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Local Protocol #: PBTC-039
ClinicalTrials.gov Identifier: NCT01964300

TITLE: Phase II study of Peginterferon alfa-2b (SYLATRON) for pediatric patients with unresectable or recurrent craniopharyngioma

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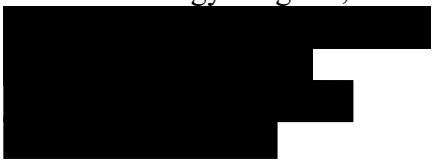

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SCHEMA

Stratum 1: Patients with progressive unresectable or recurrent craniopharyngiomas treated with surgery alone who have not received radiation therapy. **Patients with unresectable craniopharyngiomas (i.e., residual measurable disease following surgical resection) will be enrolled at the time of progression**

Stratum 2: Patients with progressive or recurrent craniopharyngiomas following radiation therapy.

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1 OBJECTIVES

1.1 Primary Objectives

1.1.1 To estimate the 1-year disease stabilization rate associated with the use of PEGINTERFERON ALFA-2B in patients with progressive unresectable or recurrent craniopharyngiomas following surgery alone who have not received radiation therapy.

1.1.2 To estimate the sustained objective response rate (PR+CR) to PEGINTERFERON ALFA-2B in patients with craniopharyngiomas which progress or recur following radiation therapy.

1.2 Secondary Objectives

1.2.1 To estimate the response rate in patients with progressive unresectable or recurrent craniopharyngioma treated with PEGINTERFERON ALFA-2B by study stratum.

1.2.2 To estimate the progression-free survival distribution for patients with unresectable or recurrent craniopharyngiomas treated with PEGINTERFERON ALFA-2B by study stratum.

1.2.3 To evaluate the toxicity profile of PEGINTERFERON ALFA-2B in children with unresectable or recurrent craniopharyngiomas.

1.2.4 To compare the protocol specific disease assessment criteria to MacDonald criteria during the first year of treatment in stratum I and also at the time of objective response and progressive disease in both strata.

1.2.5 To characterize evidence of WNT and MAPK pathway activation in resected tumor tissue in patients with craniopharyngiomas by immunohistochemistry and pyrosequencing and correlate these results with outcome and response data.

2 BACKGROUND

2.1 Study Disease(s)

Craniopharyngiomas account for approximately 4% of brain tumors in patients younger than 15 years of age.[1] They are believed to arise from embryonic squamous cell rests along the hypophyseal-pharyngeal duct.[2] Complete surgical resection is often not possible without significant morbidity because of the tumor's proximity to the optic chiasm, third cranial nerve, hypothalamus and internal carotid arteries and branches. Despite complete resection, recurrence rates range from 20% to as high as 50%.[3-5] Subtotal resection followed by radiation therapy achieves at least comparable results in terms of recurrence rates and survival.[6-8] Therefore, either complete resection or subtotal resection followed by radiation therapy is considered standard of care for patients with newly diagnosed craniopharyngiomas.

Unfortunately, permanent deleterious effects on behavior, learning and endocrine function following surgery and/or radiation therapy are common in children with craniopharyngioma and can be devastating.[9,10] Multiple endocrinopathies are almost universal, but the effects of hypothalamic damage including hypothalamic obesity and impaired socialization and poor

academic performance ("hypothalamic syndrome") are often not remediable. The effects of radiation are relatively age dependent, with more significant damage occurring in younger children. An effective medical therapy that can defer the need for radiation therapy, particularly for young children, or salvage those tumors that have recurred following radiation therapy would be of tremendous benefit both in terms of overall survival as well as quality of life.

2.2 SYLATRON (Peginterferon alpha-2b)

2.2.1 Rationale for alpha-interferon

The interferons are a family of naturally occurring, small proteins produced and secreted by virtually all eukaryotic cells in response to viral infections or to various biologic and synthetic inducers. Interferons exert antitumor activity through direct antiproliferative and cytotoxic effects as well as modulation of the host immune response.[11] Interferon is also a potent inhibitor of angiogenesis as evidenced by its utility in the treatment of life-threatening hemangiomas of infancy.[12]

Craniopharyngiomas and squamous cell skin carcinoma are believed to have the same embryologic origin. Squamous epithelium, usually with some evidence of keratinization, is characteristically found in both the cystic lining and the solid component of craniopharyngiomas.[2] When administered both intralesionally and systemically, interferon alpha has significant activity against squamous cell skin carcinoma. Intralesional injections of alpha interferon for 3 weeks resulted in histologically proven eradication of squamous cell carcinoma in 33 out of 34 patients.[13] Treatment with subcutaneous alpha-2a interferon (3 million IU/d) and oral cis-retinoic acid for two months in patients with advanced squamous cell carcinoma resulted in an overall response rate of 68%, and a 93% response rate for those with localized disease.[14]

Based on this, a Phase II study of alpha-interferon was performed in pediatric patients with progressive or recurrent craniopharyngiomas.[15] Interferon alpha-2a was administered subcutaneously daily for 16 weeks followed by a 32 week maintenance phase where the interferon was given three times/week. Three of 12 evaluable patients showed a minor response (n=1), partial response (n=1) or complete response (n=1); the patient with the PR also showed improvement in visual fields. The median time to progression was 25 months (range 3-37+ months with 3 patients without progression as of last follow-up). The cystic component of the tumor often increased temporarily during the first several months of treatment. Toxicities requiring temporary discontinuation and/or dose reduction were common during the initial 16 weeks of therapy. All patients developed fever shortly after receiving the first dose of IFN, usually accompanied by chills and myalgias. Two patients with panhypopituitarism developed hypotension and lethargy during the fever, requiring stress dose steroids. Temporary discontinuation and/or dose reduction was required for toxicity in nine (60%) of the 15 patients during the first 8 weeks of treatment but resolved after temporary discontinuation and/or dose reduction. These toxicities included worsening seizures, transaminase elevations, rash and anorexia/weight loss.

Intralesional interferon-alpha has also shown efficacy against craniopharyngiomas. In a multi-center study, 60 patients with predominantly cystic craniopharyngiomas were treated with every other day intra-cystic interferon-alpha. Forty-seven (78%) of the 60 patients had a > 50%

decrease in the size of the cyst.[16] A separate study of 8 patients with cystic craniopharyngiomas treated with intra-cystic alpha-interferon showed an increase in the apoptotic factor soluble FasL concentrations in the cyst fluid of all 8 patients as the cyst decreased in size in response to treatment, suggesting that interferon works by inducing Fas-mediated apoptosis.[17]

2.2.2 Rationale for Pegylated Interferon (PEGINTERFERON ALFA-2B)

In tumor cell lines, continuous and prolonged exposure to interferon optimizes both the anti-proliferative and anti-angiogenic effect[18-21] and the highest response rates in patients with metastatic melanoma have been obtained with uninterrupted schedules.[18] When interferon was removed from the medium, glioma cell line growth rapidly returned to the pretreatment rate.[20]

Conjugating proteins with poly-ethylene-glycol (PEG) almost invariably lengthens the plasma half-life by reducing sensitivity to proteolysis, thereby increasing the area under the curve (AUC) and providing protracted activity.[22] Pegylation of interferon enhances the therapeutic ratio in patients with hepatitis C, and was more effective than a regimen of non-pegylated interferon given 3 times/week.[23] PegIntron has received FDA approval for this indication at a dose of 1 mcg/kg/dose/week when given as a single agent.

2.2.3 Rationale for PEGINTERFERON ALFA-2B Dose

Although interferon-alpha has been used to treat a variety of neoplasms, the optimal dose in oncology has not been established. In vivo studies have not shown a clear dose-response relationship in solid tumors, other than possibly for melanoma[24]. In CML, low dose interferon is just as effective as higher doses[25] whereas toxicity is clearly dose-related.

A Phase I study of PegIntron alpha-2b in pediatric patients with neurofibromatosis-related plexiform neurofibromas has recently been published.[26] The recommended Phase 2 dose (RP2D) was 1 mcg/kg/week with fatigue and intolerable behavioral toxicities seen at higher doses. There was only one DLT (myoclonus) in 12 patients treated at the RP2D. This toxicity had not been seen previously and was felt to be possibly related, although it continued intermittently even after the drug was discontinued. Only 1 other patient required a dose reduction for grade 3 elevation of transaminases. This dose is also the FDA approved dose for the treatment of hepatitis C in adults when used as monotherapy. Although a higher dose of PEGINTERFERON ALFA-2B is used in adult patients with melanoma, where there is a known dose-response curve, a dose of 1 mcg/kg/week resulted in a prolonged CR in one of the patients in the pilot study.[27]

Many, if not most patients with craniopharyngiomas have panhypopituitarism and require stress doses of steroids to remain hemodynamically stable in the face of high fever and/or chills, which are common dose-related side effects of interferon, and almost universally seen with higher doses, particularly with short acting interferon. A dose of 1 mcg/kg/week has been found to be well tolerated in pediatric patients[26], causing only mild to moderate constitutional symptoms which subside over time, and has shown efficacy in the pilot study at Children's Hospital of Pittsburgh.[27] Therefore, a dose of 1 mcg/kg/week will be utilized for all patients in this protocol, regardless of age.

2.3 Pediatric Clinical Trials

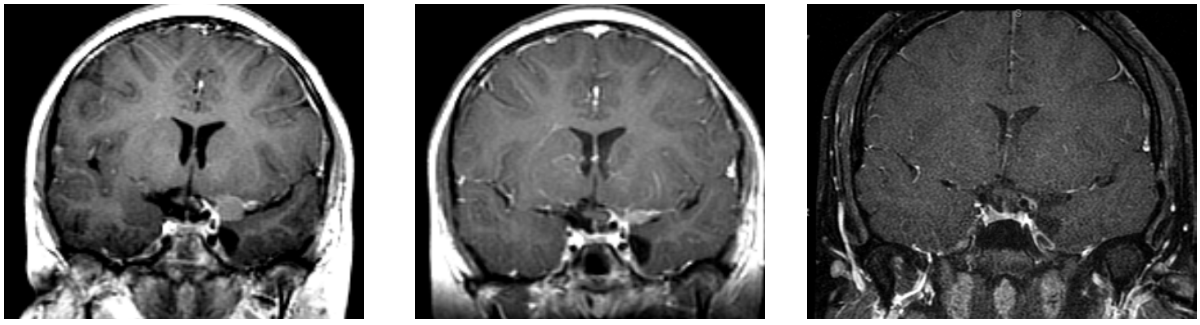
As stated in Section 2.2.1, a Phase II study of alpha-interferon was performed in pediatric patients with progressive or recurrent craniopharyngiomas.[15] Interferon alpha-2a was administered subcutaneously daily for 16 weeks followed by a 32 week maintenance phase with the interferon given three times/week. Three of 12 evaluable patients had an objective response and one patient also showed improvement in visual fields: the median time to progression was 25 months.

2.3.1 Children's Hospital of Pittsburgh experience with pegylated interferon

A single institution pilot study of pegylated interferon in children with recurrent craniopharyngiomas has recently been published.[27] From 2001-2011, 14 patients at the Children's Hospital of Pittsburgh developed recurrence of their craniopharyngiomas. Seven patients underwent repeat resection, 2 patients underwent 3 gamma-knife procedures and 5 children were treated with pegylated interferon. All 5 patients have responded or experienced prolonged disease stabilization. Case summaries are provided below:

a. Patient #1 was diagnosed with a craniopharyngioma at the age of 9 years. The tumor re-grew within 3 months of a gross total removal, and she was started on PegIntron. The predominantly cystic tumor initially increased in size during the first 3 months of therapy, but then progressively decreased until there was complete disappearance of tumor. She was treated with PegIntron for 2 years and has remained NED 10.5 years after beginning treatment.

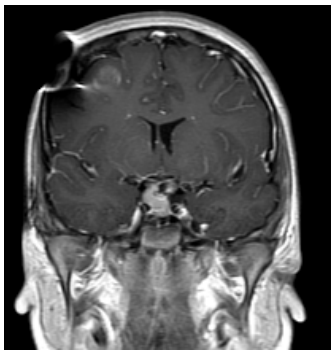
Patient #1

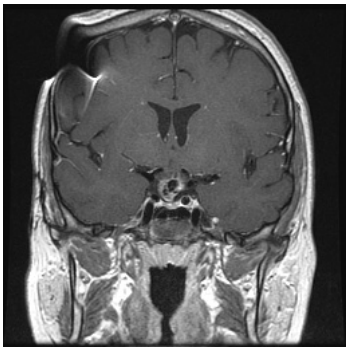


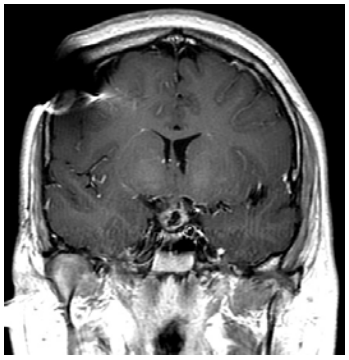
Pre-Therapy **7 Months Later** **10 Years Later**

b. Patient #2 was diagnosed with a craniopharyngioma at the age of 8 years and underwent a subtotal resection followed by radiation therapy. The tumor regrew 3.6 years later and he was treated with PegIntron for 2 years. The cystic component completely disappeared 4 months after starting PegIntron and a calcified residual mass remains stable over 5 years later.

Patient #2

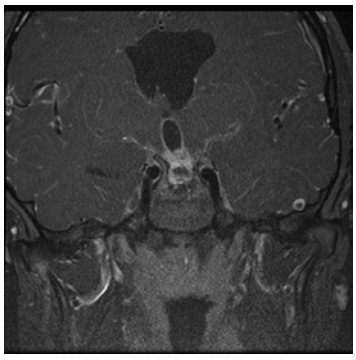

Pre-Therapy

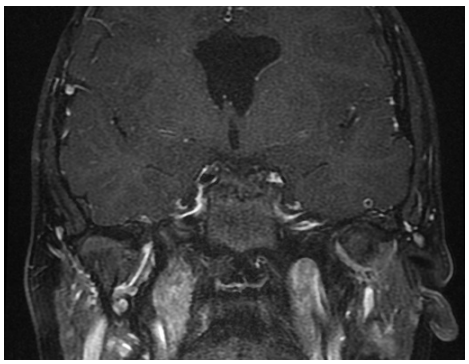

Four Months Later


Six Years Later

c. Patient #3 was diagnosed with a craniopharyngioma at the age of 4 years and underwent three gross total resections of the tumor over the next 7 years. The tumor recurred 8 months after the third surgery and he was treated with PegIntron for 15 months. He had a complete response by 7 months of treatment with PegIntron and remained on treatment for 15 months. He remains NED 2 1/2 years after starting treatment.

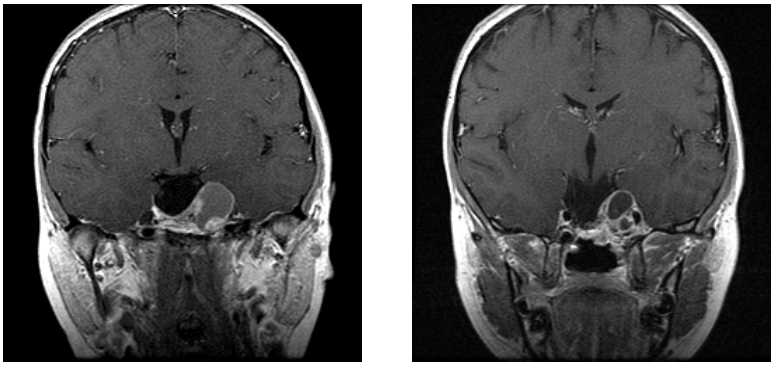
Patient #3


Pre-Therapy


7 and 21 Months Later

d. Patient #4 was diagnosed with a large craniopharyngioma at the age of 13 years and underwent a two-staged subtotal resection. The tumor progressed within a few months and he started treatment with PegIntron. He showed a 30% decrease in the size of the cystic component by 4 months, which was maintained until 12 months, when the cyst increased in size.

Patient #4



Pre-Therapy **Eight Months Later**

e. Patient #5 was diagnosed at the age of 14 years and underwent a gross total resection. The cystic tumor re-grew within 6 months and she started treatment with PegIntron. She remains stable 17 months after starting treatment.

These patients were treated for variable amounts of time, but all for > 1 year and at least one patient continued to show tumor shrinkage and eventual complete tumor disappearance after 2 years of treatment. The duration of treatment for this protocol will therefore be 2 years.

2.4 Rationale for Changing Study Drug PegIntron to SYLATRON

Merck has decided to voluntarily discontinue the manufacture of the PegIntron vials, Injection, for subcutaneous use, for distribution in the United States for business reasons. The decision is not based on any safety or efficacy findings with this product. This decision is due to scientific advancement, changes in treatment practices, and the consequent reduction in the demand for PegIntron. SYLATRON, which has the same active ingredient as PegIntron (Peginterferon alfa-2b) with different Dosage Strength, is proposed to replace PegIntron as the study drug of PBTC-039.

2.5 Rationale for Correlative Studies

2.5.1 WNT and MAPK pathway activation

Recent genomic studies have demonstrated that each of the two histologic subtypes of craniopharyngioma (adamantinomatous and papillary) is characterized by the presence of a specific genetic alteration.[28] Adamantinomatous craniopharyngiomas, which are most common in children, exhibit near-universal mutation of beta-catenin (*CTNNB1*), confirming recent evidence that craniopharyngiomas arise from activation of beta-catenin (a Wnt pathway gene) in pituitary progenitors during embryogenesis[29]. Of note, craniopharyngiomas with mutations in *CTNNB1* can be reliably identified by detection of nuclear immunoreactivity for the beta-catenin protein, which is the most commonly-used clinical test for alterations in this gene. These results confirmed an earlier study where all 10 cases of adamantinomatous craniopharyngioma harbored beta-catenin mutations and stained for nuclear expression of beta-catenin.[30] Papillary

craniopharyngiomas, in contrast, are characterized by frequent *BRAF* V600E mutations, indicating activation of the MAPK signaling pathway.[28] Although in general mutations in *CTNNB1* and *BRAF* are mutually-exclusive in craniopharyngiomas, cases have been identified in which both genes are mutated in the same tumor.[31] We propose to validate these observations using immunohistochemistry for nuclear beta-catenin and pyrosequencing for detection of *BRAF* V600E in FFPE sections in this pediatric series of craniopharyngiomas.

2.5.2 MRI Study

Standard high resolution MR imaging dedicated to the suprasellar/sellar region with gadolinium has been used in previous studies of interferon in patients with recurrent craniopharyngioma.[15,27] Volumetric analyses of tumor size have been reported to more accurately detect change in tumor volume than the diameter method.[32]

The product of the greatest perpendicular linear diameters will be compared to central volumetric analysis of the cystic and solid component of the tumor and compared to assessment of disease response.

3 PATIENT SELECTION

3.1 Eligibility Criteria

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within three (3) weeks prior to registration and 4 weeks of starting therapy. All subjects must have baseline MRI scans of the brain with thin cuts through the sella (see Section 9.3).

All other evaluations necessary to establish eligibility for study entry must be done within two (2) weeks prior to registration.

3.1.1 Tumor

Patient must have a histologically verified diagnosis of craniopharyngioma.

Stratum 1: Patients with progressive unresectable or recurrent craniopharyngiomas treated with surgery alone, who have not received radiation therapy. Patients with unresectable craniopharyngiomas, (i.e. residual measurable disease following surgical resection) will be enrolled at the time of progression.

Stratum 2: Patients with progressive or recurrent craniopharyngiomas following radiation therapy. The patient must be at least 6 months post-irradiation to be eligible.

3.1.2 Disease Status

All patients must have measurable residual disease defined as tumor measurable in two perpendicular diameters on MRI. Measurements are required for both the solid and cystic components

3.1.3 Prior Therapy

Subjects must have recovered from the acute toxicities of all prior therapy before entering this

study. For those acute baseline adverse events attributable to prior therapy, recovery is defined as a toxicity Grade ≤ 2, using CTCAE v.4.0, unless otherwise specified in the Inclusion and Exclusion Criteria.

3.1.4 Myelosuppressive chemotherapy:
Subjects must have received their last dose of known myelosuppressive anticancer chemotherapy at least three (3) weeks prior to study registration or at least six (6) weeks if nitrosourea.

3.1.5 Investigational / Biologic agent:
Subjects must have received their last dose of investigational or biologic agent ≥ 7 days prior to study registration.

- In the event that a subject has received an investigational or biologic agent and has experienced ≥ Grade 2 myelosuppression, then at least three (3) weeks must have elapsed prior to registration.
- If the investigational or biologic agent has a prolonged half-life (≥ 7 days) then at least three (3) weeks must have elapsed prior to registration.

3.1.6 Monoclonal antibody treatment:
Subjects must have completed at least 3 half-life periods from the last dose of monoclonal antibody prior to registration.
Note: A list of half-lives of commonly used monoclonal antibodies is available on the PBTC website under Generic Forms and Templates

3.1.7 Radiation
Stratum 1: Patients must not have received radiation therapy.
Stratum 2: Patients must have received radiation therapy, which may include gamma knife or P32:

- More than 6 months from the time of enrollment if the recurrence is predominantly solid
- More than 12 months from the time of enrollment if the recurrence is predominantly cystic

3.1.8 Growth factors:
At least 7 days since the completion of therapy with a hematopoietic growth agent (filgrastim, sargramostim, and erythropoietin) and 14 days for long-acting formulations.

3.1.9 Performance Status
Karnofsky Performance Scale (KPS for ≥ 16 yrs of age) or Lansky Performance Score (LPS for < 16 years of age) ≥ 60 assessed within two weeks prior to registration (See Appendix A)

3.1.10 **Age:**
18 months – 25 years (Minimum weight 20 Kilogram is required to be eligible for the study, since the minimum injection volume of SYLATRON is 0.05 ml, 20 mcg, SQ as suggested by Merck)

3.1.11 Organ Function:

Patients must have evidence of normal organ function as defined by:

- ANC≥ 1000/µl (unsupported)
- Platelets ≥ 100,000/µl (unsupported)
- Hg≥ 8g/dL (unsupported)
- ALT ≤ 2.5 x the upper limit of institutional normal
- Total bilirubin ≤ x 1.5 upper limit of institutional normal
- Serum creatinine ≤ 1.5 x the upper limit of normal for age, or calculated creatinine clearance or nuclear GFR ≥ 70 ml/min/1.73 m^2

Table 1

Serum Creatinine for Age/Gender		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.1.12 Radiographic Progression

Patients must have evidence of radiographic progression as defined below:

- **Stratum 1**:
  - defined as ≥ 25% increase in the product of the greatest perpendicular diameters of the tumor as a whole (solid and cystic component) AND ≥ 0.4 cm increase in each of at least two dimensions of the tumor as a whole OR any new or worsening neurologic/vision deficit in conjunction with a lesser change in the solid or cystic component.
- **Stratum 2**:
  - For patients more than 6 months following RT (including radiosurgery or P32), progression is defined as a ≥ 25% increase in the product of the greatest perpendicular diameters of the solid component AND ≥ 0.4 cm increase in each of at least two dimensions of the solid component;

  - For patients more than 12 months following RT (including radiosurgery or P32), progression is defined as ≥ 25% increase in each of the product of the greatest perpendicular diameters of the solid tumor AND ≥ 0.4 cm increase in each of at least two dimensions of the solid tumor. Patients demonstrating predominantly cystic progression more than 12 months after RT must show a continued increase in the cystic component on two serial MRI scans performed at least 4 weeks apart

OR re-accumulation of the cyst following one or more cyst aspirations. Patients with progressive neurologic signs and/or symptoms associated with isolated cyst formation or progression are eligible if the neurologic signs and/or symptoms do not improve within 4 weeks of cyst aspiration.

3.1.13 Pregnancy Status:
Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative serum or urine pregnancy test. (Pregnancy test must be repeated within 72 hours prior to the start of therapy).

3.1.14 Pregnancy Prevention:
Subjects of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

3.1.15 Informed Consent:
Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Stratum 1 patients: must not have had > 3 surgical debulking procedures/resections.

3.2.2 Patients may not have received prior interferon, either systemic or intra-cystic.

3.2.3 Patients must not have evidence of metastatic tumor or other cancer.

3.2.4 Patients must not be on steroids other than for physiologic replacement.

3.2.5 Patients must not have a severe psychiatric illness, including major depression or any previous suicide attempts.

3.2.6 Patients must not be on phenytoin, warfarin or methadone due to potential drug interactions.

3.2.7 Patients must not have known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Steven-Johnson syndrome, and toxic epidermal necrolysis to interferon alpha or any other products component.

3.2.8 Subjects with inability to return for follow-up visits or obtain follow-up studies required to assess toxicity to therapy.

3.3 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this trial.

3.4 Treatment at Primary Institution

All experimental protocol therapy should be dispensed and all imaging studies must be obtained at the primary institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA-certified laboratory of the investigator's choice.

3.5 Criteria to Start Treatment

3.5.1 Subjects must start therapy within seven (7) days of registration.

3.5.2 Laboratory tests used to assess eligibility must be repeated if therapy starts more than seven (7) days after obtaining labs to assess eligibility. If a test that is repeated after registration and prior to start of therapy is outside the limits for eligibility, it must be rechecked 48 hours prior to the start of therapy. If the recheck is still outside the limits for eligibility, the subject may not receive protocol therapy and will be considered off study.

3.5.3 A urine or serum pregnancy test must be repeated and be negative within 72 hours of beginning the study agent for all females of childbearing potential.

4 REGISTRATION PROCEDURES

4.1 General Guidelines

4.1.1 Prior to Consent

Prior to consent the protocol's status should be verified via the PBTC Protocol Status web page, to ensure study is open to accrual.

4.1.2 Informed Consent

Informed consent must be obtained prior to subject registration. Furthermore, consent should be obtained prior to the initiation of any clinical procedures or assessments performed for the purpose of determining protocol eligibility, which would not otherwise be consistent with the institution's standards of clinical practice.

4.2 Registration Process

Subjects must be registered prior to any protocol treatment. Subject registration is only available to authorized personnel using the PBTC automated registration system. The registration procedures are available in the CRA manual, which is posted on the PBTC members' website. The PBTC Protocol Coordinator listed on the protocol cover page for assistance in the registration process.

Reservations may also be made through the registration system providing time to assess the subject's eligibility. Reservations will be held for a maximum of seven (7) calendar days by which time the subject must have been registered on study. The subject's reservation should be canceled as soon as it is determined that the subject is not eligible or that the family/subject has decided not to consent to the trial.

5 TREATMENT PLAN

- **Stratum 1:** Patients with progressive unresectable or recurrent craniopharyngiomas treated with surgery alone, who have not received radiation therapy. Patients with unresectable craniopharyngiomas (i.e. residual measurable disease following surgical resection) will be enrolled at the time of progression.

- **Stratum 2:** Patients with progressive or recurrent craniopharyngiomas following radiation therapy.

5.1 Agent Administration
SYLATRON will be administered as a weekly subcutaneous injection for up to 18 courses with 6 injections per course. Six consecutive weeks will constitute one course and subsequent courses will immediately follow, with no break in the administration of the drug. All patients will receive a dose of 1 mcg/kg/week. The patient's actual weight (in kilograms) should be used when calculating the dose of SYLATRON and doses should be re-adjusted if necessary at the time of each clinic evaluation. See Appendix C for the SYLATRON dosage calculation and dosage chart. Patients or parents will be taught to administer the medication in the outpatient setting (see Appendix B for a parent handout on administering subcutaneous injections)**.** Patients or their guardians will keep a diary to document SYLATRON administration (available on the PBTC-039 webpage).

Since constitutional symptoms (e.g., fatigue, myalgias, fever) are generally the most severe after the first few doses, acetaminophen (15 mg/kg up to max dose of 1000 mg) should be given 30 minutes prior to administering the first six doses (first course) of SYLATRON and prior to subsequent doses if needed. For fever that develops after a dose of SYLATRON, Acetaminophen (15 mg/kg up to max dose of 650 mg PO) can be given q 4-6 hours as needed, but should not exceed 75 mg/kg/day for a total dose of up to 3000 mg/day. Acetaminophen can also be alternated with ibuprofen (10 mg/kg up to a max dose of 600 mg) every 6-8 hours as needed. Patients who are on replacement steroids for adrenal insufficiency should receive stress dose steroids for any fever > 101 degrees Fahrenheit (38.3 degrees Centigrade). Please see Appendix D for suggested stress steroid dosing for SYLATRON related fever.

It is recommended that a follow-up call be placed to the patient or parent within 72 hours of the first dose to evaluate for toxicities and review optimal management.

5.2 Criteria for Starting Subsequent Courses
A course may be repeated every 6 weeks if the subject has no evidence of progression and has again met laboratory parameters as defined in Section 3.1.11. If a subject does not meet these parameters at the end of the treatment course, then SYLATRON should be held until parameters meet the eligibility criteria. If the next course is delayed >21 days due to failure to meet laboratory parameters of eligibility criteria or drug-related toxicity, the subject should be taken off protocol therapy.

5.3 Duration of Therapy
In the absence of treatment delays due to adverse event(s), treatment may continue for up to 18 courses:

5.3.1 On-Study Data Submission Schedule
Pre-treatment, on-study and off-treatment data, as well as subject response data are to be recorded in the electronic data collection screens using the PBTC RDC database. See the Required Data and Timetable for Submission form located on the PBTC-039 protocol and resources webpage for the schedule. For assistance, contact the PBTC Protocol Coordinator,

listed on the cover page of the protocol. An optional roadmap is located on the PBTC-039 protocol and resources webpage.

5.3.2 Off Treatment Criteria

At the discontinuation of treatment, the "Off Treatment Date" is to be recorded in the eCRF and is to be consistent with the reason given for going off treatment. The "Last Treatment Date" is defined as the last date that the patient received protocol based therapy. Date of "off treatment" must be the greatest of the date of last treatment, date of procedure, date of patient assessment, notification of patient/family decision, or decision made by the physician that resulted in the patient being taken off protocol treatment. The reason for discontinuation of treatment must be documented by the attending investigator in the medical record and recorded in the eCRF.

- Disease progression as defined in Section 11.1.3
- Development of a medical or psychiatric illness that in the investigator's judgment renders the patient incapable of further therapy on this protocol.
- Unacceptable toxicity as outlined in sections 6.
- Patient, parent or legal guardian refuses further treatment on this protocol
- Pregnancy or breastfeeding
- Subject is unable to complete the study evaluations/visits
- Patients who develop significant depression and/or suicidal ideations will be taken off treatment.

5.4 Off Treatment Duration of Follow Up

Patients who are off protocol therapy must be followed until an "Off Study Criterion" is met (see section 5.6).

5.4.1 Patients who have had progression/recurrence will be followed for 30 days after the last dose of SYLATRON or until the resolution of all SYLATRON related toxicities, whichever is longer.

5.4.2 Patients who discontinue for reasons other than progression/recurrence of disease should continue to be followed for progression/recurrence, i.e. until they meet the Off Study criteria (below). Follow-up data will be required.

5.4.3 Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and they meet one of the Off Study criteria (below).

5.5 Criteria for Removal from Study

The date and reason for the subject coming off study must be documented in the eCRF and the Operations, Biostatistics and Data Management Core must be notified according to standard reporting guidelines (see Section 7 and the Required Data and Timetable Submission form located on the PBTC-039 protocol and resources webpage).

- Subject determined to be ineligible.
- Parent, subject, or guardian withdraws consent for continued participation.
- Subject death while on study. The IRB, Study Chair and OBDMC must be notified as per Section 7.
- Subject has completed all trial-specified evaluations and follow-up.

- Subject has started another therapy or experienced disease progression (section 11.1.3).

5.5.1 Off-Study Data Submission Schedule

No data will be collected documenting treatment or reporting events or disease status that occur subsequent to the official "off study" date with the exception of adverse events with an attribution of possible, probable, or definite that occur after the "off study" date (per protocol Section 7).

5.6 General Concomitant Medication and Supportive Care Guidelines

The only contraindicated medications are Phenytoin, Warfarin, and Methadone, which are listed in the eligibility/exclusion criteria. Patients should be asked and should inform their healthcare providers about any OTC medications that they are taking, particularly those containing acetaminophen, in order to avoid over-dosage.

6 DOSING DELAYS/DOSE MODIFICATIONS

If patients drop below 20 kg during SYLATRON treatment, they can have SYLATRON held for up to 3 weeks for increasing nutrition. If they can gain weight and return to ≥ 20 kg, they could restart SYLATRON and not make up lost weeks. This could happen twice before being removed from study.

6.1 Constitutional Symptoms

Every attempt should be made not to stop the drug for constitutional symptoms during the first three weeks, since these symptoms usually improve. Patients with persistent (i.e. lasting > 48 hours) grade 2 or higher constitutional symptoms occurring after the fourth dose should have their dose reduced to 0.6 mcg/kg/week. If symptoms do not improve after 3 weeks of the reduced dose, patients may have their dose reduced to 0.3 mcg/kg/week. If symptoms do not improve after 3 weeks of the second dose reduction, the patient should be taken off treatment.

6.2 Transaminase Elevations

No delays or dose modifications should be made for grade 1-2 elevation of SGOT/SGPT. For grade 3-4 elevations, the dose modifications below should be followed.

6.3 Non-hematologic toxicity other than constitutional symptoms

- Subjects who experience a grade 4 non-hematologic toxicity, or subjects who experience grade 2 or higher cardiopulmonary toxicity that is at least possibly-related to SYLATRON should be removed from protocol treatment and should not restart the drug.

- The development of any other SYLATRON related grade 3 non-hematologic toxicity should result in immediate discontinuation of the drug. Following the discontinuation of the drug, patient should be monitored and may restart the drug if following conditions are met:

  Subjects who develop grade 3 SYLATRON-related non-hematologic toxicity other than constitutional symptoms should have the drug withheld until the toxicity resolves to grade ≤1. If the toxicity resolves to Grade 1 or better within 3 weeks of discontinuation of SYLATRON, patients may restart therapy at 0.6 mcg/kg/week.

Toxicity that does not resolve within 3 weeks will require the subject to be removed from protocol therapy. If the toxicity recurs at the 0.6 mcg/kg/week dose, the dose should be decreased to 0.3 mcg/kg/week, provided toxicity has decreased to Grades 0-1 within 3 weeks of discontinuation of SYLATRON. Recurrent Grade 3 non-hematologic toxicity following two dose reductions will require the subject to be removed from protocol therapy. No subsequent dose escalations are permitted after dose reduction for non-hematologic toxicity.

- Subjects who develop persistent (≥7 days) grade 2 non-hematologic SYLATRON - related toxicities (other than constitutional symptoms and transaminase elevations) that are considered sufficiently medically significant or sufficiently intolerable by patients as to warrant treatment interruption and/or dose reduction should have SYLATRON withheld until the toxicity resolves to grade ≤1. If the toxicity resolves to Grade 1 or better within 3 weeks of discontinuation of SYLATRON, patients may restart therapy at the same dose. Toxicity that does not resolve within 3 weeks will require the subject to be removed from protocol therapy. If the grade 2 toxicity recurs, the SYLATRON dose should be withheld again until the toxicity resolves to grade 1 or better, at which point the dose should be decreased to 0.6 mcg/kg/week, provided toxicity has decreased to Grades 0-1 within 3 weeks of discontinuation of SYLATRON. If the toxicity recurs at the 0.6 mcg/kg/week dose, the dose should be decreased to 0.3 mcg/kg/week, provided toxicity has decreased to Grades 0-1 within 3 weeks of discontinuation of SYLATRON. Recurrent Grade 2 non-hematologic toxicity following two dose reductions will require the subject to be removed from protocol therapy. No subsequent dose escalations are permitted after dose reduction for non-hematologic toxicity.

6.4 Dose Modification for Hematologic Toxicity

Any subject who has an ANC <1000/μL or platelet count <100,000/μL should have the test repeated within 1 week (prior to the next dose of SYLATRON). The criteria for dose modification are as follows:

- Absolute neutrophil count (grade 4) <500/μL
- Platelets (grade 3) <50,000/ μL

Whenever a subject's blood count(s) drop below the criteria shown above, the SYLATRON will be held until the count(s) recover to Grades 0-1 and the dose will be reduced to 0.6 mcg/kg/week. Toxicity must recover to Grades 0-1 within 3 weeks of discontinuation of SYLATRON in order to allow re-initiation of treatment at the reduced dose. Toxicity that does not resolve within 3 weeks will require the subject to be removed from protocol therapy. Should the toxicity recur at the 0.6 mcg/kg/week dose level, a second dose reduction to 0.3 mcg/kg/week should be performed provided the toxicity has decreased to Grades 0-1 within 3 weeks of discontinuation of SYLATRON. If there is again recurrence of hematologic toxicity meeting the above requirements for dose reduction (i.e., following the second dose reduction) treatment with SYLATRON will be discontinued permanently. No subsequent dose escalations will be permitted after dose reduction for hematologic toxicity.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Adverse Events and Potential Risks

7.1.1 Adverse Event List(s) for SYLATRON (Peginterferon alfa-2b). See package insert for further information.

COMMON, SOME MAY BE SERIOUS In 100 people receiving Peginterferon alfa-2b, more than 20 and up to 100 may have:
• Nausea, vomiting, loss of appetite • Chills, fever • Reaction during or following injection of the drug which may cause fever, chills, rash, low blood pressure • Swelling and redness at the site of the medication injection • Tiredness • Pain • Dizziness, headache • Depression • Hair loss • Liver damage which may cause belly pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Peginterferon alfa-2b, from 4 to 20 may have:
• Anemia which may require blood transfusions • Abnormal heartbeat which may cause fainting • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Bleeding of the eye • Bruising, bleeding • Confusion • Change in personality • Sensing things that are not there • State of mind that involves a "loss of contact with reality" • Thoughts of suicide or harming others • Low blood pressure

RARE, AND SERIOUS In 100 people receiving Peginterferon alfa-2b, 3 or fewer may have:
• Blood clot • Blurred vision with chance of blindness

Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for recording AEs in the RDC database. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for expedited AE reporting. CTCAE version 5.0 will be utilized for expedited AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE versions 4.0 and 5.0. A copy of the CTCAE versions 4.0 and 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.2 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.2.1).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made by telephone at 901-595-2715 to the PBTC Operations Office for instances when the Internet fails. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site. Also, if internet connectivity is not re-established within 24 hours, notify the following by telephone and or email.

PBTC-039 Study Chair:
Stewart Goldman, MD
Ann & Robert H. Lurie Children's Hospital of Chicago
Neuro-Oncology
[redacted]

PBTC OBDMC:
Shujie Han, MD, Ph.D., CCRA
St. Jude Children's Research Hospital
Department of Biostatistics
[redacted]

Local IRB

CTEP-AERS is programmed for automatic electronic distribution of reports to the following

individuals: Study Coordinator of the PBTC, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

The OBDMC will fax the SAE / CTEP-AERS report, within 48 hours of their awareness of the event to Merck Sharp & Dohme, Corp worldwide product safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Merck Sharp & Dohme, Corp will submit a report of the SAE to the FDA using the FDA's reporting form (FDA 3500A MedWatch Form) and guidelines. The report should describe the event as fully as possible. Supporting documentation (lab reports, summary notes, and autopsy report) should accompany the report. A fatal or immediately life-threatening SAE will be reported to the FDA within 7 calendar days of the receipt of the initial report by the sponsor. A non-fatal, no-life threatening SAE will be reported to the FDA within 15 calendar days of receipt of the initial report by the Sponsor.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. This submission will be cross referenced according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.1 Expedited Reporting Guidelines

Use the NCI protocol number and the PBTC patient accession number assigned during trial registration on all reports.

Note: A death on treatment requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3 Routine Adverse Event Reporting

Adverse Events **must** be reported in routine study data submissions as outlined below:

- Any baseline (pretreatment) abnormalities observed during the initial physical examination should be recorded in the PBTC RDC database.
- Only record adverse events Grades 1 and 2 if the attribution is at least possibly related to SYLATRON. Record all adverse events Grades 3 through 4 and deaths (while on treatment or within 30 days of treatment), regardless of attribution on the electronic case report forms (PBTC RDC database).

7.4 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*,

treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia i.e. AML)
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.5 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

Merck has decided to voluntarily discontinue the manufacture of the PegIntron vials, Injection, for subcutaneous use, for distribution in the United States for business reasons. The decision is not based on any safety or efficacy findings with this product. This decision is due to scientific advancement, changes in treatment practices, and the consequent reduction in the demand for PegIntron. SYLATRON, which has the same active ingredient as PegIntron (Peginterferon alfa-2b) with different Dosage Strength, is proposed to replace PegIntron as the study drug of PBTC-039.
A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 SYLATRON (PEGINTERFERON ALFA-2B) (NSC # 720033)

PEG_{12000}-IFN is a covalent conjugate of recombinant Intron® A with monomethoxy polyethylene glycol (PEG, with an average molecular weight of 12,000 daltons). The conjugate is synthesized by reacting Intron® A with an electrophilic derivative of PEG.

8.1.1 Agent Ordering

Study Agent/s may be requested by the Principal Investigator (or their authorized designees) at each participating institution. All regulatory document requirements, as described by the PBTC, must be current and up to date prior to requesting study agents.

8.1.2 Drug Requests:

Drug request forms and instructions can be found on the PBTC-039 protocol and resources webpage. Peginterferon alfa-2b (SYLATRON) drug requests should be sent to Almac Clinical Services.
Brandon Sortman
Project Manager - Distribution
Almac Clinical Services
[redacted]

8.1.3 Product description:
PEG_{12000}-IFN Powder is a white to off-white lyophilized powder supplied in 2-ml vials for subcutaneous use.

8.1.4 Solution preparation:
Each vial of SYLATRON contains 296 mcg of PEGINTERFERON ALFA-2B with dibasic sodium phosphate, monobasic sodium phosphate, sucrose and polysorbate 80. Following reconstitution with 0.7 mL of Sterile Water for Injection USP (or equivalent), each 0.5 mL contains 200 mcg PEGINTERFERON ALFA-2B. No more than 0.5 mL should be taken from any single vial. This allows for an overfill volume to compensate for residual volume in the vial and syringe/needle hub during withdrawal, as well as for volume displacement by the excipients during reconstitution. The clear, colorless solution has a pH of 6.5 to 7.1, is iso-osmotic, and unless otherwise specified, is intended to be used directly from the vial for SQ injection.

8.1.5 Storage requirements:
SYLATRON should be stored at 25°C, excursions permitted to 15-30°C. Do not freeze. Keep away from heat. After reconstitution with supplied diluent, the solution should be used immediately, but may be stored up to 24 hours at 2 to 8°C. The reconstituted solution contains no preservative, is clear and colorless. Upon completion of the study, all remaining study drug will be destroyed and disposed of pursuant to the ICH/GCP Guidelines and Institutional policies.

8.1.6 Stability:
The reconstituted solution is stable for 24 hours when stored refrigerated between 2-8°C (36-46°F). However, it is recommended that the solution be used within 3 hours after mixing.

8.1.7 Route of administration:
SYLATRON (PEGINTERFERON ALFA-2B) will be administered subcutaneously. The following syringes and needles are recommended: B-D disposable syringes (Tuberculin syringes), B-D Number 30963; Needle gauge: 27; Length: 1/2 inches (13 mm). Dosing instructions are provided in Appendix C

9 PATHOLOGY, CORRELATIVE AND IMAGING STUDIES
Information for the collection, shipping and handling for all exploratory correlative studies, neuropathology review and research imaging is located in this section. The table below identifies the tests, sample type and amount, analyzing laboratory and whether it is required or optional. For additional details, please review the associated section below.

Test Name	Sample Type and Amount	Analyzing Laboratory	Required or Optional	Section ID
Tumor Biology • IHC for WNT Pathway • Pyrosequencing for BRAF V600E mutation	FFPE unstained slides and Scrolls	Adekunle Adesina, TXCCC	Optional	9.1
Neuropathology Review	1 H&E slide	PBTC CRB	Required	9.2
Imaging	Routine MRI	NIC	Required	9.3

9.1 Pathology and Exploratory Correlative Studies

As of July 19, 2015, the decision was reached to ship the existing PBTC-039 FFPE tumor material collected for the required Tumor Biology studies to the PBTC Central Review and Biorepository (CRB) for distribution to the Correlative laboratory for analysis. Patients enrolled prior to this amendment who are still in follow-up should be asked to consider tissue submission to the PBTC CRB. The PBTC CRB's function is to collect, distribute and store specimens for central pathology review and planned correlative studies which support the laboratory objectives of this protocol.

The CRB will also serve as a central repository for left over tumor tissue, from consenting patients on this protocol. These samples will be stored in the repository for undefined future studies which support the mission of the PBTC. If the patient does not consent to participation in the storage for future studies, remaining correlative study samples for the biology objective will be destroyed once the PBTC-039 analysis is complete.

9.1.1 Specimens from Existing Patients

Formalin fixed, paraffin embedded (FFPE) tumor materials which have been prepared and are pending shipment are to be labeled with the PBTC Accession # and the PBTC study for which the sample is provided. These samples are to be shipped to the repository (see section 9.1.4) for distribution to the Correlative laboratory for analysis.

If the samples have not been prepared and the patient is available, please discuss submission to the repository for analysis and storage for future studies. If the patient consents to participate in the repository, follow the guidance in Section 9.1.2 to prepare the samples for submission.
If the patient does not consent to the repository, prepare the samples as described in Section 9.1.7 and ship to the repository (see Section 9.1.4) for distribution to the Correlative lab for analysis. Unused samples will be destroyed once the PBTC-039 analysis is complete unless the patient has consented to long term storage of unused sample.

9.1.2 Specimens from Future Patients

If the patient consents to provide slides for submission to the repository at the time of participation in a PBTC trial the following should be submitted:

- Tumor material
  Slides from the original and/or recurrent surgery should be prepared for storage. The site should provide up to twenty (20) unstained sections cut at 4µm in thickness on (+) slides from the most representative section. Microcentrifuge tubes containing 3 x20 µm scrolls are also requested. Preference is for tissue that has not previously been frozen. The corresponding pathology report (s) including immunohistochemical, special stains, and molecular/genetic results is to be uploaded to the PBTC using the secure File Upload system. These reports will be made available to the pathologist via a link in ProtoLab.

- Suitability of sections should be established by preparing one (1) H&E to ensure that the sections meet the following criteria:
  - histologically representative of the reported lesion
    for unstained slides, tissue should contain at least 60% viable tumor

  - no more than 40% necrosis
  - for scrolls, tissue blocks with greater than 80% tumor component are preferred.

- Peripheral Blood Mononuclear Cells
  PBMC may be collected by processing a 2-5 mL whole blood specimen with Ficoll or collecting the specimen in a BD Vacutainer™ CPT™ Cell Preparation Tube with Sodium Citrate as noted below. Once separated, all pellets must be snap frozen and stored at least at -20ºC prior to dry ice shipment.

Specimen Collection and Processing by Ficoll tube

- Collect 2 - 5mL of fresh blood into an EDTA tube.
- Transfer blood into a sterile 50-mL tube and add double the amount of PBS. MIX GENTLY.
- Set up another tube containing half of its total volume of Ficoll. For example, if there is 15 mL of blood + PBS, then use 7.5 mL of Ficoll (2:1 ratio).
- At very slow pace (approx. 2 mL/minute), layer the blood + PBS mixture onto the Ficoll so that the solutions DO NOT MIX. Spin the blood/Ficoll at 750 g in slow mode for 30 minutes @ 25ºC. After spin you will see four distinct layers: plasma (top layer), white fluffy ring (2nd layer), Ficoll (3rd layer), and blood (bottom layer).
- Remove plasma layer down to about 1 mL above the white fluffy ring and discard.
- Collect the entire white fluffy ring. If ring is hard to see, also take extra liquid above. Then discard everything else.
- Place this fraction of white blood cells into a fresh 50 mL sterile tube with 20 mL of PBS. Spin down for 10 minutes @ 25ºC, 750 g in fast mode. Remove the supernatant. Add back to pellet 1 mL of PBS and spin for 5 min. at 4°C at 10000rpm. Remove supernatant.
- Freeze the pellet of WBCs and store at -80ºC until shipment.
- Ensure that all tubes are clearly labeled with the PBTC patient accession number. Please ensure that the labeling system used is designed to withstand temperatures down to -80ºC. Samples should be stored at -80ºC until shipment. For short term storage (2-3 weeks) -20ºC is acceptable. NOTE 4ºC IS NOT ACCEPTABLE STORAGE.

If it is not possible to collect the PBMC by Ficoll gradient then separation of PBMC can be conducted using CPT tube separation as an alternative. However the PBMC pellet MUST BE frozen immediately and stored at -80ºC.

Collection and Processing by CPT tube

- Peripheral blood should be collected in a BD Vacutainer CPT™ Cell Preparation Tube with Sodium Citrate. 8 mL and 4 mL CPT tubes can be obtained from Fisher Scientific (Cat# 02-685-125, 02-688-81) or Becton-Dickinson (BD No.362761, 362760). The 8 mL tubes have a 6 mL minimum draw and the 4 mL tubes have a 3 mL minimum draw.
- Centrifuge the CPT™ tube at 1500 x g for 30 minutes at room temperature (20º C to 25º C). DO NOT APPLY THE BREAK ON THE CENTRIFUGE. Use acceleration 5, brake 0 (“slow mode”).
- It may be necessary to spin the tube longer to ensure that all of the red blood cell components have been separated from the plasma layer through the polyester gel barrier.

- The tube should be removed immediately from the centrifuge. The mononuclear layer and plasma lie above the polyester gel plug.
- Using a sterile pipette, remove as much of the plasma component (upper half of the CPT tube) without disturbing the mononuclear layer if possible and discard.
- Transfer mononuclear cell layer (and some residual plasma layer) to a labeled 15- mL conical centrifuge tube and add 5 mL sterile room temperature magnesium or calcium-free phosphate buffered saline (PBS) to fill the conical tube and recap.
- Centrifuge at 450 x g for 10 minutes at room temperature (20º C to 25º C). Use acceleration 9, brake ("fast mode").
- Remove supernatant, being careful not to aspirate the cellular pellet at the bottom of the tube.
- Add 1 mL of sterile PBS to the pellet and gently re-suspend by pipetting up and down. Transfer the entire suspended pellet to the labeled cryovial.
- Centrifuge the cryovial at 450 x g for 5 minutes (or spin down the microcentrifuge tube at 1300 x g for 5 minutes) at room temperature. Discard the supernatant. Store the cell pellet cryovial frozen at -80ºC. For short term storage (2-3 weeks) -20º C is acceptable.

If the patient consents to other correlative studies as outlined in sections 9.1.5, the following specimens may also be submitted to the CRB for distribution and storage:

- Scrolls: if sufficient tissue is available, 2 scrolls at 10 micron thickness

9.1.3 Handling of Specimens

- Slides are to be labeled with the patient PBTC Accession # and these slides should be designated as PBTCRB # (where the # assigned from 1 to 20, or the highest number of unstained sections prepared, sequentially) or PBTCCRB H&E for the H&E stained section. The tubes containing scrolls are to be labeled with the PBTC Accession # and the PBTC study for which the sample is provided.

- Scrolls of Formalin Fixed, Paraffin Embedded (FFPE) tumor materials are to be labeled with the PBTC Accession # and the PBTC study for which the sample is provided. Scrolls of FFPE tumor material should be shipped at room temperature.

- PBMCs are to be labeled with the PBTC Accession # and the PBTC study for which the sample is provided. Samples should be shipped overnight in a separate box with a 2-day supply of dry ice.

9.1.4 Shipment of Specimens

Samples collected for distribution and storage in the repository should be sent to the PBTC CRB via FedEx by completing the Internet form at http://www.fedex.com/us/ and using the cc function to email PBTC CRB, the repository contact. FedEx user ID and password for pathology shipping can be found at PBTC-039 protocol. Samples are to be shipped to:

PBTC CRB
Research Support and Biorepository Services
Children's Hospital Los Angeles

[redacted]

9.1.5 Assessment of WNT and MAPK Pathway Activation

FFPE tissue is obtained for diagnostic purposes in virtually all brain tumor resections, unlike frozen tumor material, which is obtained at the discretion of the neurosurgeon. Tumor material submission is optional but strongly encouraged for exploration for evidence of WNT pathway activation by immunohistochemistry (IHC) for nuclear beta-catenin protein and MAPK pathway activation by pyrosequencing for BRAF V600E mutation in tumor tissue. Investigators should make every effort possible to obtain tissue when available and must review with the study chair or co-chair if tissue is not available.

- WNT Pathway Activation IHC :

FFPE tumor sections will be evaluated for evidence of WNT pathway activation through staining for nuclear and cytoplasmic beta-catenin expression (phospho-β catenin, β-catenin supplied by New England Biolabs, Beverly, MA). The assays have been developed and validated previously on medulloblastoma samples. [33]

- Detection of BRAF V600E mutation by pyrosequencing

FFPE tumor sections will be evaluated for evidence of MAPK pathway activation through detection of the BRAF V600E mutation by pyrosequencing, using protocols currently in use in the Molecular Neuropathology laboratory, Department of Pathology, Texas Children's Hospital.

9.1.6 Collection of Specimen(s)

- Twenty slides (5-6 μm) of unstained FFPE tissue are requested for IHC of *WNT* pathway to evaluate evidence of *WNT* pathway activation in resected tumor tissue. The referring pathology departments should cut and send slides to the PBTC-CRB see Section 9.1.4.
- Scrolls should be cut (3 x 20 μm) into 1.5ml microfuge tubes. Tubes should be labeled with the patient's PBTC Accession number.

9.1.7 Site Performing Correlative Study

Analysis will be performed by Adekunle M. Adesina, MD, PhD, in the Department of Pathology Texas Children's Hospital/Baylor College of Medicine.

9.2 Central Pathology Review

Central pathology review is required for this study. Pathologist review for this study will include the following elements:

- For each subject one H&E stained slide per one representative block from the brain tumor, removed either at initial diagnosis or relapse, should be submitted for review.
- Review of the corresponding pathology report(s) of the immunohistochemical, special stains, and molecular/genetic results from current and/or original primary tumor
- If necessary, review of immunohistochemical or special stained slides. Slides submitted to the PBTC CRB will be digitized to 40X. H&E stained sections will be retained and

filed at the CRB. Original immunohistochemical or special stain slides will be returned to the submitting institution.

9.2.1 Pathology Central Review and Data Collection

The slides from the submitting institution will be sent to the PBTC CRB for central review. The accompanying complete pathology evaluation should be uploaded to the PBTC using the secure File Upload system. The slides will be logged into ProtoLab to document receipt of the samples. Slides will then be scanned at 40X using Leica Aperio Whole Slide Scanner. The slides will be made available for remote review by the assigned reviewer and the corresponding reports will be available via a link in ProtoLab. The reviewer will be able to access the Protolab database to enter and review results via a VPN connection accessed by assigned usernames/passwords.

9.3 Imaging Studies

9.3.1 Description of the study:

Brain MR with and without gadolinium focused on the sellar and suprasellar regions will be obtained preferably on the 3T magnet consisting of high resolution sagittal T1 images (slice thickness 3mm skip 0, 20cm FOV), high resolution coronal T1 images (slice thickness 3mm skip 0, 16 cm FOV), axial T2 images (slice thickness 2.5mm thickness skip 0, 20 cm FOV), axial T2 FLAIR images(slice thickness 4.0 mm, 20 cm FOV), high resolution coronal T2 images (slice thickness 2.0mm FOV 16cm), post gadolinium high resolution coronal T1 images (slice thickness 3mm skip 0, 16 cm FOV) and post gadolinium sagittal T1 high resolution images (slice thickness 3mm skip 0, FOV 16 cm) followed by axial T1 post-gadolinium images through the whole brain (slice thickness 4mm skip 0, FOV 20 cm).

Imaging protocol sequences will be sent to the participating sites of the PBTC. Imaging specific protocols will also be sent for 1.5T magnets with the following parameters: high resolution sagittal T1 (slice thickness 3.0mm skip 0, FOV 20 cm), axial T2 images of the whole brain (slice thickness 4.0mm skip 0, FOV 20cm), axial T2 FLAIR of whole brain(slice thickness 4.0 mm skip 0, FOV 20cm), axial T1 images of the whole brain (slice thickness 4mm skip 0, FOV 20cm), coronal FSE T2(slice thickness 3 mm, interleaved, FOV 16 cm), coronal T1 (slice thickness 3mm interleaved, FOV 16 cm), post-gadolinium high resolution coronal T1 and sagittal T1 images (3mm skip 0, FOV 16 cm).

9.3.2 Outcome Measure

See section 11 for the linear parameters used to assess response, depending on the stratum and whether the tumor is predominantly solid or cystic or both.

9.3.3 Timing of Assessment

Imaging studies will be done at baseline prior to PEGINTERFERON ALFA-2B therapy and every 12 weeks for the first 9 courses (approximately 1 year) then every 18 weeks thereafter until subjects develop evidence of disease progression, unacceptable toxicity or completion of 18 courses (approximately 2 years) of PEGINTERFERON ALFA-2B therapy.

9.3.4 Image Transfer

Only the MRI scans specified below for the two strata will be electronically transferred to the PBTC to be submitted to the PBTC Neuroimaging Center (NIC). All subject specific data will be stripped from the images and will be replaced with PBTC Accession numbers by the PBTC prior to sending images to the NIC. All image data transfer is accomplished using PGP (pretty-good-privacy) 128-bit encryption, which meets industry standard for secure communication.

Stratum I:
All imaging studies obtained during the first 9 courses of treatment (approximately 1 year) will be centrally reviewed by the NIC. In addition if they occur beyond the first 9 courses of treatment imaging studies documenting smallest disease measurement recorded since the start of protocol, responses, confirmation of responses (follow-up scan approximately 3 months later) and documenting PD will also centrally reviewed and the protocol criteria for disease assessment will be compared to the MacDonald criteria.

Stratum II:
Central review of imaging studies will be carried out only in patients with a response or progressive disease while on study. For these patients, central review of smallest disease measurement recorded since the start of protocol, imaging studies documenting responses, confirmation of responses (follow-up scan approximately 3 months later) and studies documenting PD will be carried out and the protocol criteria for disease assessment will be compared to the MacDonald criteria.

10 STUDY CALENDAR

Table 2
Standard Clinical and Laboratory Assessments

	Pre-Therapy	Course 1	Course 2-9	Course 10-18	End of Treatment
PHYSICAL ASSESSMENTS					
Complete History	X				
Interval History		X[A]	X[C]	X[F]	X
Psychiatric History**	X	X[A]	X[C]	X[F]	X
Performance status	X	X[A]	X[C]	X[F]	X
Physical including neurologic exam	X	X[A]	X[C]	X[F]	X
Visual field evaluation (as feasible)	X		X[C]	X[F]	
Ophthalmology evaluation	X		X[C]	X[F]	
Vital signs	X	X[A]	X[C]	X[F]	X
LABORATORY EVALUATION					
CBC (WBC, Hgb, Hct, Platelets, ANC, ALC)	X	X[A]	X[C]	X[F]	X
Serum Chemistries (Electrolytes, BUN, Creatinine, SGOT(AST), SGPT(ALT), Total Bilirubin, TSH	X	X[A]	X[C]	X[F]	X
Urinalysis for protein (Urine Dip)	X	X[A]	X[C]	X[F]	X
Serum or urine pregnancy test (for females of childbearing potential)	X	X[C]	X[C]	X[F]	
IMAGING EVALUATION					
Brain MRI with thin cuts through the sella[D]	X		X[B]	X[G]	X
OTHER					
Biology Studies (assessment of WNT and MAPK pathway activation)	X[E]				
FFPE tumor tissue for PBTC CRB	X[E]				
PBMC for PBTC CRB	X[E]				

[A] Assessments should be done prior to starting course 2, i.e. prior to the 7th injection.
[B] Obtain every 12 weeks at time of visit and at time of progression as feasible
[C] Obtain every 12 weeks at time of visit
[D] See section 9.3 9.3.1
[E] See section 9.1.
[F] Obtain every 18 weeks at time of visit
[G] Obtain every 18 weeks at time of visit and at time of progression as feasible

*** NOTE: Patients who do not have a Brain MRI performed at or after 9 courses (approximately 12 months) will be considered failures for the purpose of assessing the primary objective according to the statistical design. See section 13.4.1.**

** Psychiatric History: patient/family will be queried about mood, depression and suicidal ideations at each study visit. If there are any concerns about significant depression or any suicidal ideation, patient should be referred to Psychiatrist.

11 MEASUREMENT OF EFFECT

Response will be assessed on MRI scans, neurologic examinations and visual field evaluations when applicable. Best response will be defined as below, based on the definitions used in the pilot study of non-pegylated interferon[15]:

11.1 Tumor Response Criteria

Please note, measurements are required for both the solid and cystic components

11.1.1 Complete response (CR):
Total disappearance of all radiographically detectable tumor. Response must be sustained on the follow-up scan 3 months later.

11.1.2 Partial response (PR):
At least 50% decrease in the product of the greatest perpendicular diameters of the tumor as a whole, i.e., solid and cystic components. Response must be sustained on the follow-up scan 3 months later.

11.1.3 Progressive disease (PD):
The definitions of PD vary by strata and time on treatment given that transient increases in cyst size can be seen both during interferon therapy as well as for a prolonged period of time after radiation therapy.

Stratum 1:

- Within the first 12 months of treatment: ≥ 25% increase in the product of the greatest perpendicular diameters of the solid component AND ≥ 0.4 cm increase in each of at least two dimensions of the solid component (note that these do not have to be the same measurements used to determine the product of the greatest perpendicular diameters) compared to the smallest disease measurement recorded since the start of protocol OR any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the solid component OR any new or worsening significant neurologic/vision deficit associated with solely a change in the cystic component that does not at least stabilize following a simple cyst aspiration. Isolated cystic enlargement is not considered progressive disease during the first 12 months of treatment unless more than 1 cyst aspiration is required for symptom control.

- After the first 12 months of treatment: ≥ 25% increase in the product of the greatest perpendicular diameters of the tumor as a whole (solid and cystic component) AND ≥ 0.4 cm increase in each of at least two dimensions of the tumor as a whole compared to the smallest disease measurement recorded since the start of protocol OR any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the tumor as a whole. If cyst aspiration is required for symptom control, the patient will be considered to have PD.

Stratum 2:

- Within the first 12 months of treatment: ≥ 25% increase in the product of the greatest

perpendicular diameters of the solid component AND ≥ 0.4 cm increase in each of at least two dimensions of the solid component (note that these do not have to be the same measurements used to determine the product of the greatest perpendicular diameters) compared to the smallest disease measurement recorded since the start of protocol OR any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the solid component. Isolated cystic enlargement in the post- irradiation cohort is not considered progressive disease during the first 12 months of treatment, and it is anticipated that patients may already have or may need an Ommaya reservoir for repeated cyst taps as needed to control symptoms.

- After the first 12 months of treatment: ≥ 25% increase in the product of the greatest perpendicular diameters of the solid component AND ≥ 0.4 cm increase in each of at least two dimensions of the solid component of the tumor compared to the smallest disease measurement recorded since the start of protocol OR any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the solid component. An isolated increase in the cystic component in an asymptomatic patient is not considered progressive disease. Patients with progressive neurologic signs and/or symptoms associated with isolated cyst formation or progression will be considered to have PD if the neurologic signs and/or symptoms do not improve within 4 weeks of cyst aspiration or if > 2 cyst aspirations are required to control symptoms.

11.1.4 **Stable disease (SD):**
Those patients don't meet the criteria for PD or response.

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Data reporting

12.1.1 On-Study Data Submission Schedule
Pre-treatment, on-study and off-treatment data, as well as subject response data are to be recorded in the electronic data collection screens using the PBTC RDC database. See the Required Data and Timetable for Submission form located on the PBTC-039 protocol and resources webpage for the schedule. For assistance, contact the PBTC Protocol Coordinator, listed on the protocol title page. An optional roadmap is located on the PBTC-039 protocol and resources webpage.

12.1.2 Method
This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. A protocol and subject-specific CDUS "Abbreviated" data set will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website (http://ctep.cancer.gov/reporting/cdus.html).

12.2 CTEP Multicenter Guidelines

NA

12.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study and the data will be released to an unauthorized third party without the prior written approval of the Pediatric Brain Tumor Consortium (PBTC).

The PBTC protocol coordinators, other authorized representatives of the sponsor, regulatory representatives, PBTC auditors, representatives of the IRB or the pharmaceutical collaborator supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Source documents which are the original records of clinical findings, observations or activities in a clinical trial are to be maintained at each participating site. Sites must upload all source documentation which supports the eligibility of the participant to the PBTC. In the event the patient experiences unexpected events, additional source documentation may be requested to complete the event review. These documents may include but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda and radiographic images.

Study participant study related data, which is for purposes of statistical analysis and scientific reporting will be submitted to the Pediatric Brain Tumor Consortium. This will not include the participant's contact or identifying information. Rather, research participants and their research data will be identified by a unique study identification number assigned at the time of screening or registration. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

The study data entry and study management systems used by clinical sites and by the PBTC will be secured and password protected. At the end of the study, all study data is maintained on a secure server.

After the study is completed, the data collected will be maintained on a server and may be used by other investigators, including those outside the study. With the participant's approval and as approved by local IRBs, biological samples labeled only with the participant's protocol specific identification number will be stored at the PBTC Central Review and Biorepository and could be made available to other investigators for future unspecified research. Investigators conducting future studies will not have access to the key for stored data collected while the participant is on study. Clinical data will be de-identified before it is shared with other investigators.

If the participant agrees to submit a repository sample, those samples contain genetic information that may be used for research related to brain tumors and their treatment. They may also be used to develop tests/assays to improve diagnosis and treatment of these diseases in the future.

Genetic research may consist of the analysis of one or more genes or the analysis of genetic markers throughout the genome.

13 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoints

Stratum 1: Rate of disease stabilization for 1 year (i.e. 9 courses of treatment).
Stratum 2: Sustained Objective Response (PR+CR) rate in the cystic and/or soft tissue component observed during the first year of treatment (i.e. 9 courses of treatment). Response must be sustained for 3 months.

13.2 Secondary Endpoints

Stratum 1: Sustained objective response rate and progression free survival
Stratum 2: Progression free survival

13.3 Sample Size/Accrual Rate

Stratum 1:
The design will be based on proportion of patients who complete 9 courses of treatment (approximately 1-Year) without an event (PD or death for any reason). Even though the primary outcome variable for this stratum has a long duration, since the PBTC (or the COG) has no historical data available on which we could base a design, we chose to use a binomial endpoint. While the use of a binomial outcome variable results in some loss of information, it allows us to avoid making distributional assumptions which cannot be checked due to unavailability of historical data. Patients in stratum 1 will be enrolled at the time of progression.

A summary of the proposed design for this stratum are provided in the table below. For patients who have never received radiation, >50% 1-year disease stabilization rate is felt to be the minimal acceptable threshold, since radiation can achieve high rates of disease control for at least a year with reported long term disease control rates of 75-90%[13-15]. In this study we are targeting 75% as the desirable rate for 1-year disease stabilization. More specifically, PEGINTERFERON ALFA-2B will be deemed not worthy of further investigation in this patient population, if the true 1-year disease stabilization rate is less than 50% and the design will have 90% statistical power for a true disease stabilization rate of 75%. These parameter settings coupled with type I error rate set at 10% lead to a sample size of 28 eligible and evaluable patients based on a 1-sample 1-sided exact binomial design. If 18 or more patients experience disease stabilization that lasts for at least 1 year, then we will conclude that PEGINTERFERON ALFA-2B is sufficiently active in this disease to warrant recommendation for continued investigation. We will conduct an interim analysis for futility once 12 patients have been enrolled and followed for 1 year (accrual will not be stopped for interim analysis). If we observe 6 or fewer patients who complete 1-year without an event among the 1st twelve patients treated, then we will stop accrual early for lack of evidence of adequate activity. If the true 1-year disease stabilization rate is 50%, there is a 61.6% chance that the trial will stop early for lack of efficacy. On the other hand, if the true 1-year disease stabilization rate is 75%, the probability that we will

stop early is 5.0%. The attained significance level and power of this design are 0.082 and 0.902, respectively.

Table 3

One-Sample Group Sequential Exact Binomial Design for Efficacy Monitoring
Efficacy: Unacceptable ≤ 50%, Desirable ≥ 75%
(α=β=0.1)

	n	Efficacy
Stage 1	12	Stop if number of "successes" ≤ 6
Final	28	Reject if number of "successes" ≤ 17

Accrual Duration:
Based on our informal survey prior to the initiation of this study, PBTC sites estimated that they each saw 1-2 patients per year who would be eligible to enroll on this stratum. Hence we originally estimated that it will take approximately 2.5-3 years to complete accrual taking into account the long outcome assessment window which is our main reason for not considering a Simon-type design where accrual would have to be suspended at the time of the interim analysis. As of amendment 3, the actual accrual rate proved to be substantially slower than this estimate with approximately 4 patients per year, taking into account the initial period when sites put the protocol through their IRBs etc. So based on this revised accrual estimate, we expect to complete accrual to this stratum in 5-6 years. The timing of the interim analysis is difficult to estimate but we expect that it will occur approximately 3.0-3.5 years after initiating accrual.

Stratum 2:
Objective response (CR+PR) rate observed during the first year of treatment (more specifically during the first 9 courses) is the primary endpoint for this stratum. In order to count towards the success criteria, objective responses observed during the first year must be sustained for 3 months. Simon's optimal two-stage design will be employed in this stratum, where accrual will stop, i.e. the trial will terminate early if evidence accumulates that the efficacy is lower than the specified acceptable levels. For patients who have failed radiation, >10% response rate will be the minimal acceptable threshold for response, but > 35% will be the threshold to establish efficacy. More specifically PEGINTERFERON ALFA-2B will be deemed not worthy of further investigation in this patient population if the true sustained objective response (CR+PR) rate during the first year of treatment is less than 10% and the design will have 90% statistical power for a true response rate of 35%. These parameter settings coupled with type I and II error rates set at 10% lead to a sample size of 19 eligible and evaluable patients based on a Simon's optimal design. Eleven (11) patients will be accrued in the first stage and if one (1) or fewer sustained objective responses are observed among the first 11 patients during their 1st year of treatment, the stratum will be closed to accrual and we will conclude that PEGINTERFERON ALFA-2B does not merit continued investigation in this disease due to lack of efficacy. Otherwise accrual will continue until 19 evaluable patients have been treated and assessed for objective response and toxicity. If four or more (≥4) patients experience sustained objective responses (CR+PR), then

we will conclude that PEGINTERFERON ALFA-2B is sufficiently active in this disease to warrant recommendation for continued investigation. With this design if the true response rate is 10%, the probability that the trial will stop early is 70%. However, if the 'true' response probability is 35%, then there is a 6% chance that the trial will terminate in stage 1. While it is possible that the study will be closed to accrual for an extended period (up to 15 months) to assess outcome at the time of the interim analysis, considering the very low efficacy thresholds established for this stratum, and the relatively slow expected accrual rate, it is unlikely that this will be the case. If we reach 10 patients and we only have 1 response, it would be prudent to suspend accrual until the outcome for the last patient is available in order to avoid exposing additional patients to an ineffective agent.

Table 4

Simon's Optimal Two-Stage Design for Efficacy Monitoring
Efficacy: Unacceptable ≤ 10%, Acceptable ≥ 35% **(α=β=0.1)**

	n	**Efficacy**
Stage 1	**11**	**Stop if number of "successes" ≤ 1**
Final	**19**	**Reject if number of "successes" ≤ 3**

Accrual Duration:
During the planning stages of the trial, the PBTC sites estimated similar numbers (perhaps slightly lower than Stratum I) for accrual in this stratum (i.e., 1-2 patients per year/site). Based on this information, we estimated that it will take Approximately 1.5 years to reach the interim analysis sample size and approximately 2.5 years to finish accrual (not including any prolonged closure at the time of the interim analysis). As of amendment 3, based on the slower than expected accrual rate, we are revising the accrual estimates to 6 patients per year and thus we estimate that the trial will complete accrual in 3-4 years with an expected interim analysis to be performed approximately 2 years after initiating accrual.

Combined accrual for Strata I and II:
This is the first PBTC study for this patient population and therefore we do not have specific accrual data for patients with craniopharyngiomas. Thus the estimates in the table below are based on enrollment information from recent PBTC studies for other brain tumors. The maximum total planned accrual to this trial is 47 eligible and evaluable patients. Taking into account the possibility of some patients being declared ineligible or inevaluable, we estimate that we will enroll no more than 52 patients on this trial.

Table 5

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	3	4	7

Non-Hispanic	23	22	45
Ethnic Category: Total of All Subjects	26	26	52
Racial Categories			
American Indian/Alaskan Native	0	0	0
Asian	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
Black or African American	3	4	7
White	20	19	39
More Than One Race	2	2	4
Racial Categories: Total of All Subjects	26	26	52

Analysis Plan:
At the time of reporting, exact confidence interval estimates will be provided for the true, unknown rates of objective response for each stratum separately and 1-year disease stabilization rate for stratum 1. In addition to the usual estimates of response, we will estimate the confirmed sustained objective response rate (CR+PR) observed during treatment by cumulative incidence functions for each stratum. This provides not only an overall estimate of the objective response rate, but also an estimate of the timing of responses as a function of number of months of treatment. In this analysis, patients who are removed from treatment (due to disease progression, death or unacceptable toxicity) will be considered as having had a competing event. Patients who have stable disease and acceptable toxicity as of their last date of treatment will be censored on that date in the analysis. Note that this secondary analysis will include sustained objective responses that may be observed beyond the first year of treatment.

Kaplan-Meier estimates of distributions of PFS for all eligible patients who receive at least one dose of PI will be provided separately for each stratum. PFS will be measured from the date of initial treatment to the earliest date of disease progression, second malignancy or death for any reason for patients who fail; and to the date of last contact for patients who remain at risk for failure.

Both for objective response assessments as well as PFS calculations, the assessments made at the treating site will be used. Any discrepancies between the treating sites' assessments and the central review will be recorded and described.

Toxicity data will be summarized via frequency tables both for episodes and for number of patients separately for each stratum. We will also tabulate the data related to dose reductions and treatment discontinuation due to toxicity.

Analysis Plan for Central Imaging Review:
All imaging studies obtained during the first year of treatment in Stratum I as well as all scans with the smallest disease measurement recorded since the start of protocol and scans documenting objective response or progressive disease in both strata will be centrally reviewed at the end of the study. We will summarize any discordance between site's assessment and the central review across patients within a stratum as well as on a per patient basis taking into account the longitudinal data that will be available especially in Stratum I. Specific attention will

be given to PD assessment as we anticipate that there will be cases where PD criteria will be satisfied based on protocol definition but not by MacDonald criteria and vice-versa.

Analysis Plan for the WNT pathway activation data:
We will summarize the frequency of nuclear beta-catenin by IHC in FFPE tumor sections. We will also explore associations between presence of nuclear beta-catenin and outcome. Separately in each stratum, if we observe 10 or more responses among patients from whom biology data are available, we will use exploratory logistic regression models to look for associations between biological markers and response. Similarly, if we observe 10 or more progressions among patients from whom biology data are available in a stratum, we will explore associations between biological markers and PFS. Otherwise association with response and PFS will be summarized descriptively.

13.4 Stratification Factors

Stratum 1: Patients with progressive unresectable or recurrent craniopharyngiomas treated with surgery alone, who have not received radiation therapy.

Stratum 2: Patients with progressive or recurrent craniopharyngiomas following radiation therapy.

13.4.1 Definition of Evaluable Patients

In both strata, all patients who receive at least 1 dose of PEGINTERFERON ALFA-2B will be considered evaluable for the purposes of assessing the primary objectives of this trial.

In both strata, patients who withdraw, are lost to follow-up, and/or are removed from treatment and who fail to be evaluated for the primary outcome will be counted as failures.

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APPENDIX A Karnofsky/Lansky PERFORMANCE STATUS

The Karnofsky Scale is designed for recipients aged 16 years and older, and the Lansky Scale is designed for recipients less than 16 years old. Use the table below to determine the score (10-100) that best represents the recipient's activity status at the requested time point.

Table 1. Karnofsky/Lansky Scale

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	**100**	Fully active
90	Able to carry on normal activity	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	**60**	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	**40**	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	**20**	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	**10**	Completely disabled, not even passive play

APPENDIX B Instructions for Administration of Subcutaneous Injections

Subcutaneous injections are given beneath the skin and not in a muscle. For small children, two persons may be needed. One holds and distracts the child and the other gives the injection. Before the injection is given, EMLA cream or ice can be applied to numb the area.

You will need:

- Alcohol swabs
- Syringe and needles
- Medication vial (powder)
- Diluent vial (liquid)
- Band-Aid

Procedure for Preparing the Medication:

- Select an area away from food and pets.
- Gather all of the equipment
- Wash your hands
- Open the syringe
- Clean the top of the vials (bottles) with alcohol
- Remove the cap from the syringe. Do not touch the needle.
- Pull back the plunger and fill the syringe with 0.7cc of air. Put the needle into the diluent (liquid) vial, and inject the air.
- Repeat the step above for the vial with the medicine (powder)
- With the tip of the needle in the vial with the liquid, turn the vial upside down and pull the plunger back to fill the syringe with 0.7 cc of the liquid. (Remember to keep the needle below the level of liquid).
- Remove the syringe and needle from the vial.
- Hold the syringe upright and tap on the sides to remove any air bubbles from the syringe.
- Push the plunger gently to remove bubbles.
- Recheck the syringe to make sure there is 0.7 cc of liquid.
- With the tip of the needle in the vial with the powder push the plunger and inject the liquid into the vial.
- Swirl the vial, do not shake, until the powder is dissolved. When the powder is completely dissolved it will be clear, colorless and without particles.
- After the powder is dissolved, clean the vial with an alcohol swab again.
- Take the second syringe, pull back the plunger and fill the syringe with the amount of air that is the same as your prescribed dose.
- With the tip of the needle in the vial, turn the vial upside down and pull the plunger back to fill the syringe with the cc amount of your prescribed dose. (Remember to keep the needle below the level of liquid).
- Hold the syringe upright and tap on the sides to remove any air bubbles from the syringe.
- Push the plunger gently to remove bubbles.
- Recheck the syringe to make sure there is the correct amount of cc in the syringe.

- Replace the cap loosely onto the syringe.

Procedure for Giving the Medication:

- Remove clothing from the injection site
- Clean the injection area with alcohol using a circular motion. Start in the center and move outward.
- Let the skin air dry.
- Remove the cap from the needle.
- Grasp and raise the skin ½ to 1 inch.
- Insert the needle into the skin with a quick darting motion at a 45-90 degree angle.
- Release your grasp on the skin.
- Pull back the plunger and check for any blood in the syringe.
- If there is blood, remove the needle from the skin and begin again using a new needle.
- If there is no blood, push the plunger slowly until the syringe is empty.
- Remove the syringe quickly from the skin.
- If necessary, put a Band-Aid over the injection site.
- Make sure to throw the syringe into a puncture resistant container.
- Keep a record on your medication diary.

Storage: SYLATRON (PEGINTERFERON ALFA-2B) should be stored at 25°C, excursions permitted to 15-30°C. Do not freeze. Keep away from heat. After reconstitution with supplied diluent, the solution should be used immediately, but may be stored up to 24 hours at 2 to 8°C. However it is recommended that the solution be used within 3 hours after mixing. The reconstituted solution contains no preservative, is clear and colorless.

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APPENDIX C SYLATRON (PEGINTERFERON ALFA-2B) Dosage Calculation and Chart

Dosage calculation:
The total dose of SYLATRON is calculated based on subject weight. The following formula should be used to calculate the dose:

$$\text{Dose in mL} = \frac{\text{Weight (kg) x Dose (“X” µ/kg)}}{\text{Reconstituted Vial Strength (µ/ml)}}$$

Note: Vials are available in 200 mcg per 0.5 mL

Example

Vial Strength= 200 µg/0.5mL (400 µg/ml)
Subject Weight=60 kg

$$\text{Dose in mL} = \frac{60 \text{ kg} \times 1.0 \text{ µg/kg}}{400 \text{ µg/mL}}$$

Dose = 0.15 mL SYLATRON

* Reconstitute vial with 0.7 ml and use no more than 0.5 ml from each vial.

Weight 20 kg to 120 kg (patients with weights less than 20 kg are ineligible)

Weight (Kilogram, Kg)	Dosage Strength	Volume to be administered subcutaneously	Dose to administer
20	200 mcg/0.5ml	0.05 ml	20 mcg
24	200 mcg/0.5ml	0.06 ml	24 mcg
28	200 mcg/0.5ml	0.07 ml	28 mcg
32	200 mcg/0.5ml	0.08 ml	32 mcg
36	200 mcg/0.5ml	0.09 ml	36 mcg
40	200 mcg/0.5ml	0.1 ml	40 mcg
44	200 mcg/0.5ml	0.11 ml	44 mcg
48	200 mcg/0.5ml	0.12 ml	48 mcg
52	200 mcg/0.5ml	0.13 ml	52 mcg
56	200 mcg/0.5ml	0.14 ml	56 mcg
60	200 mcg/0.5ml	0.15 ml	60 mcg
64	200 mcg/0.5ml	0.16 ml	64 mcg

68	200 mcg/0.5ml	0.17 ml	68 mcg
72	200 mcg/0.5ml	0.18 ml	72 mcg
76	200 mcg/0.5ml	0.19 ml	76 mcg
80	200 mcg/0.5ml	0.2 ml	80 mcg
84	200 mcg/0.5ml	0.21 ml	84 mcg
88	200 mcg/0.5ml	0.22 ml	88 mcg
92	200 mcg/0.5ml	0.23 ml	92 mcg
96	200 mcg/0.5ml	0.24 ml	96 mcg
100	200 mcg/0.5ml	0.25 ml	100 mcg
104	200 mcg/0.5ml	0.26 ml	104 mcg
108	200 mcg/0.5ml	0.27 ml	108 mcg
112	200 mcg/0.5ml	0.28 ml	112 mcg
116	200 mcg/0.5ml	0.29 ml	116 mcg
120	200 mcg/0.5ml	0.3 ml	120 mcg

APPENDIX D Stress-Dose Steroid Dosing

Suggested stress-dose steroid dosing for patients on physiologic replacement hydrocortisone

- If the patient develops fever between 38-40 degrees Celsius without vomiting within 72 hours of a dose of PEGINTERFERON ALFA-2B, the next dose of hydrocortisone should be doubled.
- If the patient develops fever > 40 degrees Celsius without vomiting within 72 hours of a dose of PEGINTERFERON ALFA-2B, the next dose of hydrocortisone should be tripled.
- If the patient develops vomiting or poor perfusion and is not able to tolerate PO meds, 100 mg IM hydrocortisone should be administered.