Weill Cornell Medical College

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**TITLE: Phase II randomized controlled trial of pegylated interferon alpha-2b in early primary myelofibrosis**


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## SCHEMA

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by the monoclonal proliferation of a multipotent hematopoietictic stem cell (HSC), and its pathologic effects on bone marrow stroma leading to marrow fibrosis, osteosclerosis, neoangiogenesis, and eventual marrow failure. Morbidity and mortality result from profound cytopenias, massive splenomegaly (from extramedullary hematopoiesis), its consequences, and leukemic transformation.

Current treatments for PMF attempt to target the abnormal HSC proliferation as well as the pathologic stromal reaction and fibrotic process. However, these are often irreversible once the disease is in intermediate to advanced stages, when patients commonly become symptomatic and start treatment. Although allogeneic bone marrow transplantation is often the only “curative” option, most patients are unable to undergo this procedure owing to advanced age or poor performance status due to advanced disease.

Recombinant Interferon alpha (rIFNα) has shown substantial anti-tumor activity in bcr-abl negative MPNs, particularly in polycythemia vera (PV) and essential thrombocythemia (ET) [24]. Recent observational evidence, including that from a pilot trial performed at our institution, suggests that when used as monotherapy in early PMF, rIFNα-2b resulted in clinical improvement, decreased spleen size, and improved bone marrow morphology, with overall response in nearly 80% of patients.

Therefore, we plan to expand on this observation by conducting a randomized controlled phase II trial of pegylated interferon alpha 2b (Pegintron) in patients with early PMF, with the hypothesis that starting treatment in the early phase of the disease will result in symptomatic improvement, retardation of bone marrow fibrosis, and improvement in overall survival.

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# 1. OBJECTIVES

## 1.1. Primary Objectives

Primary efficacy objectives:
1. The primary efficacy objective in patients treated with peginterferon alfa-2b, is improved clinical status, which is defined as clinical improvement (CI) in the response criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

Clinical improvement (CI) requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no less than 8 weeks):

i. A minimum 20-g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100 g/L). ‡

ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.§

iii. A minimum 100% increase in platelet count and an absolute platelet count of at least 50,000 x $10^9$/L (applicable only for patients with baseline platelet count below 50 x $10^9$/L).

iv. A minimum 100% increase in ANC and an ANC of at least 0.5 x $10^9$/L (applicable only for patients with baseline absolute neutrophil count below 1 x $10^9$/L).

v. Normalization of bone marrow cellularity and architecture, including reduction in reticulin and collagen fibrosis, normalization of cellularity, and decreased megakaryocyte atypia

vi. Complete or partial (≥ 50%) reduction in cytogenetic abnormalities, if present at diagnosis

‡ Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the previous month for a hemoglobin level of less than 85 g/L, not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin level of 85 g/L or more is discouraged unless it is clinically indicated. (It is presumed that patients in this study will not have transfusion requirements, since it will primarily enroll those with early stage disease)

§ In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

1.2. **Secondary Objectives**

1. Assessment of progression free survival and overall survival at study completion
2. Decrease in myelofibrosis symptom burden (MF-SB) as assessed by a 50% reduction in MPN-SAF TSS[51,54].

## 2. BACKGROUND

2.1 **Disease**

### A. Primary Myelofibrosis: Pathogenesis and pathophysiology

The myeloproliferative neoplasms (MPNs) comprise a heterogeneous group of disorders that arises from the abnormal clonal expansion of a pluripotent hematopoietic stem cell [1-2]. Of the three classical BCR-Abl negative MPNs (PV, ET and PMF), primary myelofibrosis (PMF) has the worst overall morbidity and mortality[3]. The quality of life for patients with PMF is compromised by progressive anemia, marked hepatosplenomegaly, severe constitutional symptoms including cachexia, and eventual leukemic transformation in up to 20% during their disease course [2-3]. Median age at diagnosis is 60 years, and 10% of patients are less than 45 years of age at diagnosis[4].

The clonal proliferation of a pluripotent hematopoietic stem cell (HSC) and its pathologic interaction with the bone marrow stroma (microenvironment) are thought to be the primary pathogenetic mechanisms of disease in PMF. Results of clonality studies, including X-chromosome inactivation studies in female patients with PMF[6] and G6PD isoenzyme analysis[7], strongly suggest monoclonal expansion of a mutated HSC as the disease initiating factor. Furthermore, the presence of the clonal abnormality in terminally differentiated myeloid and lymphoid cells, suggests that the originating HSC clone retains the ability to fully mature into myeloid and lymphoid cell lines[8, 9]. Although cytogenetic studies have shown a variety of chromosomal abnormalities in PMF, including del(20)(q11;q13), del(13)(q12;q22), trisomy 8, trisomy 9, and others, there is no consistent cytogenetic pattern in this disease, analogous to BCR-Abl in CML[5]. Aside from the JAK2V617F mutation (seen in up to 50% of patients) and mutations in MPL (8% of patients), there are few molecular abnormalities that are consistently seen in PMF[10].

The bone marrow stromal cells play a large role in the pathophysiology of PMF. These include cells derived from mesenchymal stem cells (MSCs), and endothelial cells[1]. Although the clonal abnormality in the HSC is not present in bone marrow stromal stem cells [11, 12], and they exhibit normal growth and function *ex vivo* [13], the bone marrow in PMF is characterized by increased collagen fibrosis, neo-angiogenesis, and abnormal bone formation (osteosclerosis) [1, 5]. This supports the notion that a maladaptive interaction of the abnormal HSC clone and its progenitors with an otherwise normal bone marrow stroma, leads to the characteristic changes in

bone marrow histology in PMF. This is further supported by the observation that the pathologic stromal changes in the marrow are reversed after allogeneic stem cell transplantation in patients with PMF [17].

Several lines of evidence strongly implicate the megakaryocyte derived from the clonal HSC in altering the bone marrow stroma through elaboration of cytokines including transforming growth factor-beta (TGF-beta), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet derived growth factor (PDGF) [1,5,14-16]. As a result of the alteration in the bone marrow microenvironment, there is an egress of HSC stem cells from the bone marrow as the disease progresses, with a drastic increase in extramedullary hematopoiesis in the spleen, liver, and lungs [1,5], resulting in hepatosplenomegaly and pulmonary hypertension that are characteristic of the disease.

The aforementioned disease mechanisms have important therapeutic implications. In order for meaningful clinical benefit, a drug should effectively target both the HSC clonal proliferation and retard or reverse the abnormal stromal reaction in the bone marrow and extramedullary sites of hematopoiesis.

## B. Diagnostic and Prognostic Criteria

The WHO diagnostic criteria for PMF incorporate both bone marrow morphological and clinical features, and distinguish between early (pre-fibrotic) and advanced disease[18,19]. The WHO major bone marrow morphologic criterion is the presence of megakaryocyte proliferation and atypia with or without reticulin and/or collagen fibrosis [18]. In the absence of reticulin fibrosis, megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease) [18]. Minor diagnostic criteria include palpable splenomegaly, anemia, leukoerythroblastosis, and elevated LDH [18,19].

The IWG-MRT Dynamic International Prognostic Scoring System (DIPSS) stratifies PMF into four risk categories (low, intermediate 1, intermediate 2, and high risk), based on 5 clinical factors; Age>65, Hemoglobin <10gm/dL, WBC>25,000/uL, peripheral blasts>1%, and constitutional symptoms[20,21]. The median overall survival ranges from 135 months to 27 months for DIPPS low risk to high risk disease, respectively[20,21]. Risk factors independent of the DIPSS have also been identified and include platelet count<100[47], and cytogenetic risk profile [48].

Patients with pre-fibrotic and early fibrotic (reticulin fibrosis grade 0 to +1) PMF have hypercellular bone marrows with aforementioned atypical megakaryocytes in clusters, granulocytic proliferation, relative erythroid hypoplasia, and peripheral thrombocytosis[18,19]. This early phase of the disease, also referred to as the “cellular phase” of PMF, may be more responsive to treatment[22,23].

## 2.2 Pegylated Interferon alpha 2b (peg-IFNα-2b)

### A. Mechanism of Action

Recombinant Interferon alpha (rIFNα) has shown substantial anti-tumor activity in bcr-abl negative MPNs, particularly in PV and ET[24-26]. The use of rIFNα in PMF is based upon its effectiveness in treating polycythemia vera with fibrosis,[24,25, 27, 28] and on its biological effects on megakaryopoiesis and hematopoietic stem cells.[29-34] Effects on megakaryopoiesis include decreasing megakaryocyte density and size,[29] inhibiting thrombopoietin-induced signaling,[30] and antagonizing the action of platelet-derived growth factor,[31] all of which play a major role in the pathogenesis of PMF.[32,33] IFNα directly inhibits colony forming unit megakaryocyte proliferation and differentiation by blunting *in vitro,* possibly by inhibiting the JAK/STAT signaling responses that occur in response to thrombopoietin (TPO), and impairing TPO-induced intracellular signaling by up-regulating SOCS-1 expression[45]. Furthermore, IFNα directly inhibits cytoplasmic maturation and platelet production by megakaryocytes without affecting proliferation of megakaryocyte progenitor cells endomitosis of human megakaryocytes[45].

Recent evidence of the pro-apoptotic effects of rIFNα in a variety of tumor cells of diverse origin also indicated potential for treating patients with PMF.[34] *In* vitro studies have shown that IFNα can reduce the colony-forming ability of myeloid progenitor cells in PV and PMF[40], with suggestion of an increased sensitivity of the abnormal clone to IFNα compared to the normal counterpart[41]. *In vivo* studies from patients with PV have shown reconstitution of polyclonal hematopoiesis in patients treated with IFNα[41]. It is generally agreed that rIFNα has no beneficial effect in advanced PMF, when the marrow is extensively myelofibrotic and/or osteosclerotic without residual hematopoietic cells.[22,35,36]

Pegylated interferon alfa 2b (peg-IFNα-2b) is produced by attaching a 12,000-Da monomethoxypolyethylene glycol (PEG12,000) polymer to the native IFN-a-2b[37]. This increases drug solubility and stability, thereby increasing serum half life, and allows weekly administration, instead of 2 to 3 times per week dosing of rIFNα-2b[37]. The toxicity profile is comparable to rIFNα-2b[40].

### B. Clinical Studies

In a pilot study which used rIFNα to treat patients with early PM, 17 patients meeting WHO PM diagnostic criteria received either rIFNα-2b 500,000-3,000,000 units thrice weekly, or peg-rIFNα-2a 45 or 90 mcg weekly[38]. Dose was adjusted based upon response and tolerance. IWG-MRT prognostic and response criteria were used. Eleven patients were women, and 6, men. The median age at diagnosis was 57 years. Median baseline leukocyte, hematocrit, hemoglobin, and platelet values were 8.7 K/uL, 35.5%, 11.7 g/dL, and 404,000/uL, respectively, and did not change

substantially with treatment. Eleven patients were low risk, and 6, intermediate-1 risk. Two achieved complete remission, 7 partial remission, 1 clinical improvement, 4 stable disease, and 3 progressive disease. Ten of 17 (58.8%) derived clinical benefit, and 4 (23.5%), disease stability. Thus, more than 80% derived clinical benefit or stability. Control of splenomegaly was maintained in 15 of 17. Reduction in myelofibrosis and improvement in megakaryocyte morphology occurred in 4. Toxicity was acceptable, and detailed below (see safety profile).

A recent multicenter retrospective study of peg-IFNα-2a in 18 patients with primary and secondary myelofibrosis showed complete remission and/or major responses in 44% of patients, with only 2 discontinuations due to loss of efficacy or symptomatic phase of disease[46]. Anemia improved in 80% of patients and, peg-IFNα-2a had a more specific and rapid response in those patients with leukocytosis or thrombocytosis at start of treatment, illustrating its anti-proliferative effects. The majority of hematologic responses were seen within 3 to 6 months[46].

A recent phase II trial of peg-IFNα-2b in 40 patients with various MPNs including PV, ET, PMF, hypereosinophilic syndrome, and unclassified MPN, showed variable response rates for each specific disease, with 1 of 11 patients with PMF achieving response[37]. However, the stage of PMF was unspecified in this study. Overall response was 45% with a median duration of response of 20 months and 3 sustained responses (>24 months). Although toxicity was reported in 26% of patients, high starting doses of 3mcg/kg/week were used, a dose which can cause more adverse effects including decreased neutrophil counts[39]. Another phase II study of rIFNα-2b in MPNs reported objective responses and/or disease stabilization in PV, ET, and PMF, with reversal of splenomegaly and resorption of fibrosis in some patients[40].

## C. Pharmacokinetics

The 12kDa Peg-IFNα-2b is administered subcutaneously and has an absorption half-life of 4.3 hours (compared with 2.1 hours for rIFNα-2b), a volume of distribution of 0.99L/kg, a serum peak to trough ratio>10 (with multiple doses), and an elimination half-life of 40 hours[42]. This translates to relatively rapid absorption, and wide volume of distribution. The relatively large volume of distribution usually necessitates body weight-based dosing during the induction phase of treatment, in order to achieve reasonable drug levels[42]. Soon after injection, peg-IFNα-2b breaks down to release free IFNα-2b, which is renally excreted. Therefore, dose modification is required in patients with impaired renal function (creatinine clearance<50mL/min), with 25% dose reduction for moderate renal dysfunction (CrCl 30-50mL/min) and 50% dose reduction for severe renal dysfunction (CrCl 10-29 mL/min).

## D. Safety profile in studies of rIFNα-2b in MPNs

The side effects most commonly observed with peg-IFNα-2b are similar to those seen with rIFNα-2b, namely fever and flu-like symptoms, neuropsychiatric symptoms including depression, and peripheral cytopenias, including neutropenia and thrombocytopenia[42]. A summary analysis of 35 clinical trials of rIFNα-2b in ET and PV showed an average discontinuation rate of 25% with approximately half the withdrawals occurring during the first year of therapy[41]. In the pilot study of 17 patients with PMF, toxicity was generally mild (grade 1 or 2) and included asthenia, fatigue, myalgias not requiring dose reduction. Eleven patients had hematologic toxicity including anemia (n=7: 6 grade 1-2,1 grade 4), thrombocytopenia (n=5: 4 grade 1-2, 1 grade 3), and leukopenia (n=3: all grade 1). Ten patients had metabolic toxicity: 9 with grade 1-2 LFT abnormalities, 3 with grade 1 hypocalcemia, and 1 patient with hyperthyroidism requiring discontinuation of rIFNα-2b[38].

**E. Safety profile of peg-IFNα-2b in treatment of hepatitis C**

In a phase 3 randomized controlled trial with 1,210 patients comparing rIFNα-2b to peg-IFNα-2b as initial monotherapy for hepatitis C, the two drugs were similar with respect to safety and tolerability[43]. Three doses of peg-IFNα-2b (0.5mcg/kg/wk, 1.0 mcg/kg/wk, and 1.5 mcg/kg/wk) were compared to 3 MIU rIFNα-2b TIW. The incidence of serious adverse reactions was similar (about 12%) in all treatment groups. The most common adverse events were flu-like symptoms, and a two-fold increase in injection site reactions with peg-IFNα-2b. Dose reduction due to neutropenia occurred infrequently for both drugs, with 5% requiring dose reduction in the 1.5mcg/kg group and 2-3% in the lower dosage groups. Incidence of dose reduction and adverse events was dose related and increased with higher doses[43].

## 2.3 Rationale

Primary Myelofibrosis is characterized by stem cell-derived clonal myeloproliferation, ineffective erythropoiesis, abnormal leukocyte and platelet production, extramedullary hematopoiesis, and bone marrow fibrosis and osteosclerosis. Patients with PMF have shortened survival and their quality of life is compromised by progressive anemia, marked hepatosplenomegaly, and severe constitutional symptoms including cachexia. After decades of ineffective therapy, patients are now being treated earlier in their disease with approaches such as interferon alpha. Such progress calls for standardization of response criteria to accurately assess the value of new treatment modalities, to allow accurate comparison between studies, and to ensure that the definition of response reflects meaningful health outcome. Accordingly, the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), an international panel of experts, delineated 3 response categories: complete remission (CR), partial remission (PR), and clinical improvement (CI) [44]. These criteria address improvement in all of the aforementioned characteristic features of PMF. Bone marrow histologic and hematologic remissions characterize CR and CR/PR, respectively. CI reflects an improvement in quality of life, as measured by improvement in anemia, thrombocytopenia, neutropenia, and hepatosplenomegaly.

## 3. PATIENT SELECTION

### 3.1 Inclusion Criteria

3.1.1 Patients must meet laboratory, and bone marrow histological criteria for primary myelofibrosis based on the WHO diagnostic criteria as outlined in Table 1[18].

Table 1: Proposed Criteria for PMF

| |
|---|
| **Major Criteria (must meet both major critieria)**<br>1. Presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie. prefibrotic cellular-phase disease)<br>2. Not meeting WHO criteria for PV, CML. MDS, or other myeloid neoplasm |
| **Minor Criteria (must meet at least two minor criteria)**<br>1. Leukoerythroblastosis<br>2. increase in serum LDH<br>3. Anemia<br>4. Palpable splenomegaly<br>5. Platelet count > 450,000/µL*<br>*This criterion is based on clinical observations of early, pre-fibrotic cases of myelofibrosis in the absence of any of the 4 minor criteria proposed by WHO in 2008. |

3.1.2 Patients must have Low or Intermediate 1 stage of disease as defined by International Working Group (IWG) risk stratification of primary myelofibrosis in the dynamic international prognostic scoring system (DIPSS). Patients must have >15% of marrow biopsy area showing hematopoietic marrow, irrespective of degree of fibrosis (reticulin and/or collagen)as defined by Manoharan criteria[49].

3.1.3 Patients should NOT have had prior therapy for primary myelofibrosis. This includes treatment with cytoreductive drugs (Hydroxyurea), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), JAK2 inhibitors, or other therapies specifically for myelofibrosis. If they received these classes of drugs for indications other than PMF, treatment should be discontinued at least 6 weeks prior to randomization.

3.1.4 Age $\geq$18 years.

3.1.5 performance status $\leq$ 2

3.1.6 Patients must have normal organ and marrow function as defined below:

| | |
|---|---|
| o WBC | ≥3,000/μL |
| o ANC | ≥1,500/μL |
| o Platelets | ≥100,000/μL |
| o Total bilirubin | within normal limits |
| o AST(SGOT)/ALT(SGPT) | ≤2.5 X upper limit of normal |
| o Creatinine Clearance | ≥50 ml/min |

3.1.7 The effects of peg-IFNα-2b on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

## 3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 6 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 6 weeks earlier.

3.2.2 Patients with Intermediate 2 or High risk stage of disease as defined by International Working Group (IWG) risk stratification of primary myelofibrosis in the dynamic international prognostic scoring system (DIPSS) and/or less than 15% of bone marrow biopsy area showing hematopoietic marrow, irrespective of degree of reticulin fibrosis (by Manoharan criteria[49]), or collagen fibrosis, or osteosclerosis..

3.2.3 Patients may not be receiving any other investigational agents.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to peg-IFNα-2b

3.2.5 Other Exclusion Criteria

- Female patients who are pregnant or breast feeding
- History of depression or active treatment for depression
- History of non-compliance to medical regimens

- History of autoimmune diseases
- History of hypothyroidism or hyperthyroidism
- Clinical evidence of neuropathy

3.2.6 Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant and lactating women are excluded from the study because the risks to an unborn fetus or potential risks in nursing infants are unknown.

## 4. REGISTRATION PROCEDURES

### 4.1 Central Patient Registration

Patients will be centrally registered with the Department of Medicine, Joint Clinical Trials Office (JCTO). To register a patient, email the following documents to the JCTO at raa2017@med.cornell.edu and nec2006@med.cornell.edu (registrations can also be faxed to 646-962-1610 but an email/phone call should accompany the fax to confirm receipt of registration packet):

- WCMC Patient registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse/study coordinator
- Documentation of any eligibility waivers granted
- De-identified source documentation to confirm eligibility
- For inpatients, signed consent documentation template (WCMC only)

Central registration information is reviewed and entered into the Hem/Onc centralized research database. (For WCMC only) Documentation of patient registration will be faxed to the Investigational Pharmacy to allow for release of study agent. Patient is eligible to begin treatment once a confirmation email has been sent to study team. (For sub-sites) Once email confirmation from WCMC is received, follow your institutional pharmacy guidelines on releasing drug.

## 5. TREATMENT PLAN

### 5.1 Agent Administration

Treatment will be administered on an outpatient basis. Patients will be randomized to either the treatment arm or the control arm of the study with a 2:1 allocation ratio. There will be a total of 47 patients in the study. Thirty-one patients will be in the peg-interferon alfa-2b arm and 16 patients in the control arm.

Starting dose in the treatment arm will be 50 micrograms (mcg) of peginterferon alfa-2b subcutaneously (SC) per week. If a partial response (PR) or clinical improvement (CI) (as defined by IWG-MRT criteria) is not seen in the first 8 weeks, and toxicity (hematologic and non-hematologic) is no more than Grade 2, dose will be increased to the next defined dose level as outlined in section 6.2. The dose will be escalated every 8 weeks until at least PR or CI is achieved, at which point the dose will be maintained, provided toxicity does not exceed Grade 2 in severity. The maximum dose of peg-IFNα-2b will be 150 mcg Qweek.

Given that observation until disease progression is a generally accepted standard of care for low and intermediate 1 stage PMF[53], patients in the observation arm will be followed closely at 4 to 8 week intervals. If patients in the observation arm develop disease progression to the next higher DIPSS stage from diagnosis or have an increase in marrow fibrosis detectable by reticulin stain on sequential bone marrow biopsies, they will cross over to the treatment arm.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for peg-IFNα-2b are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

## 5.2 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient's medical records. The administration of anticancer agents including chemotherapy and biologic agents are NOT permitted.

Once on study, if cytoreductive therapy is required for patients randomized to the observation arm, only hydroxyurea may be used. Other cytoreductive drugs are not allowed.

## 5.3 Duration of Therapy and Criteria for Removal From Study

In the absence of treatment delays due to adverse event(s), treatment may continue for 3 years or until one of the following criteria applies:

- Disease progression[55] defined as:
  - Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM, OR
  - A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5 to 10 cm, OR
  - A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm, OR
  - Leukemic transformation confirmed by a bone marrow blast count of ≥20%, OR
  - A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 x 10(9)/L that lasts for at least two weeks, OR
  - Painful splenomegaly
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient becomes pregnant

### 5.4 Duration of Follow Up

Patients will be followed for a minimum of 3 years or study completion (to be defined). Patients will be followed at regular 4 to 8 week intervals during the study and after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Bone marrow biopsy from the posterior iliac crest will be performed once yearly during study follow up period. Bone marrow biopsies will undergo blinded hematopathologic evaluation by Dr. Attilio Orazi, Chief of the Division of Hematopathology at Weill Cornell Medical College.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 All interruptions, reductions, or any changes in study drug administration will be captured on the flow sheets.

6.2 With the exception of grade 3 or 4 non-hematologic toxicity, any patient receiving a reduced dose and who does not achieve or maintain a partial response (PR), complete response (CR), or clinical improvement (CI), may have the dose re-escalated to the preceding dose after a minimum of 6 weeks of therapy provided no toxicities ≥ grade 2 were observed at the reduced dose.

**Treatment Dose Levels**

| Dose Level* | Peg-IFNα-2b Dose |
|---|---|
| -2 | 25 mcg SC Qweek |
| -1 | 40 mcg SC Qweek |
| 0 | 50 mcg SC Qweek |
| +1 | 80 mcg SC Qweek |
| +2 | 96 mcg SC Qweek |
| +3 | 120 mcg SC Qweek |
| +4 | 150 mcg SC Qweek |

6.3 **Grade 2 Non-hematologic toxicity**
If a patient experiences grade 2 non-hematologic toxicity lasting for more than 3 days at a specific dose level, peg-IFNα-2b must be withheld until the toxicity has resolved to less than grade 1. Peg-IFNα-2b may then be restarted at the same dose level. If grade 2 toxicity recurs, peg-IFNα-2b may be resumed at the next lower dose level as outlined in the table above.

6.4 **Grade 3-4 Non-Hematologic Toxicity**
If a patient experiences grade 3-4 non-hematologic toxicity at a specific dose level, peg-IFNα-2b must be withheld until the toxicity has resolved to less than grade 1. Peg-IFNα-2b may then be restarted at the next lower dose level as outlined in the table above. If grade 3-4 toxicity recurs again, treatment will be stopped, and further treatment after any interruptions of more than 2 weeks is not permitted. The subject will go off study and alternative treatment may be pursed if deemed appropriate.

6.5 **Grade 1 or 2 Hematologic Toxicity**
No dose reductions or interruptions in treatment will occur for grade 1 or 2 hematologic toxicity

6.6 **Grade 3 or 4 Hematologic toxicity**

If a patient experiences grade 3 or 4 hematologic toxicity, defined as an ANC<1.0x$10^9$/L or a platelet count <50x$10^9$/L, peg-IFNα-2b must be withheld until the toxicity has resolved to ≤ grade 2. ANC will take precedence over a WBC count in the determining the degree of neutropenia (doses should be interrupted for a patient with a WBC count < 2.0x$10^9$/L even if ANC >1.0x$10^9$/L). If the toxicity resolves within 2 weeks, treatment may be resumed at the same dose level. If the grade 3 or 4 toxicity recurs or persists for longer than 2 weeks, peg-IFNα-2b must be withheld and reduced to the next lower dose level once toxicity has resolved to ≤ grade 2.

## 7. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

### 7.1 **Pegylated IFN-alfa 2b Risks**

Common adverse events associated with the dosage range for peg-IFN-alfa 2b that will be used in this study include flu-like symptoms, gastrointestinal symptoms, psychiatric symptoms, and dermatologic symptoms. The relative frequency of these adverse events that were seen in a phase III randomized controlled trial of 1,299 patients comparing peg-IFN-alfa 2b to Interferon alfa 2b in hepatitis C, are shown in table 2.

Table 2: Adverse Event Frequency observed in phase III trial of Peg-IFNα-alfa 2b monotherapy in hepatitis C [43]

| **Toxicity** | **Peg-IFN-alfa 2b 0.5mcg/kg QW** | **Peg-IFN-alfa 2b 1.0mcg/kg QW** | **Peg-IFN-alfa 2b 1.5mcg/kg QW** |
|---|---|---|---|
| **Influenza like symptoms** | | | |
| Headache | 61 | 64 | 58 |
| Fatigue | 43 | 51 | 50 |
| Chills | 34 | 40 | 33 |
| Fever | 31 | 45 | 30 |
| Myalgia | 48 | 54 | 53 |
| Muskuloskeletal pain | 19 | 28 | 22 |
| **Gastrointestinal symptoms** | 21 | 26 | 20 |
| Nausea | 10 | 20 | 17 |
| Anorexia | | | |
| **Psychiatric Symtpoms** | | | |
| Irritability | 19 | 18 | 24 |
| Insomnia | 17 | 23 | 23 |
| **Dermatologic Symptoms** | | | |
| Alopecia | 20 | 22 | 22 |
| Injection site reactions | 44 | 42 | 16 |

## 7.2 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 AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **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.

## 7.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

## 7.4 Serious Adverse Event (SAE) Reporting

### 7.4.1. Definition of SAE

SERIOUS ADVERSE EVENTS include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, diagnosis of a new malignancy, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 7.4.2. Reporting of SAE to WCMC IRB

All SAEs occurring on this study will be reported to the WCMC IRB according to the WCMC IRB policy. The WCMC IRB requires immediate reporting (within 48 hours) of all unexpected and study-related (definite or probable) adverse events that results in an increased harm or risk to study participants. The following procedure will be utilized for reporting SAEs to the WCMC IRB:

- Complete the WCMC SAE Cover Sheet, the WCMC IRB Immediate Reporting Form, and the Voluntary MedWatch Form (Form FDA 3500).

- Submit this form within 48 hours of investigator notification of the event.
- Sub-sites: Follow local IRB guidelines for reporting to your IRB. If your IRB requires a revision to the consent form, notify WCMC immediately.
- SAEs that do not meet the immediate reporting criteria listed above should still be reported to the WCMC IRB within 48 hours. For these SAEs, only send the WCMC SAE Cover Sheet and the Voluntary MedWatch Form (Form FDA 3500).

**A request for SAE forms or questions regarding SAEs may be directed to Elizabeth Christopher via email at elc2025@med.cornell.edu.**

### 7.4.3. Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form and sent to Merck.

### 7.4.4. Reporting of SAE to Merck

Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) will be provided with copies of all serious adverse experiences, within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) regardless of drug relationship.

A copy of all 15 Day Reports and Annual Progress Reports is submitted by the investigator as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. 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 & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with pegylated IFN-alfa 2b can be found in Section 7.1.

### 8.1 Pegylated Interferon-alfa 2b

PegIntron, peginterferon alfa-2b, is a covalent conjugate of recombinant alfa-2b interferon with monomethoxy polyethylene glycol (PEG). The average molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular

weight of the PegIntron molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alfa-2b is approximately 0.7 × 108 international units/mg protein. Interferon alfa-2b is a protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of Escherichia coli bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

**8.2 Availability**

Peg-IFNα-2b is an investigational agent supplied to investigators by Merck to WCMC and all other sub-sites. It will be shipped in 50 microgram pre-filled syringes or the REDIPEN formulation. Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the pharmacist or designee accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment should be documented in the study files. The investigator must notify Merck and WCMC of any damaged or unusable study treatments supplied to the investigator's site.

The study drug should be stored, under adequate security, in the pharmacy at the study center in a refrigerator at a temperature of 2C to 8C (36F to 46F) until taken by the study patients.

**8.3 Pegylated Interferon alfa 2b Ordering**

The study drug may be requested from MERCK by the Principal Investigator (or their authorized designee) at each participating site. Transfer of drugs between institutions is not permitted.

To order drug, fill out the drug supply request form and fax it to **Michael Gregor @ 267-305-6534** or send the request via e-mail at **michael.gregor@merck.com**

**8.4 Pegylated Interferon alfa 2b Accountability**

Pegylated Interferon-alfa 2b Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from *Sponsor* on a Drug Accountability Record Form (DARF). If the study drug expires, each site will destroy the drug following their Institution's SOP and will document the drug destruction. Copies of this log must then be sent to MERCK for drug accountability. Send all accountability documents to Michael Gregor.

At the completion of the study, there will be a final account of drug shipped, drug consumed, and drug remaining. This accounting process will be logged on the drug accounting form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug

destroyed on site will be documented in the study files.

## 9. CORRELATIVE/SPECIAL STUDIES

### 9.1 Laboratory Correlative Study

9.1.1 **Testing for JAK2V617F:** Blood samples, at least 30mL, from all patients will be collected and stored in the Hematology and Medical Oncology Translational Core lab in Weill Cornell Medical College. The samples will be stored for potential future research testing that may include JAK2 quantitative testing, along with other mutation analysis.

Instructions on collection and specimen shipment will be provided in a specimen instruction form.

### 9.2 Special Studies

9.2.1 **Quality of life assessment using MPN-SAF**

Measure changes in quality of life (QOL) of patients in treatment and non-treatment arms using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), a validated patient reported outcome (PRO) instrument[51,54]. This will be completed by the patient and reviewed by the trial coordinator on follow up visits every 4 weeks

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to administration of protocol therapy, with the exception of the bone marrow procedure which must be completed within 12 weeks. The pregnancy results should be confirmed if performed more than 14 days from the start of treatment; a urine pregnancy test may be performed for confirmation. The following study calendar outlines study visit intervals for a period of 1 year during the study. The schedule will apply for the entire 3 year duration of the study.

| | Pre-Study | Wk 1 | Wk 5 | Wk 9 | Wk 13 | Wk 17 | Wk 21 | Wk 25 | Wk 29 | Wk 33 | Wk 37 | Wk 41 | Wk 45 | Wk 49 | Wk 53 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pegylated IFNα-2b[a]** | | X | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | X |
| Informed consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Concurrent meds | X | X | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | X |
| Physical exam | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Height | X | | | | | | | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Performance status | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| CBC w/diff, plts | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Serum chemistry[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| EKG (as indicated) | X | | | | | | | | | | | | | | |
| Pregnancy test[c] | X | | | | | | | | | | | | | | |
| Fundoscopic eye exam[d] | X | | | | | | | | | | | | | | |
| Bone marrow aspiration & biopsy | X | | | | | | | | | | | | | X | |
| Adverse event evaluation | | X | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | ---------- | X |
| Thyroid function tests | X | | | | | | X | | | | | | X | | |
| Correlative Study | X | | | | | | | | | | | | | | |
| JAK2V617F Quatitative Mutational Analysis | X | | | | | | | X | | | | | | X | |
| Special study (MPNSAF) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

a: Pegylated IFNα -2b: Starting dose of 50mcg SC Qweek
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
c: Serum pregnancy test (women of childbearing potential); urine sample will be taken to confirm results within 7 days of treatment start date.
d: Full eye examination should be performed if subject complains of vision problems

# 11. MEASUREMENT OF EFFECT

## 11.1 Response Criteria

Response will be evaluated according to the criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Responses are measured as complete response (CR), partial response (PR), stable disease (SD), clinical improvement (CI), progressive disease (PD), and relapse[44].

## 11.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

# 12. DATA REPORTING / REGULATORY CONSIDERATIONS

## 12.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled patients.

### 12.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

## 12.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Merck will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

Prior to implementing this protocol at WCMC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the WCMC Institutional Review Board (IRB). Prior to implementing this protocol at the participating sites, approval for the WCMC IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to WCMC before the participating site can be initiated and begin enrolling participants:

- Original FDA form 1572
- Administrative guidelines for participating site participation
- Letter/memo from participating sites' Conflicts Management Office stating that they manage their conflicts
- Participating Site IRB approval letter, approved consent form, and HIPAA authorization
- CV and medical license of site delegated Principal Investigator

Upon receipt of the required documents, WCMC will formally contact the site and arrange for a teleconference site initiation visit (SIV). Once the SIV is performed, the site will receive an activation letter granting permission to proceed with enrollment. The participating sites are responsible to maintain all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) in the regulatory binder on site.

## 12.3 Data Safety Monitoring Board

This study will utilize the Weill Cornell Medical College (WCMC) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring this study for safety concerns, with ongoing updates from the Study Chair on an ongoing basis. The interim analysis will be performed by the DSMB and the decision to proceed or stop the trial will be provided to the Study Chair. In addition, an independent safety monitor, Dr. Steven Allen at The North Shore University Hospital-Monter Cancer Center (450 Lakeville Road, Lake Success, NY 11042) will perform annual monitoring of the safety of subjects throughout the trial including risks and benefits, as well as efficacy of the study.

The WCMC DSMB is comprised of medical specialists and advisors on human rights issues in human subjects research. The DSMB currently has 9 members, meets at quarterly intervals during the year, and carries out ongoing review of protocols submitted throughout the year. Once a protocol has been submitted and approved by the Institutional Review Board (IRB) and is recommended for oversight by the DSMB, the Board determines if the protocol will be reviewed quarterly, semi-annually, or annually.

The DSMB evaluates the accumulated data from the study in order to monitor the safety of subjects throughout the trial and reviews the risks and benefits, as well as the efficacy, of the study. The DSMB will also evaluate the overall trial conduct and progress. Ultimately, the DSMB validates the continuation of the trial or determines if a study needs modification or termination.

Reports to the DSMB will include the following items for review:
1. Completed DSMB Periodic Review Form.
2. Synopsis of the study to date.
3. IRB approved consent form.
4. IRB current protocol.
5. Summary table of study results, compromised of enrollment and response data
6. Adverse event table outlining all grade 3 and 4 toxicities, including serious adverse events
7. Data safety monitoring plan.

After the first six months of the study, the Principal Investigator will provide the WCMC DSMB with a list of grade 3 and 4 toxicities, a summary of all serious adverse events, and a summary of the study results, including enrollment and response data. The DSMB will review the data from WCMC and all participating sub-sites and determine if the study can continue to operate as is or if the study needs modification or termination. From here on out, the DSMB will review all the aforementioned items on a yearly basis.

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subject research projects and to protect the safety of human subjects. Safety monitoring can be viewed as any process during a clinical trial that involves the review of accumulated outcome data for groups of patient-subjects to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998, 2000) specify that all clinical trials should have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities will be commensurate with the nature, size, and complexity of the trial in accordance with institutional policies and will be determined after IRB and DSMB review of the protocol immediately prior to study activation. For a small, single-center study, the monitoring is usually performed by a statistician in

conjunction with a Safety Officer. For those single-site, high risk trials, a DSMB may be appropriate. For larger, single or multi-site studies, the monitoring is usually performed by a committee, often called a Data Safety Monitoring Board (DSMB). Ongoing review of the data by an independent individual or committee assures the investigators, the IRB, the study's sponsor, and the funding agency that the trial can continue without jeopardizing subjects' safety.

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

This prospective, randomized, controlled, multi-center, phase II study will be designed to determine the safety and efficacy of peg-interferon alfa-2b in treating patients with early primary myelofibrosis (PMF). The primary objective of this study is to compare the clinical improvement rate between patients treated with peginterferon alfa-2b [Arm A] and untreated patients (clinical observation arm) [Arm B], in patients with early primary myelofibrosis.

Patients will be randomized to either the treatment arm or the control arm of the study with a 2:1 allocation ratio. There will be a total of 47 patients in the study (31 patients in the peginterferon alfa-2b arm and 16 patients in the control arm).

### 13.2 Sample Size/Accrual Rate

With a sample size of 31 patients in the peginterferon alfa-2b arm and 16 patients in the observation arm, (total sample size=47), the study is designed to have approximately 93% power to detect a difference in the clinical improvement rate of 45% between the two groups (5% in observation arm vs. 50% in peginterferon alfa-2b arm), with a two-sided alpha level of 5%. The expected clinical improvement rate of 50% in the treatment arm is based on a pilot study that used rIFN to treat patients with early PM. In the pilot study, 10 of 17 patients (58.8%) achieved clinical improvement.

A single interim analysis will be performed at 52 weeks for the purpose of assessing early efficacy (with statistical significance for the interim analysis set at $P<0.0001$); this will allow for patients in the observation arm to cross-over to the treatment arm if clear early efficacy is observed in the treatment arm.

## 13.3 **Stratification Factors**

Randomization Plan:

A series of randomized blocks of 3 will be generated with a 2:1 allocation ratio. This will provide assurance that after three patients are enrolled, there will be two patients assigned to the peginterferon alfa-2b arm and one patient assigned to the observation arm. The blocked randomization will be stratified by participating institution.

If patients in the observation arm develop disease progression to the next higher DIPSS stage from diagnosis or have an increase in marrow fibrosis detectable by reticulin stain on sequential bone marrow biopsies, they will cross over to the treatment arm. However, patients cannot switch over from the treatment arm to the observation arm.

## 13.4 **Analysis of Endpoints**

Fisher's exact test will be used to evaluate 1) the difference in the clinical improvement proportion between the treatment arm and the observation arm (primary efficacy endpoint) and 2) the difference in the toxicity proportions between the treatment arm and the observation arm (primary safety endpoint). Ninety-five percent confidence intervals (95% CI) for differences in the improvement and toxicity proportions between the two arms will be calculated to assess the precision of the obtained estimates.

With adequate follow-up time, Kaplan-Meier survival analysis will be used to evaluate overall survival in the treatment/ observation arms and the log-rank test will be employed to compare overall survival between the treatment and observation arms. Overall survival will be defined as the time from first treatment day until death or until date of last follow-up.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses will be performed in SAS Version 9.2 (SAS Institute Inc., Cary, NC). All statistical analyses will be performed by the Division of Biostatistics and Epidemiology in the Department of Public Health at Weill-Cornell Medical College.

## 13.5 **Reporting and Exclusions**

13.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with peg-IFNα-2b

13.5.2 **Evaluation of response.** All patients included in the study will be assessed for response to treatment if they have received at least 6

months of treatment. Consultation with the Biostatistics Office will allow for completion of this section.

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# APPENDIX A

## Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

# APPENDIX B

## WCMC IRB SAE Reporting Forms

**The WCMC IRB SAE Reporting Forms can be obtained by contacting Ramsey Abdallah via email at raa2017@med.cornell.edu.**