. **Obtain other studies prior to start of subsequent cycles and as otherwise indicated.**

STUDIES TO BE OBTAINED	Pre-study [1] (Baseline)	Prior to Each Cycle	Q2 weeks Cycle 1	Prior to cycle 4,7,10,13 16,19,22,25	Every six months	When patient is removed from protocol Therapy **
History	X	X	X			X
Physical Exam with neurological exam (Wt, Ht and VS)	X	X	X			X
Performance Status	X	X				X
CBC, platelets and differential	X	X	X[5]			X
CMP, magnesium phosphorous, calcium, Uric acid	X	X	X[5]			X
PT, PTT	X					
AM cortisol, Free T4, TSH, (growth hormone if clinically indicated)	X				X	X
Urinalysis / urine dipstick	X			X		X
Urine or serum pregnancy test	X[2]					
MRI of brain w/wo contrast	X[3]			X		X
MRI spine	X[4]			X[6]		X
LP for CSF cytology	X[9]			X[10]		
Opthalmology Evaluation [7]	X				X	X
QOL questionnaire[8]	X			X		X
Pegylated interferon Diary		X	X			X
Assessment of clinical toxicity/adverse events						X

1-Must be performed within 14 days prior to receiving the study drug with the exception of MRI of brain and spine. MRI of the brain and or spine can be done in within **30 days** prior to enrollment.

2-Required for all females of childbearing potential as a baseline study, then continue to follow institutional guidelines regarding pregnancy testing.

3- With and without contrast; within **30 days** prior to enrollment.

4-For patients with a known history of spinal disease, within **30 days** prior to enrollment on the study or when it is clinically indicated by the treating physician.

5-If no > Grade I toxicity during the previous cycle, then every month in subsequent cycles through cycle 27.

6-For patients with history of spinal disease; obtained at the same time points as MRI brain until no evidence of disease on 2 consecutive spine MRIs. Also when patient is removed from protocol therapy.

7-Opthalmology evaluation only needed for patients with optic pathway gliomas. (Sooner than interval designated if indicated by neuro-opthalmologist/opthalmologist)

8- Children younger than 7 years and older will complete the parent survey only. For any child older than 7 years will complete also the patient questionnaire for Quality of life. QOL questionnaires are only available for English speaking patients. They have not been validated in other languages.

9- LP only if there is evidence of tumor dissemination on spine MRI.

10-Repeat only if cytology showed tumor cells at study entry, until you have 2 consecutive negative cytologies.

** To be completed when patient comes off therapy unless it has been completed within the last 14 days and no toxicity greater than grade 1 was found.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

History and Physical Examination: This should include signs and symptoms caused by the tumor/cancer, and determination of performance status or Lanski score. Patients must have a baseline neurological exam and neurological exam at the start of each new cycle. Weight, height and VS must be recorded.

Laboratory Evaluation:

-Hematology: Complete blood count, differential and platelet count every 2 weeks during the first cycle. If the patient does not experience any >Grade 1 hematologic toxicity during the first cycle, a CBC can be performed every 4 weeks on subsequent cycles, and as clinically indicated. If a patient experiences >Grade 1 hematologic toxicity (except for lymphopenia), they will continue to have weekly lab work until they have a cycle with no >Grade 1 toxicity. Following that cycle the lab work will be performed every 4 weeks (+/- 5 days) and as clinically indicated until completion of therapy. If the patient remains on-study beyond this and is hematologically stable, the patient will require lab work prior to every cycle as long as there is no >Grade 1 hematologic toxicity.

-Chemistries: CMP, magnesium, phosphorous, calcium and uric acid every other week during the first cycle. If the patient does not experience any >Grade 1 laboratory toxicity on the first cycle which is possibly, probably, or definitely related to Pegylated interferon, these can be performed every month on subsequent cycles, and as clinically indicated. If a patient experiences >Grade 1 laboratory toxicity they will continue to have weekly lab work until they have a cycle with no >Grade 1 toxicity. Following that cycle the lab work will be performed every 4 weeks and as clinically indicated until end of therapy.

If the patient remains on-study beyond this, the patient will require lab work prior to every cycle as long as there are no >Grade 1 laboratory toxicities.

-Calcium, phosphorous, magnesium and uric acid will be performed prior to each cycle and as clinically indicated.

-PT and PTT will be obtained at a baseline. Obtain later on only if clinically indicated.

-Endocrine Function Tests: First morning cortisol, free T4, TSH every six months or sooner if clinically indicated. Growth hormone testing to be done if clinically indicated.

-Urinalysis or urine dipstick is acceptable. Urinalysis will be obtained if urine dipstick is abnormal. If urine evaluation is normal, then check at the same time points as the brain MRI.

-Urine Pregnancy Test or Serum Pregnancy Test: required for females of childbearing potential. Additional pregnancy test per institutional guidelines. At Aflac, monthly pregnancy test for females of childbearing potential.

Radiology:

MRI of the brain/and or spine will be performed every 3 cycles throughout the duration of the treatment. Initial evaluation will be performed at the end of the cycle #3. Patients with a history of spinal disease will undergo a spine MRI at the same time points until there is no evidence of disease on 2 consecutive spine MRI's. All brain MRIs will include, if possible, diffusion-weighted, dynamic-enhanced, dynamic susceptibility, DT-MRI, and other MR sequences in addition to the standard MR sequences. All MRI's will be reviewed and interpreted with the neuroradiologist.

Quality Of Life Questionnaire:

- We have choosen the Peds**-FACT-Br:** Pediatric - For patients with Brain cancer, ages 7 to 12 year old or greater than 12 years. Additionally, we will include the parent QOL questionnaire. There are 2 versions, for patients younger than 12 years and for patients 12 years or older. To be administered prior to start therapy and q3 months at the same interval as MRIs. See appendix 2A, 2B, 2C and 2D.
- QOL questionnaires are not available for non -English speaking patients and they have not been validated in other languages. QOL questionnaires are not required for non-english speaking patients

Post-Therapy Evaluation

The following tests and procedures should be performed, if possible, at the time a patient comes off therapy, regardless of the reason for coming off therapy, unless the test or procedure has been performed in the past 14 days.

- History and physical examination.
- Performance status.
- Assessment of clinical toxicity/adverse events.
- Laboratory Assessment:
    - Complete blood count, differential and platelet count
    - SGPT (ALT), bilirubin (total and direct), BUN, creatinine, electrolytes, calcium,
    - Magnesium, phosphorus, uric acid.
    - Urinalysis
- MRI of Brain and/or spine.
- QOL questionnaire
- Ophthalmology evaluation

7.2 Follow-up

- See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 **Criteria for Removal from Protocol Therapy**

a) Progressive disease (see definition in Section 10.4).
b*)* Significant toxicity at least possibly attributed to Pegylated interferon despite two dose reductions (as statedin Section 5.0).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of 26 cycles of protocol therapy.
e) Physician determines it is in patient's best interest.
f) Development of a second malignancy.
g) Patient becomes pregnant while on study.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 **Off Study Criteria**

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another treatment study with tumor therapeutic intent.
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 **Sample Size and Study Duration**

This study will enroll patient without NF-1 and patients with NF-1. Based on the established accrual goals and incidence of pediatric low grade gliomas 17 patients can be accrued within 36 months of protocol activation, given an average of 1 patient per 2.1 months. Assuming 15% of patients are not evaluable or eligible, 20 patients total will be required to be enrolled on this study.

9.2 **Study Design**

The study is designed using Simon's two stage optimal design with a power of 80% and an alpha error of 5%. We assume an uninterested response rate of 5% and the promising response rate is 25%.In the first stage of the study, 9 eligible patients will be enrolled. If none responder among the 9 patients, the study terminates and treatment will be determined to have no improvement in the response rate. Otherwise, the study will continue with the second stage in which 8 additional eligible patients will be enrolled for a total of 17 eligible patients. At the end of total patient accrual, at least 3 of 17 eligible patients must

achieve response in order to consider the treatment interesting for further evaluation. Response is considered as either CR or PR or SD.

Optimal Two Stage Design	Optimum Design
First Stage Sample Size (n1)	9
Upper Limit For 1st Stage Rejection of Drug (r1)	0
Maximum Sample Size (n)	17
Upper Limit for 2nd Stage Rejection of Drug (r)	2
Expected Sample Size If Response Probability = P0	11.96
Probability of Early Termination at P0	0.63

9.3 **Methods of Analysis:**

9.3.1 End Points

9.3.1.1 Primary End points:

- Objective response: best response determined from the sequence of objective status described in the section 10 as response criteria.

9.3.1.2 Secondary End Points

- Time to treatment failure (Event free Survival EFS) the time from study enrollment to tumor progression, tumor recurrence, death from any cause or occurrence of a second malignant neoplasm.
- Time to death (Overall survival OS) the time from study enrollment to death from any cause.

9.4 **Analysis of Efficacy**

Each patient will be classified according to their 'best response' for the purposes of analysis of treatment effect. A responder is defined as a patient who achieves a best overall response of CR or PR at any time on the study. If a patient achieves a PR or CR and later has progressive disease or relapse, then the patient will be counted as a responder. The response rate will be calculated as the ratio of the number of patients who demonstrate response (CR or PR) divided by the number of patients evaluable for response. All patients eligible for study who receive any study drug will be considered evaluable for response. Any patient who goes off protocol therapy for any reason (patient/parent/physician choice, adverse event profile, etc.) prior to the first response evaluation will be considered a non-responder.
Disease progression will be based on the results of institutional review. Standard survival methods will be used for analysis of EFS and OS. Analyses include log rank tests and the product-limit (Kaplan-Meier) estimate for estimation of EFS and OS probability.

9.5 **Monitoring for Efficacy**

Patients will be treated with Pegylated interferon on a single arm. We will closely monitor the first 9 patients enrolled. The early stopping criterion and the decision regarding ultimate further interest in this

agent will be based on the number of objective responses and disease progressions. If the early stopping rule is met for no responses in the first 9 patients, the trial will be closed.
A true response rate of 5% is considered inadequate, whereas a true response rate of 25% would be sufficient for further interest in this agent.
The study will be a 2-stage design, with 9 evaluable patients in the first stage and 8 additional evaluable patients in the second stage (17 patients total) with decisions made as follows:

Number of Evaluable Patients	Results	Decision
Stage One: 9 evaluable patients	zero responders	Terminate enrollment with the conclusion the regimen does not demonstrate sufficient disease control
Stage Two 8 evaluable patients	3 responders	Complete the trial with the conclusion the regimen does demonstrate sufficient disease control to proceed with further development.

9.6 **Monitoring for Toxicity**

"Toxic events" will be defined as one in which a patient has two dose reductions and then experiences another significant toxicity as defined in Section 5.0, irrespective of attribution. A two-stage stopping rule will be used to monitor for an excessive number of these toxic events. All patients described below must be evaluable for toxicity. All patients who receive at least one dose of Pegylated interferon will be evaluable for toxicity. A review of treatment feasibility and patient safety will be undertaken if we observe at least 2/9 or 4/17 toxic events. The rule will be met about 4% of the time if the true incidence of toxic event is 10%, and 90% of the time if the true incidence is 30%.

9.7 **Interim Monitoring of Toxic Death**

Toxic death is death predominantly attributable to treatment-related causes. The occurrence of toxic death at any time will be a primary endpoint for safety monitoring. Any toxic death on study will be reviewed with DSMB prior to continuing enrollment on study. The study will be stopped if there is one toxic deaths on study.

9.8 **Analysis of Toxicity**

Estimates will be obtained using life-table methods, with an event defined as the first occurrence of a primary toxicity. Time scale used in the time to first occurrence of a key acute and subacute toxicity is time in days since the start of therapy. Patients who have progression or recurrence of disease will be censored in these analyses. The rates of individual toxicities in each course of treatment, the number of patients who require a dose reduction and number of patients who come off protocol therapy due to toxicity will be summarized using standard descriptive statistical methods. To evaluate hematologic toxicity of long term Pegylated interferon administration adverse event data will be collected using CTCAE version 5.0 toxicity coding. Grade 3 or greater hematologic toxicities will be recorded per reporting period.

9.9 **Subject Accrual**

Subjects of both genders, from all racial and ethnic groups are eligible for this study if they meet the criteria outlined in Section 3.2. To date, there is no information that suggests differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to extend this accrual to a representative population, but in this study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlates to gender or to ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

9.10 **Radiographic Evaluation**

MRI of brain with and without contrast must be performed within **30 days** prior to enrollment on the study. Patients will undergo baseline and follow-up imaging in the same scanner if possible. All patients will receive a standard MRI, unless contraindicated, performed on either the 1.5T or 3T scanner. (If MRI is contraindicated, patient cannot be enrolled). Patients undergoing MRI may also undergo additional MR sequences such as dynamic contrast-enhanced (DCE) or MRI, dynamic susceptibility contrast (DSC) MRI as time permits. These sequences are part of standard brain tumor protocols. Percent agreement between the sequences will be estimated as the number of follow-up scans in which the corresponding sequence agreed divided by the total number of follow-up scans. Standard error will be estimated by use of the bootstrap method 26 to account for the correlated dependent response data, and these values will be used to estimate the 95% confidence intervals. The event-free survival distributions will be compared across the MR sequences, with a proportional hazards model developed for dependent survival data by Wei et al (1989).

9.11 **Ethical Issues**

Rationale for Subject Selection: Subject accrual for the study is available to both genders, racial and ethnic groups. No groups are being excluded from participation in the trial. Some of the subjects could become cognitively impaired as a consequence of, for example, their brain tumor. Patients who are 18 years old or older will be offered the opportunity to assign DPA prior to study entry. Adults who are cognitively impaired prior to study entry and who have not previously assigned DPA to a family member or friend will not be eligible for the trial, because they cannot give informed consent.

9.12 **Participation of Children**

Patients <21 years of age will be entered on this protocol. The primary objective of this trial is to determine if there is evidence of responses for patients receiving Pegylated interferon. The interferons have been extensively studied in both adults and children, and the side effects are well-described. Although pegylated interferon alpha-2b has not been extensively studied in children, we will use doses of interferon alpha-2b previously utilized in clinical trials, therefore we expect to see similar toxicity and similar side effects. The trial will be conducted by pediatric oncologists who have extensive experience in performing investigational drug trials in children. Patients will be cared for in the Aflac Cancer and Blood Disorder Center.

9.13 **Risks and Benefits**

Patients eligible for this trial are less than 21 years old. The primary risk to patients participating in this research study is from toxicity of pegylated interferon alfa-2b The protocol provides for detailed and careful monitoring of all patients to assess for toxicity. Patients will be treated with therapeutic intent and response to the therapy will be closely monitored. Patients will also be at risk from the MRI contrast agent, Gd-DTPA (gadolinium). The risks of Gd-DTPA are well-defined and consist primarily of nausea. Allergic reactions are rare. The potential benefits from pegylated interferon alpha-2b are disease stabilization or shrinkage, a reduction in symptoms caused by the tumor/cancer, and prolonged survival and the potential to avoid and or delay radiation. Therefore, this protocol involves greater than minimal risk to children, but presents the potential for direct benefit to individual subjects.

10.0 EVALUATION CRITERIA

10.1 **Common Terminology Criteria for Adverse Events (CTCAE)**

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website

10.2 **Methodology to Determine Tumor Measurement**

All axial images should be obtained in a plane parallel to a line intersecting the bottom of the genu and of the splenium of the corpus callosum (modified AC-PC line) - to assure consistency of imaging plane. Coronal images should be obtained perpendicular to the axial images.

1) DAx TI, whole brain, 12 directions.2) Sagittal T1 weighted MP_RAGE (TR/TI 2300/900)
3 Ax T2 weighted (TR ~4500, TE ~75)
4) 3D Coronal FLAIR (TR/TI 4800/1650)
5 Coronal 2D, fat saturated TSE through the orbits and chiasm (TR ~3,500, Te ~80)
6 Axial 2d, fat saturated TSE through the orbits and chiasm (TR ~3,500, Te ~80)
Post-Contrast
7) Axial, whole brain SPGR (TR/TE ~)
8) Coronal 2d, fat saturated TSE through the orbits and chiasm (TR ~3,500, Te ~80)
9) Axial 2d, fat saturated TSE through the orbits and chiasm (TR ~3,500, Te ~80)

Series 5 and 8 should have the same slice locations.
Series 6 and 9 should have the same slice locations.

10.3 **Tumor measurement**

Given the complexity of JPA/ OPG, the tumor size/response will be assessed in different segments:
1. Optic nerve (right, left)

2. Chiasm /hypothalamus
3. Brain parenchyma / retrochiasmatic visual pathways (optic tracts, optic radiations, internal capsule, posterior fossa) (right/left).

Therefore, up to 5 measurements may be necessary.
1. Longest diameter of target lesion(s) measured from the axial plane or the plane in which the aspect of the tumor is best seen or measured, provided the same plane is used in follow ups.

2. The longest measurement of the tumor (or width, W) should be determined.

3. The perpendicular measurements (transverse (T) measurement-perpendicular to the width in the selected plane. The length (L) – tumor extent in the plane perpendicular to the selected plane will not be used for measurement purpose.

4. The lower limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).

5. An automated tool (OncoTreat) will be employed to evaluate how the values obtained with this tool compare with the manually derived values. The manually derived values will be the measurements used for the study.

10.4 **Determination of tumor progression/response.**

Progressive disease

Any patient with clinical or radiographic evidence of progressive disease following any treatment cycle will no longer receive pegylated interferon alfa-2b (see Section 5.1). Radiographic progression is defined as appearance of new tumors or an increase in any previously measurable lesion by ≥25% in the product of the two longest perpendicular diameters or by 40% in the product of the three diameters. The preferred method for tumor measurement is to use the 3 diameters when available.

If possible, tumor progression should be documented by the appropriate radiological study. For patients who develop worsening neurological symptoms, attempts should be made to distinguish progressive disease from other causes prior to removing the patient from the study

Determination of tumor response or progression will be based on the pre-study baseline scan performed closest to time of study entry. Progressive disease will be defined based on the comparison of the baseline scan to the scan demonstrating best response.

1. The amount of tumor enhancement is quite variable in LGGs from one scan to the next.
Therefore, tumor response/progression will not solely be determined by change in the amount of enhancing disease on post contrast T1 images. Measurable change in size/extent must be present on FLAIR/T2 images, or on pre-contrast T1 images.

2. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence.

Note:

- CT scans should not be used to determine response. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane and MR sequence is used in follow ups.

- The cystic components of a tumor are considered in separate tumor measurements. See options below.

Options:

- If the cyst/necrosis is eccentric, the W, T and L of the solid portion should be measured, the cyst/necrosis excluded from measurement.
- If the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion.
- If the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured.
- Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted, change in extent/thickness assessed on follow up studies.
- For patients with large cystic components (>25%): One cystic component should be identified in the baseline scan. It should be measured separately from the solid component. It should be measured in 3 dimensions in the best sequence likely the T2 sequences. (L x T x W).

10.5 **Overall Response Assessment**

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	NO	**CR**
CR	IR/SD	NO	**PR**
PR	NON-PD	NO	**PR**
CR OR PR	NON-PD	NO	**PR**
SD	NON-PD	NO	**SD**

PD	ANY	YES OR NO	**PD**
ANY	PD	YES OR NO	**PD**
ANY	ANY	YES	**PD**

Abbreviations: CR: complete response; IR: incomplete response, PD: progressive disease; PR: partial response; SD; stable disease.
The section that follows will discuss the selection and evaluation of each of these types of lesions.

10.6 Selection of Target and Non-Target Lesions

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a"target" for measurement/follow up to assess for tumor progression/response.

2. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions (including CSF positive for tumor cells).

3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).

4. Any change in size of non-target lesions should be noted, though does not need to be measured.

10.7 Response Criteria for Target Lesions:

Response criteria are assessed in 3 dimensions – the product of L x W x T. An elliptical model volume (=0.5L x W x T) is used.
To assess response/progression, the ratio is calculated:

L x W x T (current scan) / L x W x T (reference scan)

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for 3-dimensional target lesions:

Complete Response (CR): Disappearance of all target lesions.

Partial response (PR): ≥ 65% decrease in the sum of the products of the three perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): 40% or more increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.
In the rare circumstance that the length of a lesion cannot be determined, then comparison of 2 dimensional measurements, T x W (product of the longest diameter and its longest perpendicular diameter) can be used.

Response Criteria for 2-dimensional target lesions:

Complete Response (CR): Disappearance of all target lesions.

Partial response (PR): ≥50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

Progressive Disease (PD): 25% or more increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra- CNS metastasis represents distant failure. Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

10.8 Response Criteria for Non-target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesions.

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Also as part of the response evaluation, for patients who have an omaya reservoir for the cystic part and who clinically required omaya taps, we will record the frequency of the taps and the amount of the fluid removed from the omaya reservoir.

10.9 **Retrospective Response Review**
MRI imaging for all patients on study will undergo retrospective central review following the completion of treatment.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 **Purpose**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 **Reporting Adverse Events**

This study will be conducted in compliance with the Aflac Cancer & Blood Disorders Service Data Safety Monitoring Plan for Phase 1 and 2 studies. In brief, the role of the Data and Safety Monitoring Board is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMB consists of 6 members including a chair, a pharmacist, and at least one external member. The DSMB meets on a regular basis to review current study results, as well as data available to the DSMB from other related studies. The DSMB will provide recommendations for each study reviewed to change the study or to continue the study unchanged. Data and Safety Board reports for institutional review boards will be prepared. The Principal Investigator assumes responsibility for assuring that the study is carried out in accordance with the DSMB.

Adverse Event Reporting

Serious adverse event (SAE) or reaction is any untoward medical occurrence (including an abnormal laboratory finding) that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires medical or surgical intervention in order to prevent one of the previous listed outcomes. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; or development of drug dependency or drug abuse.

Unexpected adverse drug experience means any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "*Unexpected*" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Attribution: The investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:

The categories are:
Definite: The adverse event is clearly related to the study drug.
Probable: The adverse event is most likely related to the study drug.

Possible: The adverse event may be related to the study drug.
Unlikely: The adverse event is doubtfully related to the study drugs.
Unrelated: The adverse event is clearly not related to the study drug.

For an SAE, the clinical trials coordinator in the Clinical research office should be notified via phone or email within 24 hours of the study personnel becoming aware of the event, and she will notify the DSMB. A copy of the completed Serious Adverse Event form must also be sent to Shelley Mays within **3 working days** after the incident.

Copies of all serious adverse event reports will be kept on file in the Clinical Research Office of the Cancer Center.

12.0 RECORDS AND REPORTING
Refer to separate packet for reporting and submission guidelines.

12.1 **Protocol amendments, or changes in study conduct**

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by IRB.
Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB.

Examples of amendments requiring such approval are:
1. Increases in drug dose or duration of exposure of subjects
2. Significant changes in the study design (e.g. addition or deletion of a control group)
3. Increases in the number of invasive procedures.
4. Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.
If an immediate change to the protocol is felt to be necessary by the investigator, the IRB must be informed immediately.
Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

Examples of administrative changes not requiring formal protocol amendments and IRB approval include:
1. Changes in the staff used to monitor trials.
2. Minor changes in the packaging or labeling of study drug.

12.2 Protocol Deviation (NIH Definition): A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

12.3 Protocol Violation (NIH Definition): Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

APPENDIX 1. Performance Status Criteria.

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix 2A

Pediatric Functional Assessment of Cancer Therapy – Brain Tumor Survivor (Version 2)
Patient Version: Age 7-12 (Grade School)

Please tell me during the **past 4 weeks**, how true each of the following statements has been for you.

Please mark only **one** number per line when you answer.

	Physical Well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
pP1	**I lose my balance or fall down easily**	0	1	2	3	4
pP2	I have trouble getting myself dressed	0	1	2	3	4
pP3a	I have trouble running like other people	0	1	2	3	4
pP4	I get tired easily	0	1	2	3	4
pP5	My arms or legs are weak	0	1	2	3	4
pP6	I get ill easily	0	1	2	3	4
	I have trouble writing with a pen or pencil 0	0	1	2	3	4

	Emotional Well-Being & Illness Experience	Not at all	A little bit	Some-what	Quite a bit	Very much
pE1	I feel happy	0	1	2	3	4

pE2	When I try to do something, I usually believe I will do it well.....	0	1	2	3	4
pE3	The illness experience makes me a stronger person	0	1	2	3	4
pE4	The illness experience has taught me to appreciate life.....	0	1	2	3	4
pE5a	I often feel that other children are better than me	0	1	2	3	4
pE6	I worry about being sick again.....	0	1	2	3	4
pE7	**I often switch from good moods to bad moods 0**	**0**	1	2	3	4
pE8	**I worry when I go back to the hospital or clinic**	**0**	1	2	3	4
pE9	**I get nervous (frightened) easily**	**0**	1	2	3	4
pE10	**I worry about having a good life in the future**	**0**	1	2	3	4

	Social and family Well-Being	Not at all	A little bit	Some-what	Quite a bit	Very much
pSF 1a	**Other people pick on (tease) me 0**	0	1	2	3	4
pSF 2a	**I think I have fewer friends than others 0**	0	1	2	3	4
pSF 3a	**Other people avoid hanging out with me because of my illness history 0**	0	1	2	3	4
pSF 4	I feel lonely	0	1	2	3	4
pSF 5a	I WOULD RATHER DO SOMETHING BY MYSELF THAN WITH OTHER PEOPLE 0	0	1	2	3	4

	Additional Concerns	Not at all	A little bit	Some-what	Quite a bit	Very much
pB 1	**(ii) I am bothered by being shorter than other people my age 0**	0	1	2	3	4
pB 2	I am bothered by being unable to see well	0	1	2	3	4
pB 3	I am bothered by being unable to hear well	0	1	2	3	4
pB 4	I am bothered by headaches	0	1	2	3	4
pB 5	**When I speak, people have trouble understanding me 0**	0	1	2	3	4

pB 6	I need to work harder than other people to get my school work done.....	0	1	2	3	4
pB 7	My grades are worse than they were before I was sick.....	0	1	2	3	4
pB 8	I forget things easily	0	1	2	3	4
pB 9	It is hard for me to concentrate in school	0	1	2	3	4
pB 10	I have to read things several times so I can understand them	0	1	2	3	4
pB 11	When I play games or sports, I react more slowly than most people my age	0	1	2	3	4
pB 12	**(iii) It is hard for me to find the right words to say what I mean**	0	1	2	3	4

Appendix 2B.

Pediatric Functional Assessment of Cancer Therapy – Brain Tumor Survivor (version 2)
Patient Version (age 12 years and older)

Please tell me during the **past 4 weeks**, how true each of the following statements has been for you.

Please mark only **one** number per line when you answer.

	Physical Well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
pP1	**I lose my balance or fall down easily**	0	1	2	3	4
pP2	I have trouble getting myself dressed	0	1	2	3	4
pP3a	I have trouble running like other people	0	1	2	3	4
pP4	I get tired easily	0	1	2	3	4
pP5	My arms or legs are weak	0	1	2	3	4
pP6	I get ill easily	0	1	2	3	4
	I have trouble writing with a pen or pencil 0	0	1	2	3	4

	Emotional Well-Being & Illness Experience	Not at all	A little bit	Some-what	Quite a bit	Very much
pE1	I feel happy	0	1	2	3	4
pE2	When I try to do something, I usually believe I will do it well.....	0	1	2	3	4

pE3	The illness experience makes me a stronger person 0	1	2	3	4
pE4	The illness experience has taught me to appreciate life 0	1	2	3	4
pE5a	I often feel that other people are better than me 0	1	2	3	4
pE6	I worry about being sick again 0	1	2	3	4
pE7	**I often switch from good moods to bad moods 0** **0**	1	2	3	4
pE8	**I worry when I go back to the hospital or clinic** **0**	1	2	3	4
pE9	**I get nervous (frightened) easily** **0**	1	2	3	4
pE10	**I worry about having a good life in the future** **0**	1	2	3	4
pE11a	**I worry about being able to date because of my illness history** **0**	1	2	3	4
pE12a	**I worry about being able to go to college because of my illness history** **0**	1	2	3	4
pE13a	**I worry about getting a job to support myself because of my illness history** **0**	1	2	3	4

	Social and Family Well-Being	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
pSF1a	**Other people pick on (tease) me 0**	0	1	2	3	4
pSF2a	**I think I have fewer friends than others 0**	0	1	2	3	4
pSF3a	**Other people avoid hanging out with me because of my illness history 0**	0	1	2	3	4

pSF 4	I feel lonely	0	1	2	3	4
pSF 5a	I WOULD RATHER DO SOMETHING BY MYSELF THAN WITH OTHER PEOPLE 0	0	1	2	3	4

	Additional Concerns	Not at all	A little bit	Some-what	Quite a bit	Very much
pB 1	**(ii) I am bothered by being shorter than other people 0**	0	1	2	3	4
pB 2	I am bothered by being unable to see well	0	1	2	3	4
pB 3	I am bothered by being unable to hear well	0	1	2	3	4
pB 4	I am bothered by headaches	0	1	2	3	4
pB 5	**When I speak, people have trouble understanding me 0**	0	1	2	3	4
pB 6	I need to work harder than other people to get my school work done.....	0	1	2	3	4
pB 7	My grades are worse than they were before I was sick.....	0	1	2	3	4
pB 8	I forget things easily	0	1	2	3	4

pB 9	It is hard for me to concentrate in school	0	1	2	3	4
pB 10	I have to read things several times so I can understand them	0	1	2	3	4
pB 11	When I play games or sports, I react more slowly than most people my age	0	1	2	3	4
pB 12	**(iii) It is hard for me to find the right words to say what I mean**	0	1	2	3	4

Appendix 2C.

Pediatric Functional Assessment of Cancer Therapy – Brain Tumor Survivor (Version 2)
(iv) Parent Version: Age 12 - adults (High School and Older)

Please tell me during the **past 4 weeks**, how true each of the following statements has been for your child.

Please mark only **one** number per line when you answer.

	Physical Well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
pP1	**My child loses balance or falls down easily.....**	0	1	2	3	4
pP2	My child has trouble getting dressed on his/her own.....	0	1	2	3	4
pP3a	My child has trouble running like other people	0	1	2	3	4
pP4	My child gets tired easily	0	1	2	3	4
pP5	My child's arms or legs seem weak	0	1	2	3	4
pP6	My child gets ill easily	0	1	2	3	4
	My child has trouble writing with a pen or pencil 0	0	1	2	3	4

	Emotional Well-Being &Illness Experience	Not at all	A little bit	Some-what	Quite a bit	Very much
pE1	My child seems happy	0	1	2	3	4

pE2	When my child tries to do something, s/he usually believes s/he will do it well.....	0	1	2	3	4
pE3	The illness experience makes my child a stronger person	0	1	2	3	4
pE4	The illness experience has taught my child to appreciate life	0	1	2	3	4
pE5a	My child often feels inferior to other people.....	0	1	2	3	4
pE6	My child worries about getting another cancer/tumor	0	1	2	3	4
pE7	**My child is moody or irritable 0**	**0**	1	2	3	4
pE8	**My child worries when we go back to the hospital or clinic**	**0**	1	2	3	4
pE9	**My child gets nervous (frightened) easily**	**0**	1	2	3	4
pE10	**My child worries about having a good life in the future**	**0**	1	2	3	4
pE11a	**My child worries about being able to have a girlfriend or boyfriend because of his/her illness history**	**0**	1	2	3	4
pE12a	**My child worries about being able to go to college because of his/her illness history**	0	1	2	3	4
pE13a	**My child worries about getting a job because of his/her illness history**	**0**	1	2	3	4

	Social and Family Well-Being	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
pSF1a	**Other people pick on (tease) my child 0**	0	1	2	3	4

pSF 2a	**My child has fewer friends than others 0**	0	1	2	3	4
pSF 3a	**Other people avoid hanging out with my child because of his or her illness history 0**	0	1	2	3	4
pSF 4	My child seems lonely.....	0	1	2	3	4
pSF 5a	MY CHILD PREFERS TO DO SOMETHING ALONE 0	0	1	2	3	4

	Additional Concerns	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
pB 1	My child is bothered by being shorter than his/ her peers.....	0	1	2	3	4
pB 2	My child is bothered by poor vision	0	1	2	3	4
pB 3	My child is bothered by poor hearing	0	1	2	3	4
pB 4	My child is bothered by headaches.....	0	1	2	3	4
pB 5	My child's speech is hard for others to understand.....	0	1	2	3	4
pB 6	My child needs to work harder than his/ her peers to get school work done.....	0	1	2	3	4
pB 7	My child's school performance is worse than it was before s/he was diagnosed	0	1	2	3	4

pB 8	My child forgets things easily	0	1	2	3	4
pB 9	It is hard for my child to concentrate in school.....	0	1	2	3	4
pB 10	My child has to read things several times so s/he can understand them	0	1	2	3	4
pB 11	When my child plays games or sports, s/he reacts more slowly than his/ her peers	0	1	2	3	4
pB 12	My child has difficulty using the right words	0	1	2	3	4

Appendix 2D.

Pediatric Functional Assessment of Cancer Therapy – Brain Tumor Survivor (Version 2)
Parent Version: Age less than 12 years old

Please tell me during the **past 4 weeks**, how true each of the following statements has been for your child.

Please mark only **one** number per line when you answer.

	Physical Well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
pP1	**My child loses balance or falls down easily.....**	0	1	2	3	4
pP2	My child has trouble getting dressed on his/her own.....	0	1	2	3	4
pP3a	My child has trouble running like other people	0	1	2	3	4
pP4	My child gets tired easily.....	0	1	2	3	4
pP5	My child's arms or legs seem weak	0	1	2	3	4
pP6	My child gets ill easily.....	0	1	2	3	4
	My child has trouble writing with a pen or pencil 0	0	1	2	3	4

	Emotional Well-Being &Illness Experience	Not at all	A little bit	Some-what	Quite a bit	Very much

pE1	My child seems happy	0	1	2	3	4
pE2	When my child tries to do something, s/he usually believes s/he will do it well.....	0	1	2	3	4
pE3	The illness experience makes my child a stronger person	0	1	2	3	4
pE4	The illness experience has taught my child to appreciate life	0	1	2	3	4
pE5a	My child often feels inferior to other people.....	0	1	2	3	4
pE6	My child worries about getting another cancer/tumor	0	1	2	3	4
pE7	**My child is moody or irritable 0**	**0**	1	2	3	4
pE8	**My child worries when we go back to the hospital or clinic**	**0**	1	2	3	4
pE9	**My child gets nervous (frightened) easily**	**0**	1	2	3	4
pE10	**My child worries about having a good life in the future**	**0**	1	2	3	4
pE11a	**My child worries about being able to have a girlfriend or boyfriend because of his/her illness history**	**0**	1	2	3	4
pE12a	**My child worries about being able to go to college because of his/her illness history**	0	1	2	3	4
pE13a	**My child worries about getting a job because of his/her illness history**	**0**	1	2	3	4

	Social and Family Well-Being	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
pSF1a	**Other people pick on (tease) my child 0**	0	1	2	3	4

pSF 2a	**My child has fewer friends than others 0**	0	1	2	3	4
pSF 3a	**Other people avoid hanging out with my child because of his or her illness history 0**	0	1	2	3	4
pSF 4	My child seems lonely.....	0	1	2	3	4
pSF 5a	MY CHILD PREFERS TO DO SOMETHING ALONE 0	0	1	2	3	4

	Additional Concerns	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
pB 1	My child is bothered by being shorter than his/ her peers.....	0	1	2	3	4
pB 2	My child is bothered by poor vision	0	1	2	3	4
pB 3	My child is bothered by poor hearing	0	1	2	3	4
pB 4	My child is bothered by headaches.....	0	1	2	3	4
pB 5	My child's speech is hard for others to understand.....	0	1	2	3	4
pB 6	My child needs to work harder than his/ her peers to get school work done.....	0	1	2	3	4
pB 7	My child's school performance is worse than it was before s/he was diagnosed	0	1	2	3	4

pB 8	My child forgets things easily	0	1	2	3	4
pB 9	It is hard for my child to concentrate in school.....	0	1	2	3	4
pB 10	My child has to read things several times so s/he can understand them	0	1	2	3	4
pB 11	When my child plays games or sports, s/he reacts more slowly than his/ her peers	0	1	2	3	4
pB 12	My child has difficulty using the right words	0	1	2	3	4

Appendix 3: Eligibility Checklist

A Phase II Study Of Pegylated Interferon Alfa-2b In Children With Refractory/ Recurrent juvenile pylocytic astrocytomas or optic gliomas.

Last Name: _____ First Name: _____ MI: _____ ID #: _____ Date of Birth: _____ (mm/dd/yyyy)

Age: _____ Race: _____ (White, Hispanic, Black, Asian, Other)

To be eligible, questions 1-10 must be marked Y (Yes) or NA (Not Applicable), and questions 11-14 must be marked N (No).

1. Is the patient older than 3 years and less than or equal to 25 years of age? _____

2. Has the patient been diagnosed with an optic pathway glioma or JPA? _____

a. Is there radiographic evidence of optic pathway glioma or JPA? _____

3. Has the patient received 5 or fewer chemotherapy regimens? _____

4. Does the patient have a performance status of more than 50? _____

5. Does the patient have an adequate bone marrow function as defined below?

-peripheral absolute granulocyte count of >1000/mm3, _____

-hemoglobin >8 gm/dL _____ (transfusion dependent)

-platelet count >100,000/mm3_____ (transfusion independent)

6. Does the patient have adequate hepatic function (total bilirubin <2.0x the upper limit of normal and direct bilirubin within normal limits and SGPT <2.5 x the upper limit of normal) or for patients with a diagnosis of Gilbert's disease an indirect bilirubin of < 6mg/dl and a direct bilirubin of < .5mg/dl? _____

7. Have one of the following two criteria for renal function been met? _____

a. Creatinine clearance =60 mL/min/1.73 m2

b. Maximum age-adjusted normal serum creatinine?

i. Five years of age or younger: 0.8 mg/dl

ii. Ten years of age or younger, but must be greater than five years of age: 1.0 mg/dl

iii. Fifteen years of age or younger, but must be greater than ten years of age: 1.2 mg/dl

iv. Greater than fifteen years of age: 1.5 mg/dl

8. Has the patient, their legal guardian, or a Durable Power of Attorney (for those patients 18 to 21 years of age) signed a document of informed consent? _____

9 Does the patient have evidence of measurable disease in brain MRI? _____

10. Has the patient received prior radiation more than 24 months ago?_____

11. Is the patient currently receiving other investigational chemotherapeutic agents? _____

12. Does the patient have any known hypersensitivity to interferon alpha? _____

13. Is the patient pregnant or breast-feeding? _____

14. Does the patient have any clinically significant unrelated systemic illness which would compromise his/her ability to tolerate the Pegylated interferon therapy? _____

Appendix 4 Diary Pegylated Interferon

PEGYLATED INTERFERON MEDICATION DIARY

Please write down the date, time, and site of administration that you or your child takes pegylated interferon. Also please explain any problems that occurred with taking the drug. Please bring this log with you **EVERY** time you come to clinic. **COURSE #: _____**

Course Day	Date	Time	Dose and Site of Administration	Problems
Week 1, Day 1				
Week 1, Day 2				
Week 1, Day 3				
Week 1, Day 4				
Week 1, Day 5				
Week 1, Day 6				
Week 1, Day 7				
Week 2, Day 1				
Week 2, Day 2				
Week 2, Day 3				
Week 2, Day 4				
Week 2, Day 5				
Week 2, Day 6				
Week 2, Day 7				
Week 3, Day 1				
Week 3, Day 2				

Week 3, Day 3				
Week 3, Day 4				
Week 3, Day 5				
Week 3, Day 6				
Week 3, Day 7				
Week 4, Day 1				
Week 4, Day 2				
Week 4, Day 3				
Week 4, Day 4				
Week 4, Day 5				
Week 4, Day 6				
Week 4, Day 7				

Fax to Brain Tumor Office (404) 785 3511 or Bring to next clinic

13. References

1. Wisoff, J.H., et al., *Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group.* Neurosurgery, 2011. **68**(6): p. 1548-54; discussion 1554-5.
2. Merchant, T.E., et al., *Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits.* J Clin Oncol, 2009. **27**(22): p. 3691-7.
3. Ater, J.L., et al., *Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group.* J Clin Oncol, 2012. **30**(21): p. 2641-7.
4. Bouffet, E., et al., *Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma.* J Clin Oncol, 2012. **30**(12): p. 1358-63.
5. Packer, R.J., et al., *Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan.* Pediatr Blood Cancer, 2009. **52**(7): p. 791-5.
6. Hwang, E.I., et al., *Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas.* Pediatr Blood Cancer, 2012.
7. Couec, M.L., et al., *Bevacizumab and irinotecan in children with recurrent or refractory brain tumors: toxicity and efficacy trends.* Pediatr Blood Cancer, 2012. **59**(1): p. 34-8.
8. Hwang, E.I., et al., *Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas.* Pediatr Blood Cancer, 2013. **60**(5): p. 776-82.
9. Terashima, K., et al., *Long-term outcome of centrally located low-grade glioma in children.* Cancer, 2013. **119**(14): p. 2630-8.
10. Nagai, M. and T. Arai, *Clinical effect of interferon in malignant brain tumours.* Neurosurg Rev, 1984. **7**(1): p. 55-64.
11. Groves, M.D., et al., *Two phase II trials of temozolomide with interferon-alpha2b (pegylated and non-pegylated) in patients with recurrent glioblastoma multiforme.* Br J Cancer, 2009. **101**(4): p. 615-20.
12. Allen, J., et al., *Recombinant interferon beta: a phase I-II trial in children with recurrent brain tumors.* J Clin Oncol, 1991. **9**(5): p. 783-8.
13. Packer, R.J., et al., *Treatment of children with newly diagnosed brain stem gliomas with intravenous recombinant beta-interferon and hyperfractionated radiation therapy: a childrens cancer group phase I/II study.* Cancer, 1996. **77**(10): p. 2150-6.
14. Jakacki, R.I., et al., *Phase II evaluation of interferon-alpha-2a for progressive or recurrent craniopharyngiomas.* J Neurosurg, 2000. **92**(2): p. 255-60.
15. Warren, K., et al., *A phase 2 study of pegylated interferon alpha-2b (PEG-Intron((R))) in children with diffuse intrinsic pontine glioma.* Cancer, 2012. **118**(14): p. 3607-13.
16. Yeung, J.T., et al., *Pegylated interferon-alpha-2b for children with recurrent craniopharyngioma.* J Neurosurg Pediatr, 2012. **10**(6): p. 498-503.
17. Jakacki, R.I., et al., *Phase I trial of pegylated interferon-alpha-2b in young patients with plexiform neurofibromas.* Neurology, 2011. **76**(3): p. 265-72.
18. Slaton, J.W., et al., *Interferon-alpha-mediated down-regulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule.* Clin Cancer Res, 1999. **5**(10): p. 2726-34.