# Protocol Abstract and Schema

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

**Description and Rationale:**

Craniopharyngiomas account for approximately 4% of brain tumors in patients younger than 15 years of age. They are believed to arise from embryonic squamous cell rests along the hypophyseal-pharyngeal duct. 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%. Subtotal resection followed by radiation therapy achieves at least comparable results in terms of recurrence rates and survival. 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. 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.

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]. Peginterferon alfa-2b has received FDA approval for this indication at a dose of 1 mcg/kg/dose/week when given as a single agent.

This is a phase II study to estimate the 1 year disease stabilization rate associated with the use of SYLATRON in patients with progressive unresectable or recurrent craniopharyngiomas following surgery alone who have not received radiation therapy. The study will also estimate the sustained objective response rate (PR+CR) to SYLATRON in patients with craniopharyngiomas which progress or recur following radiation therapy.

## 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.

## 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.

## 2.1 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.

2.1.1 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.

2.1.2 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

2.1.3 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.

2.1.4 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.

2.1.5 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.

2.1.6 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

2.1.7 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

2.1.8 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.

2.1.9 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)

2.1.10 **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)

2.1.11 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. | | |

2.1.12 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.

2.1.13 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).

2.1.14 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.

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

**2.2 Exclusion Criteria**

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

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

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

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

2.2.5 Patients must not have a severe psychiatric illness, including major depression or any

previous suicide attempts.

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

2.2.7 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.

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