CLINICAL STUDY PROTOCOL

An Observational Pilot Study to Compare the Compliance with and Health Related Quality of Life during Therapy with Standard High-Dose Interferon Alfa (Intron® A, HDI) versus Pegylated Alfa-Interferon 2b (Sylatron™, PEG IFN) in Patients with Surgically Resected Melanoma

Protocol Number:	MISP 50442
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Lead Investigator:	Sanjiv Agarwala, MD
Development Phase:	IV
Current Protocol Version and Release Date:	Protocol Amendment (Version 2.0) 25 March 2014

Confidential

Signature Page

PROTOCOL TITLE: An Observational Pilot Study to Compare the Compliance with and Health Related Quality of Life during Therapy with Standard High-Dose Interferon Alfa (Intron® A, HDI) versus Pegylated Alfa-Interferon 2b (Sylatron™, PEG IFN) in Patients with Surgically Resected Melanoma

PROTOCOL NUMBER: MISP 50442

Sanjiv Agarwala, MD
Professor of Medicine, Temple University
Chief Oncology & Hematology, St. Luke's Cancer Center

Date

Investigator Protocol Agreement Page

I agree to conduct the study as outlined in the protocol entitled "An Observational Pilot Study to Compare the Compliance with and Health Related Quality of Life during Therapy with Standard High-Dose Interferon Alfa (Intron® A, HDI) versus Pegylated Alfa-Interferon 2b (Sylatron™, PEG IFN) in Patients with Surgically Resected Melanoma" in accordance with Good Clinical Practices as defined in the current requirements of ICH E6(R1) and local regulations. I have read and understand all sections of the protocol.

Principal Investigator's Name

Principal Investigator's Signature

Date

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Protocol Synopsis

Protocol Number:	MISP 50442
Title:	An Observational Pilot Study to Compare the Compliance with and Health-Related Quality of Life during Therapy with Standard High-Dose Interferon Alfa (Intron® A, HDI) versus Pegylated Alfa-Interferon 2b (Sylatron™, PEG IFN) in Patients with Surgically Resected Melanoma
Study Phase:	IV
Purpose/Rationale:	To evaluate the compliance with and perceptions of treatment, as well as health-related quality of life (HRQOL) in surgically resected melanoma patients undergoing HDI or PEG IFN therapy.
Study Population:	Patients with surgically resected melanoma receiving adjuvant therapy with HDI or PEG IFN.
Objectives:	The primary objective of this study is: • To evaluate compliance with the administration of standard HDI versus PEG IFN for patients with melanoma in need of adjuvant therapy The secondary objectives of this study are: • To compare the convenience and satisfaction with chemotherapy for patients on standard HDI versus PEG IFN using a chemotherapy convenience and satisfaction questionnaire (CCSQ) and to evaluate the treatment-related side effects that may impact the patient's HRQOL using the Functional Assessment of Cancer Therapy of Biologic Response Modifier (FACT-BRM) • To assess the frequency of Grade 3 and 4 toxicities, according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) for patients on standard HDI versus PEG IFN • To examine reasons for patients' choice of treatment with HDI versus PEG IFN, for those cases in which patients are presented with a choice of either treatment option • To assess Health Resource Utilization on both arms of the study
Treatments:	• High-dose interferon alfa (Intron® A, HDI) • Pegylated alfa-interferon 2b (Sylatron™, PEG IFN)
Study Design and Methodology:	This will be a nonrandomized, open-label, pilot, observational, phase IV study to evaluate the compliance with and perceptions of treatment, as well as HRQOL in surgically resected melanoma patients undergoing HDI or PEG IFN therapy. The study will consist of a pretreatment (screening) phase, an induction phase, a maintenance phase, and an end-of-study (EOS) assessment. **Pretreatment/Screening** All patients will undergo a standard medical screening within 28 days of study of the first administration of HDI or PEG IFN. **Induction Phase**

	All enrolled patients will be offered HDI or PEG IFN and, after discussion with their treating physician, will initiate the therapy of their choice. Suggested dosing per package insert is as follows, but can be altered per institutional guidelines. HDI: 20 million IU/m^2 as an intravenous (IV) infusion over 20 minutes, 5 consecutive days per week for 4 weeks or PEG IFN: 6 mcg/kg/week subcutaneously (SC) for 8 doses Patients will complete the CCSQ and evaluate the treatment-related side effects that may impact their HRQOL using the FACT-BRM at specified time points during the Induction Phase. **Maintenance Phase** During the Maintenance Phase, patients will receive: HDI: 10 million IU/m^2 as an SC injection 3 times per week for 48 weeks or PEG IFN: 3 mcg/kg/week SC for up to 5 years (only the first year of therapy will be evaluated in this study) This is again the suggested dosing per package insert, and can be altered per institutional guidelines. As in the Induction Phase, patients will complete the CCSQ and FACT-BRM evaluations at specified time points. **End-of-Study Assessment** All patients who receive HDI or PEG IFN will be requested to return for an EOS visit within 21 days of discontinuation of study treatment. Final diary collection, safety assessments, treatment perceptions and HRQOL evaluations will be conducted at this visit. Safety assessments will be conducted during the study via clinical laboratory tests and adverse event (AE) monitoring.
Inclusion Criteria:	To be eligible for enrollment in this study, each of the following criteria must be satisfied with a "YES" answer (unless not applicable): 1. Patient is a male or female at least 18 years of age 2. Patient has had surgically resected melanoma and plans to receive adjuvant therapy with HDI or PEG IFN 3. Patient is willing and able to give written informed consent 4. Patient is willing to comply with all study requirements 5. Female and male patients with female partners of child bearing potential that are using contraceptive methods
Exclusion Criteria:	To be eligible for this study, each of the following criteria must be satisfied with a "NO" answer: 1. Patient is unable or unwilling to complete QoL questionnaires or compliance diary 2. Patient has a history of anaphylaxis due to any interferon alpha product

	3. Patient has autoimmune hepatitis 4. Patient has decompensated liver disease (Child-Pugh score >6 [Class B and C]) 5. Patient has a history of any neuropsychiatric disorder (including depression) that, in the judgment of the investigator, may impair the patient's ability to successfully complete treatment or protocol-related requirements (e.g., disorders that have required past hospitalization) 6. Patients with uncontrolled cardiac disease or a history of a confirmed myocardial infarction within the last 6 months, uncontrolled diabetes mellitus, uncontrolled hyper or hypothyroidism and significant autoimmune disease requiring steroid therapy.
Primary Endpoint:	The primary endpoint is a comparison of compliance with administration of treatment to be evaluated through use of patient diaries.
Secondary Endpoints:	1. Comparison of patient-reported perceptions of treatment (CCSQ) and HRQOL (FACT-BRM) for each treatment arm 2. Comparison of the frequency of Grade 3 and Grade 4 AEs per treatment arm 3. Evaluation of the reasons for patients' choice of treatment with HDI or PEG IFN through the use of a study-specific Interferon Preference Questionnaire, for cases in which patients are presented with a choice of either treatment option
Safety Assessments:	Safety assessments will include evaluation of AEs, clinical laboratory results (hematology and serum chemistry), vital sign measurements (temperature, blood pressure and pulse rate), and physical examination findings.
Sample Size:	100 patients
Statistical Methods:	This is an observational pilot study; therefore, descriptive outcomes will be presented comparing primary and secondary endpoints between patients receiving HDI versus PEG IGN. Selected inferential statistical comparisons will be conducted for exploratory purposes only and based on estimated clinically meaningful between-group differences, rather than statistically determined effect sizes..
Date of Protocol:	Protocol Amendment (Version 2.0): 25 March 2014 Original (Version 1.0): 27 June 2013

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
CCSQ	Chemotherapy Convenience and Satisfaction Questionnaire
CRF	case report form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
FACT-BRM	Functional Assessment of Cancer Therapy of Biologic Response Modifier
FDA	Food and Drug Administration
HDI	high-dose interferon
ICH	International Conference on Harmonization
IFN	interferon
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OS	overall survival
PEG	pegylated
QoL	quality of life
QAS	quality of life adjusted survival
RFS	relapse-free survival
SC	subcutaneous
US	United States

1 Introduction

1.1 Background

Melanoma

The incidence of melanoma is rising rapidly, with over 75,000 new cases expected to occur in the United States (US) in 2013 (Siegel 2013). Despite this rising incidence, which is likely related to an increased emphasis on early detection, the mortality rate has remained relatively unchanged (Howlander 1975-2008).

Most patients with melanoma present with early stage disease. For patients with thin melanomas without other adverse pathologic features, the cure rate with surgical therapy alone exceeds 90% (Sosman 2013). Unfortunately, for patients with thicker melanomas (stage IIb or higher), the risk of recurrence is higher. For these patients, the risk of recurrence is correlated with pathologic features, including thickness of the lesion, high versus low mitotic rate, presence of ulceration and regional lymph node involvement. High-risk disease is generally considered to include patients with stage IIb disease (lesion thickness >4 mm without ulceration or >2 mm with ulceration), stage IIc disease (lesion thickness >4 mm with ulceration), and stage III disease (regional lymph node involvement).

Adjuvant therapy to reduce the risk of recurrence in high-risk patients has now become standard of care for patients with stage III disease and is often used clinically for patients with high-risk stage II disease. Currently, the Food and Drug Administration (FDA) approved adjuvant therapy for patients with high-risk non-metastatic melanoma is interferon alpha. Both the standard form (interferon alpha 2b) and pegylated interferon alpha are approved for use as adjuvant therapy.

Interferon Alfa

The use of high-dose interferon (HDI) as adjuvant therapy following surgical resection of high-risk melanoma began in the early 1990s. The Eastern Cooperative Oncology Group (ECOG) 1684 trial examined the efficacy of 1-year HDI in patients with stage IIb-III melanoma (Kirkwood 1996). Patients were randomly assigned to receive HDI at a schedule of 20 MU/m^2/day intravenously (IV) for 5 consecutive days for 4 weeks (induction) followed by 10 MU/m^2/day subcutaneously (SC) 3 times per week (maintenance) for 48 weeks or observation. HDI was shown in the first analysis to significantly increase median relapse-free survival (RFS) (1.7 years versus 1 year; p=0.0023) and to prolong median overall survival (OS) (3.8 years versus 2.8 years; p=0.0237). In a follow-up analysis, the difference in OS was no longer statistically significant; however, the improvement in RFS persisted. The prolongation of RFS was only clearly shown for patients with stage III disease; however, there were too few stage II patients in the trial to draw a meaningful conclusion regarding its benefit in this patient population. Similar results to those obtained in ECOG trial 1684 were seen in subsequent trials in high-risk patients including Intergroup trials E1690 and E1694. The results of these trials have established the treatment schedule from E1684 as a standard of care for the adjuvant therapy of high-risk melanoma. A subsequent trial (E1697) was also performed to compare 1 month of induction therapy to observation for patients with stage IIa

disease. Accrual to this trial was halted when a planned interim analysis showed no difference in RFS or OS.

Pegylated Interferon Alfa (PEG IFN)

PEG IFN is composed of interferon covalently bound to polyethylene glycol monomethoxy ether, which increases the stability of the compound and results in a mean half-life ($t_{1/2}$) approximately 5 times greater than the $t_{1/2}$ of HDI (Eggermont 2008). In 2011, the FDA approved the drug as adjuvant treatment for patients with surgically resected melanoma based on the outcome from the European Organization for Research and Treatment of Cancer (EORTC) 1991 study (Eggermont 2012). In this study, patients with stage III melanoma after complete regional lymphadenectomy were randomized to receive either PEG IFN at a dose of 6 mcg/kg per week SC for 8 weeks followed by 3 mcg/kg per week SC for a treatment duration of up to 5 years or observation. At 7.6-year median follow-up, patients who received PEG IFN therapy had a significantly improved RFS; however, the distant metastasis free survival and OS were similar between the 2 cohorts (Eggermont 2012).

Toxicity and Quality of Life on Interferon Therapy

The use of adjuvant HDI is associated with considerable toxicity, most prominently flu-like symptoms and depression, resulting in a high rate of discontinuation. Despite this, over 60% of patients are able to complete 1 year of therapy. Treatment with PEG IFN produces similar side effects to those seen in patients treated with HDI, but at a lower intensity (Loquai 2008).

The value of HDI adjuvant therapy, with its attendant side effects, is an area of interest for prescribing physicians. Investigators question whether patients view HDI treatment positively because there is only a modest benefit in RFS without an improvement in OS. In 2002, a study was conducted to evaluate quality of life (QoL) of high-risk melanoma patients who received HDI versus observation for patients enrolled on 2 cooperative group trials (E1684 and E1690/S9111/C9190) (Kilbridge 2002). The study analyzed the trial efficacy, utility data, and quality-adjusted time without symptoms or toxicity to estimate the effect of HDI on QoL-adjusted survival (QAS). When the study evaluated patients enrolled in the E1684 study, a significant increase in QAS was found for all patient subsets but the result was statistically significant for only 16% of patients. For patients enrolled in the E1690/S9111/C9190 trial, QAS improvement was seen for 77% and a decrease was seen for 23%. Neither of the groups was statistically significant. In both trials, the change in QAS depended more on the utility for HDI toxicity than on the utility for melanoma recurrence.

A study has also been conducted to evaluate the effect of PEG IFN therapy on QoL. This study performed a retrospective evaluation using the EORTC QLQ-C30 QoL questionnaire. Both patients and physicians were asked to report on the patients' physical condition, mental health, and social life at baseline and throughout the course of treatment. The dose of PEG IFN given was lower than the current standard, at 2 mcg/kg per week for 18 months. For all functional domains analyzed, patients reported a decrease from baseline in their ability to function while on PEG IFN treatment. Similarly, as expected, there was an increase in constitutional symptoms with fatigue and loss of appetite being the most highly affected. Despite the significant impact of treatment on the QoL, patients still assessed their QoL as good on PEG IFN treatment.

1.2 Study Rationale

Previous trials have examined the quality of life of patients on either HDI or PEG IFN; however, no trials have examined whether patients prefer HDI or PEG IFN therapy. This study is a pilot, nonrandomized, observational, Phase IV study to investigate the compliance with and perceptions of treatment, as well as health-related quality of life (HRQOL) in surgically resected melanoma patients undergoing HDI or PEG IFN therapy. Patients will be offered HDI and/or PEG IFN, and, after discussion with their treatment physicians, will initiate therapy of choice. Baseline data, including medical history, perceptions of treatment and HRQOL, will be collected upon enrollment. Patients will complete treatment perception and HRQOL questionnaires and drug administration diaries to track compliance and the overall well-being of the patient while on therapy.

Accrual of 100 patients is expected to generate data adequate to determine whether a larger trial is warranted.

2 Study Objectives

2.1 Primary Objective

- To evaluate compliance with the administration of standard HDI versus PEG IFN for patients with surgically resected melanoma in need of adjuvant therapy

2.2 Secondary Objectives

- To compare perceptions of chemotherapy for patients on standard HDI versus PEG IFN using the Chemotherapy Convenience and Satisfaction Questionnaire (CCSQ) and to evaluate the treatment-related side effects that may impact the patient's HRQOL using the Functional Assessment of Cancer Therapy of Biologic Response Modifier (FACT-BRM)
- To assess the frequency of Grade 3 and 4 toxicities, according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events-CTCAE, Version 4.0
- To examine the reasons for patients' choice of treatment with PEG IFN versus HDI
- To assess Health Resource Utilization on both arms of the study

3 Study Design

This study is a non-randomized, observational, phase IV, multi-site pilot study to investigate the compliance with and perceptions of treatment, as well as HRQOL in surgically resected melanoma patients undergoing HDI or PEG IFN therapy. After discussion with their treating physician, patients will receive 1 of 2 approved adjuvant therapies for melanoma:

1. Cohort A: high-dose interferon alfa (HDI, Intron® A)
2. Cohort B: pegylated alfa-interferon 2b (PEG IFN, Sylatron™)

Although the study is not randomized, in order to attempt to discern a difference between the groups, a maximum of a 60:40 split will be allowed on the protocol. This means that a

maximum of 60% of patients will be permitted on either arm and if achieved, that particular arm will be capped at 60%.

Each treatment arm will have a pretreatment phase (within 4 weeks/28 days of starting the induction phase (4 weeks of HDI or 8 weeks of PEG IFN), a maintenance phase (treatment administration at specified times up to 1 year), and an end-of-study assessment, conducted within 21 days of discontinuation of study treatment.

The primary endpoint of this study is to compare compliance with treatment of HDI and PEG IFN. Patients will complete drug administration diaries to track compliance with the recommended dosing schedule. Secondary endpoints include comparing treatment perceptions and HRQOL between treatment groups, comparing the frequency of Grade 3 and Grade 4 adverse events (AEs) in each treatment arm, and evaluating the reasons for patients' choice of treatment with HDI or PEG IFN through the use of the Interferon Preference Questionnaire

Patients receiving HDI will complete the CCSQ and FACT-BRM at baseline, every 2 weeks during the induction phase and monthly during the maintenance phase (beginning at Day 29) for up to 1 year. Patients receiving PEG IFN will complete the CCSQ and FACT-BRM at baseline, 2 weeks, 4 weeks, 6 weeks, and monthly during the maintenance phase (beginning at Day 57) for up to 1 year. Adverse events will be monitored throughout the study. Any dose adjustments based on toxicities will be made according to investigator judgment and the package insert for each product. Patients will also be queried to determine the most important reasons for choice of treatment with HDI versus PEG IFN.

Study participation is expected to last until the completion of HDI treatment or a comparable duration for PEG IFN recipients (approximately 1 year).

Safety and tolerability will be assessed by evaluating adverse events, clinical laboratory tests (hematology and serum chemistry), physical examination, and Eastern Cooperative Oncology Group Performance Status (ECOG PS). The schedule of events for each treatment arm is presented in Table 2 and Table 3.

4 Population

The study population will consist of males and females at least 18 years of age with surgically resected melanoma in need of adjuvant therapy. Approximately 100 patients will be enrolled to compare the toxicity and compliance with standard HDI versus PEG IFN. This study is being conducted in the US at approximately 5-10 centers.

The investigator must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study.

4.1 Inclusion Criteria

1. Man or woman at least 18 years of age
2. Patient has had surgically resected melanoma and plans to receive adjuvant therapy with HDI or PEG IFN

3. Patient is willing and able to give written informed consent
4. Patient is willing to comply with all study requirements
5. Female and male patients with female partners of child bearing potential must use adequate contraceptive measures while on treatment

4.2 Exclusion Criteria

1. Patients were unable or unwilling to complete QoL or compliance questionnaires
2. Patient has a history of anaphylaxis due to any interferon alpha product
3. Patient has autoimmune hepatitis
4. Patient has decompensated liver disease (Child-Pugh score >6 [Class B and C])
5. Patient has a history of any neuropsychiatric disorder (including depression) that, in the judgment of the investigator, may impair the patient's ability to successfully complete treatment or protocol-related requirements (e.g., disorders that have required past hospitalization).
6. Patients with uncontrolled cardiac disease or a history of a confirmed myocardial infarction within the last 6 months, uncontrolled diabetes mellitus, uncontrolled hyper or hypothyroidism and significant autoimmune disease requiring steroid therapy.

5 Treatments

5.1 Identity of Investigational Product

Patients will be offered HDI and PEG IFN and, after discussion with their treating physician, will initiate the therapy of their choice (Table 1).The HDI and PEG IFN dose may modified per institutional dosing guidelines.

Table 1: Study Treatment (Suggested Dosing per Package Insert)

Treatment Group	Dose	
	Induction Phase	**Maintenance Phase**
High-dose interferon alpha (HDI)	20 million IU/m^2 IV infusion over 20 minutes, 5 consecutive days per week for 4 weeks	10 million IU/m2 as a SC injection 3 times per week for 48 weeks
Pegylated alfa-interferon 2b (PEG IFN)	6 mcg/kg/week SC for 8 doses	3 mcg/kg/week SC for up to 5 years[a]

[a] this study will only examine the first year of treatment

The proper storage conditions of HDI and PEG IFN will be described on the medication labels.

5.2 Method of Assigning Patients to Treatment Groups

This is an open-label, nonrandomized study. Patients will be offered HDI and/or PEG IFN and, after discussion with their treating physician, will initiate the therapy of their choice.

5.3 Treatment Blinding

Not applicable for this study.

5.4 Management of Clinical Supplies

Patients will receive commercially available product.

5.4.1 Treatment Discontinuation and Premature Patient Withdrawal

The investigator may at any time determine that a patient should no longer receive treatment with HDI or PEG IFN for reasons related to patient safety or for other reasons. If a patient's treatment with interferon is permanently discontinued, all study procedures will also be discontinued. All data obtained prior to treatment discontinuation will be included in the analysis set.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion case report form (CRF). Patients who are prematurely withdrawn from the study will not be replaced.

5.4.2 Early Study Termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, instructions will be provided concerning timing of final assessments. The investigator will be responsible for informing the Institutional Review Board (IRB) and/or the Ethics Committee (EC) of the early termination of the trial.

6 Visit Schedule and Assessments

Table 2 and Table 3 are suggested assessments for both treatment arms and suggested visit procedures are indicated with an "x." This study schedule is a suggested guideline and can be modified per institutional standard practice guidelines, with the exception of QoL, which is mandatory at the time points as indicated.

Table 2: Schedule of Events Cohort A: HDI Suggested schedule of events (QOL evaluation is mandatory)

Test/Assessment	Pretreatment[a]	D1	D8 [b]	D15 [b]	D22 [b]	Maintenance Phase[c]
Informed consent	X					
Medical history	X					
Interferon preference questionnaire	X					
ECOG PS	X					
Weight/vital signs[d]		X	X	X	X	X
Physical examination[e]		X				X
Hematology labs[f]		X	X	X	X	X
Chemistry labs[g]		X	X	X	X	X
Collection and Monitoring of Grade 3 and 4 AE and all SAEs [h]		X	X	X	X	X
QoL evaluations[i]		X		X		X
Drug administration diary[j]		X	X	X	X	X

Treatment: Induction Phase: Suggested dosing per package insert is 20 million IU/m^2 IV infusion over 20 minutes, 5 consecutive days per week for 4 weeks; Maintenance Phase: 10 million IU/m^2 SC injection 3 times per week for 48 weeks. Dosing can be modified per institutional guidelines.

[a] Within 4 weeks (28 days) of starting HDI

[b] For Days 8, 15, and 22, if HDI was delayed, the study assessment schedule for these dates will also be delayed

[c] . Maintenance dose begins at day 29 and then monthly until last dose of HDI.

[d] Weight should be obtained at baseline. Vital signs should be performed at each visit.

[e] Physical examination should be performed monthly or according to institutional protocol.

[f] Hematology labs will be done as clinically indicated and will include hemoglobin, hematocrit, RBC count, WBC count, platelets , as well as total and differential neutrophil counts. Hematology labs should be performed weekly during the induction phase or according to institutional protocol.

[g] Chemistry labs will be done as clinically indicated and should include albumin, creatinine kinase (CPK), urea or blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, bicarbonate (HCO_3) (CO_2; venous blood), calcium, and phosphorous. Chemistries should be performed weekly during the induction phase or according to institutional protocol. Specific individual chemistry labs may be omitted according to investigator judgment if not included in the institution's chemistry profile.

[h] All Grade 3 and 4 adverse events (regardless of whether they occur on treatment or non-treatment weeks) will be collected until the last day of treatment and submitted utilizing the corresponding AE forms. Additionally, all SAEs, regardless of grade will also be collected.

[i] Treatment perceptions and HRQOL data will be collected via CCSQ and FACT-BRM, respectively, at baseline, every 2 weeks during the induction phase, and monthly during the maintenance phase (beginning at day 29) for up to 1 year. These questionnaires are to be completed prior to the administration of the dose for that visit. .If dose is held or changed QoL is still to be completed.

[j] Patients will be instructed to record details on the receipt of HDI in the drug administration diary and will return the diary to the site at the subsequent visit. These diaries will capture the onset of AEs in relationship to the day of drug administration.

Table 3: Schedule of Events (Cohort B: PEG IFN) Suggested schedule of events (QOL evaluation is mandatory)

Test/Assessment	Pretreatment[a]	D1	D8 [b]	D15 [b]	D22 [b]		[b]	[b]	[b]	Maintenance Phase[c]
Informed consent	X									
Medical history	X									
Interferon preference questionnaire	X									
ECOG PS	X									
Weight/vital signs[d]		X	X	X	X					X
Physical examination[e]		X								X
Hematology labs[f]		X	X	X	X					X
Chemistry labs[g]		X	X	X	X					X
Collection and Monitoring of Grade 3 and 4 AE and all SAEs [h]		X	X	X	X					X
QoL evaluations[i]		X		X						X
Drug administration diary[j]		X	X	X	X					X

Treatment: Induction Phase: Suggested dosing per package insert is 6 mcg/kg/week SC for 8 doses (8 weeks); Maintenance Phase: 3 mck/kg/week SC injection for up to 5 years (this study will only evaluate the first year of treatment). Dosing can be modified per institutional guidelines.

[a] Within 4 weeks (28 days) of starting PEG IFN

[b] For Days 8, 15, 22, 29, 36, 43, and 50 if PEG IFN was delayed, the study assessment schedule for these dates will also be delayed

[c] Maintenance dose begins at day 29 and then monthly until last dose of PEG IFN, .or until treatment discontinuation or one year of therapy

[d] Weight should be obtained at baseline. Vital signs should be performed at each visit.

[e] Physical examination should be performed monthly or according to institutional protocol.

[f] Hematology labs will be done as clinically indicated and will include hemoglobin, hematocrit, RBC count, WBC count, platelets , as well as total and differential neutrophil counts.. Hematology labs should be performed weekly during the induction phase or according to institutional protocol.

[g] Chemistry labs will be done as clinically indicated and should include albumin, creatinine kinase (CPK), or urea blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, bicarbonate (HCO_3) (CO_2; venous blood), calcium, and phosphorous. Chemistries should be performed weekly during the induction phase or according to institutional protocol. Specific individual chemistry labs may be omitted according to investigator judgment if not included in the institution's chemistry profile.

[h] All Grade 3 and 4 adverse events (regardless of whether they occur on treatment or non-treatment weeks) will be collected until the last day of treatment and submitted utilizing the corresponding AE forms. Additionally, all SAEs, regardless of grade will also be collected.

[i] Treatment perceptions and HRQOL data will be collected via CCSQ and FACT-BRM, respectively, at baseline, 2 weeks, 4 weeks, 6 weeks, and monthly during the maintenance phase (beginning at Day 57) for up to 1 year. These questionnaires are to be completed prior to the administration of the dose for that visit. If dose is held or changed, QoL is still to be completed.

[j] Patients will be instructed to record details on the receipt of HDI in the drug administration diary and will return the diary to the site at the subsequent visit. These diaries will capture the onset of AEs in relationship to the day of drug administration.

Patients should be seen for all visits on the designated day or as close as possible to the designated day. **Please note that the ±1 week interval in the Maintenance Phase of the study is proposed as a guide. Visits falling outside this window should not lead to automatic patient discontinuation.**

All data obtained from the assessments listed in the schedule of events must be supported in the patient's source documentation.

6.1 Patient Demographics/Baseline Characteristics

Patient demographic and baseline characteristic data will be collected for all patients enrolled in the study, including relevant medical history.

6.2 Interferon Preference

For situations in which the investigator offered both treatment options, patients will be queried regarding their reasons for the choice of either HDI or PEG IFN using a standardized questionnaire created for this study (see Appendix 13.3).

6.3 ECOG Performance Scale

The Eastern Cooperative Oncology Group Performance Scale (ECOG PS) assesses the patients' general well-being and activities of daily life (see Appendix 13.4).

6.4 Weight and Vital Signs

Weight and vital signs (temperature, pulse rate and blood pressure) should be recorded at baseline. Vital signs should be obtained weekly during induction and monthly during maintenance or according to institutional protocol.

6.5 Physical Examination

A complete physical examination will be performed at baseline and monthly for the duration of the study or according to institutional protocol. The physical examination should include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings made after the start of treatment that meet the definition of a Grade 3 or Grade 4 adverse event must be recorded on the AE CRF.

6.6 Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed by local laboratories as clinically indicated. Routine laboratory tests (hematology and clinical chemistry) should be performed at the time points designated in the schedule of events for both treatment cohorts (Table 2 and Table 3).

6.7 Treatment Perceptions and Health-Related Quality of Life Assessments

The CCSQ will be used to ascertain patients' perceptions of their chemotherapy regimen in terms of its convenience and their overall level of satisfaction. Treatment-related side effects

that may impact the patient's HRQOLwill be evaluated using the FACT-BRM. Patients will complete these mandatory assessments at the time points specified in Table 2 and Table 3.

6.7.1 CCSQ

The CCSQ is a questionnaire for oncology patients used to evaluate their overall satisfaction with and preferences for chemotherapy. The CCSQ was generated from interviews with 70 oncology patients, 7 oncologists, 4 nurses, and focus groups of 14 nurses. Interviews took place in the US, the United Kingdom, and France and were qualitatively analyzed. The CCSQ was designed for adults with a wide range of cancer types and stages and contains 21 items and 7 domains:

1. Expectations of chemotherapy
2. Feelings about side effects
3. Oral chemotherapy compliance
4. Convenience
5. Satisfaction with chemotherapy
6. Stopping chemotherapy
7. Reasons for non-compliance

6.7.2 FACT-BRM

The FACT-BRM is a questionnaire designed to evaluate HRQOLin cancer patients who are receiving treatment with biologic response modifiers. The FACT-BRM contains 6 domains:

1. Physical well-being
2. Social/family well-being
3. Emotional well-being
4. Functional well-being
5. Additional concerns – Physical
6. Additional concerns – Mental

6.8 Treatment Compliance

Patients will complete drug administration diaries to track compliance with the recommended dosing schedule. These diaries will also capture the onset of AEs in relationship to the day of drug administration. The diaries will be returned to the Investigator at the subsequent visit.

6.9 Pregnancy

The occurrence of pregnancy in a female subject or female partner of a male subject will be reported and recorded on the CRFs. Pregnancy will be handled as per usual clinical care. If interferon therapy is interrupted due to the pregnancy, this should be recorded on the CRFs.

7 Safety Monitoring

7.1 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the treatment even if the event is not considered to be related to the treatment. Treatment includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting treatment are only considered AEs if they worsen after starting treatment. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All Grade 3 or 4 AEs and all SAEs regardless of grade, must be recorded on the AE CRF with the following information:

1. the severity grade (3 or 4 AEs and all SAEs regardless of grade)
2. its relationship to HDI or PEG IFN therapy (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (ie, further observation only); treatment dosage adjusted/temporarily interrupted; treatment permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the AE CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the treatment, the interventions required to treat it, and the outcome.

8 Data Review and Database Management

8.1 Site Monitoring

Before study initiation at any sub-sites, a study representative will review the protocol and CRFs with the investigators and their staff, and protocol training will be documented

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

All multi-site procedures outlined in the multi-site procedures manual must be followed.

No information in source documents about the identity of the patients will be disclosed.

8.2 Data Collection

Designated investigator staff must enter the information required by the protocol onto the paper CRFs, and copies of the interferon preference questionnaire, treatment perceptions, HRQOL evaluations and the drug administration diaries will be sent to the coordinating center as outlined in the multi-site procedures manual.

8.3 Database Management and Quality Control

Data from the interferon preference questionnaire, treatment perception questionnaire,HRQOL evaluations and drug administration diaries will be reviewed by the coordinating center staff following their own internal standard operating procedures.

Errors or omissions on paper CRFs will generate queries that will be returned to the investigational site for resolution. Quality control audits will be completed as outlined in the multi-site procedures manual, and prior to finalizing data.

Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

9 Data Analysis

This is an observational pilot study with no formal sample size calculation based on a previously established effect size. For both primary and secondary outcomes, descriptive data will be presented (i.e., means and standard deviations or medians and interquartile ranges for interval and ordinal data as appropriate; frequencies and percentages for nominal/categorical data). Missing data will not be imputed due to the study's exploratory nature; however, all missing data points will be recorded and assessed for possible response patterns.

Selected inferential analyses will be conducted for exploratory purposes using estimated clinically important between-group differences. The study authors will seek to maintain at least a 60:40 between-group ratio to guard against unequal variance.

- Primary outcome
    - To compare compliance with HDI and PEG IFN (percentage of doses taken as recorded in patient diaries), with a 30% between-group difference deemed clinically relevant, a mixed randomized-repeated measures analysis of variance (ANOVA) will be conducted with treatment group (HDI versus PEG IFN) as the randomized (between-group) factor and treatment period time as the repeated measures (within-group) factor. For the repeated measures factor of time, given the different induction phases for the two regimens (i.e., approximately 4 weeks for HDI versus 8 weeks for PEG IFN), the ANOVA will capture outcomes at baseline, 2 weeks, 3 months, 6

months and 12 months, with inclusion of the latter outcome dependent on the amount of missing data.

- Secondary outcomes:
  - To compare the convenience and satisfaction with chemotherapy for patients on standard HDI versus PEG IFN using a chemotherapy convenience and satisfaction questionnaire (CCSQ), with a 30% between-group difference in scores deemed clinically relevant, a mixed randomized-repeated measures ANOVA will be conducted for items CS1 – GP5 as a summation score, since these items share the same Likert scale anchors and valences. Treatment group (HDI versus PEG IFN) will comprise the randomized (between-group) factor and treatment period time represents the repeated measures (within-group) factor. For the repeated measures factor of time, given the different induction phases for the two regimens (i.e., approximately 4 weeks for HDI versus 8 weeks for PEG IFN), the ANOVA will capture outcomes at baseline, 2 weeks, 3 months, 6 months and 12 months, with inclusion of the latter outcome dependent on the amount of missing data.

    It should be noted that although the CCSQ is technically an ordinal tool, it will be treated as a continuous/interval scale for the purposes of the ANOVA, with transformation of outcomes as deemed appropriate. It should also be noted that the CCSQ has not been formally validated; therefore, certain items will be presented descriptively, rather than inferentially, as per the judgment of the study authors in keeping with the study's exploratory nature.

Item GF7, which assesses contentment with current quality of life, will be presented descriptively for the two treatment groups as a separate item due to its positively worded valence, at baseline, 2 weeks, 3 months, 6 months and 12 months. No inferential analyses will be conducted for this item.

For item CS10, which assesses satisfaction with current results of chemotherapy, the 3 separate "yes" responses will be collapsed for the sake of convenience and presented descriptively as a dichotomous outcome for the two treatment groups at 2 weeks, 3 months, 6 months and 12 months. No inferential analyses will be conducted for this item.

Items CS11 and CS12, which measure recommendation/choice of chemotherapy regimen, will be presented descriptively for the two treatment groups at 2 weeks, 3 months, 6 months and 12 months. No inferential analyses will be conducted for these items.

Item CS13, which rates the chemotherapy regimen overall, will be presented descriptively for the two treatment groups at the end of the study (i.e., 12 months). No inferential analyses will be conducted for this item.

- To evaluate the treatment-related side effects that may impact the patient's health-related QoL (HRQOL) using the Functional Assessment of Cancer Therapy of Biologic Response Modifier (FACT-BRM), with a 30% between-group difference in scores deemed clinically relevant, a mixed randomized-repeated measures ANOVA will be conducted for all items as a summation score, similar to the analysis plan described for CCSQ items CS1 – GP5 (page 23, second bullet point). Separate subscales will be presented descriptively for the two treatment groups.

- The frequency of Grade 3 and 4 toxicities, according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) for patients on standard HDI versus PEG IFN, will be presented descriptively for the two treatment groups at 2 weeks, 3 months, 6 months and 12 months. No inferential analyses will be conducted for this outcome.

- Patients' reasons for their choice of treatment with HDI versus PEG IFN, for those cases in which patients are presented with a choice of either treatment option, will be reported descriptively at the study's conclusion (i.e., 12 months). No inferential analyses will be conducted for this outcome.

9.1 Compliance

Compliance for HDI and PEG IFN will be analyzed by comparing the percentage of doses taken (as recorded in the diary) over the treatment period as prescribed by the physician.

Analysis of this primary endpoint is described on pages 22-23.

9.2 Safety

The only adverse events that will be counted will be treatment-emergent Grade 3 and 4 AEs and treatment-emergent SAEs regardless of grade. These events are those that started after the start of that treatment period, or were present prior to the start of the treatment period but increased in severity, or changed from being not suspected to being suspected to be due to treatment.

Treatment-emergent adverse events will be summarized separately for each treatment group and by body system and preferred term. Any other information collected (eg, severity or relatedness to treatment) will be listed as appropriate.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) will be provided.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

9.3 Sample Size Calculation

Due to the pilot study design, minimum sample size has not been calculated formally. The sample size of 100 patients is expected to generate data adequate to determine if a larger trial is warranted.

9.4 Interim Analysis

There is no interim analysis planned for this study.

10 Ethical Considerations

10.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC -approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

St. Luke's University Health Network (SLUHN) will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by SLUHN before submission to the IRB/EC, and a copy of the approved version must be provided to SLUHN after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to SLUHN before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to SLUHN monitors, auditors, Clinical Quality Assurance representatives, designated agents of SLUHN, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform SLUHN immediately that this request has been made.

10.4 Publication of Study Protocol and Results

SLUHN will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CRF.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by SLUHN and the IRB/EC. Only amendments that are required for patient safety may be implemented prior to IRB/EC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

12 References

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13 Appendices

13.1 Chemotherapy Convenience and Satisfaction Questionnaire (CCSQ)

Below is a list of statements that people receiving chemotherapy like yours have said are important. For each statement, please choose the reply that best fits your experience with receiving chemotherapy, and circle the number corresponding to your reply.

"Chemotherapy" means the drug(s) you receive to treat your cancer or tumor.

	Chemotherapy Experience - 1	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very Much**
CS1	Chemotherapy treatment takes up my time.	0	1	2	3	4
CS2	My chemotherapy treatment takes up my family's time.	0	1	2	3	4
CS3	I worry about side effects from chemotherapy treatment.	0	1	2	3	4
CS4	My chemotherapy treatment causes me physical pain.	0	1	2	3	4
CS5	Receiving chemotherapy is inconvenient.	0	1	2	3	4
CS6	I worry that my chemotherapy will not be effective.	0	1	2	3	4
CS7	Chemotherapy treatment seems harmful to me.	0	1	2	3	4
CS8	My chemotherapy schedule is stressful to me.	0	1	2	3	4
CS9	My chemotherapy schedule is stressful to my family.	0	1	2	3	4
GP5	I am bothered by side effects of treatment.	0	1	2	3	4
	Please answer this last question about how you have felt this past week.					
GF7	I am content with the quality of my life right now.	0	1	2	3	4

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Version 6, 11-27-02

Considering your experience with chemotherapy to date, please respond to the following questions.

	Chemotherapy Experience - 2	No, not at all	Yes, to some extent	Yes, for the most part	Yes, completely
CS 10	Are you satisfied with the current results of your chemotherapy?	0	1	2	3

		No	Maybe	Yes
CS 11	Would you recommend this chemotherapy to others with your illness?	0	1	2
CS 12	Would you choose this chemotherapy again?	0	1	2

		Poor	Fair	Good	Very Good	Excellent
CS 13	How would you rate this chemotherapy?	0	1	2	3	4

Resource Utilization

A "cycle" of therapy with interferon is defined as one month of treatment and includes the days on which you get an infusion or injection or both, and also the days after that until you get another infusion or injection. Each month is separate cycle. If you have any question about what period of time makes up one “cycle” of treatment, your doctor or nurse can tell you.

1. How many times did you go to the hospital or doctor’s office for any reason (including scheduled visits) during the previous cycle?

_____ times during the previous cycle to the hospital

_____ times during the previous cycle to the emergency room or clinic

_____ times during the previous cycle to the doctor’s office

2. What was the average length of time spent on these visits, including travel to and from, waiting time, time with doctor or nurse, drug administration time, and testing/procedure time?

_____ days during the previous cycle for an average hospital visit

_____ hours during the previous cycle for an average emergency room or clinic visit

_____ hours during the previous cycle for an average doctor’s office visit

3. How many total hours did you miss from work and/or your usual activities during your previous treatment cycle?

_____ hours missed during the previous cycle

4. How many total hours have your friends or relatives missed from work and/or their usual activities because you needed their help during your previous treatment cycle?

_____ hours missed during the previous cycle

13.2 FACT-BRM (Version 4)

FACT-BRM (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)
Copyright, 1987, 1997

FACT-BRM (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Copyright, 1987, 1997

FACT-BRM (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS - Physical	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT6	I get tired easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
BRM1	I have pain in my joints	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
BRM10	I am bothered by sweating	0	1	2	3	4

	ADDITIONAL CONCERNS - Mental					
HI8	I have trouble concentrating	0	1	2	3	4
HI9	I have trouble remembering things	0	1	2	3	4
BRM7	I get depressed easily	0	1	2	3	4
BRM8	I get annoyed easily	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
HI6	I feel motivated to do things	0	1	2	3	4

English (Universal)
Copyright, 1987, 1997

13.3 Interferon Preference Questionnaire

Study Patient number: _____

Interferon Preference Questionnaire

1. Did your physician discuss the option of taking standard high dose interferon vs. pegylated interferon (Sylatron™) with you?	Yes □ No □
If you answered "No" to question 1, there is no need to complete the remainder of the questionnaire.	
2. Please rate the following factors in terms of its importance with regard to your choice of type of interferon therapy:	
a. Frequency of treatment (how often the treatment is given)	Very important □ Somewhat important □ Not important □
b. Toxicity (side effects) of therapy	Very important □ Somewhat important □ Not important □
c. Effectiveness of therapy in preventing or delaying return of melanoma	Very important □ Somewhat important □ Not important □
d. Convenience of the treatment schedule	Very important □ Somewhat important □ Not important □
e. Length of therapy (one year vs. longer)	Very important □ Somewhat important □ Not important □
3. Do you perceive that your physician has recommended or has a preference between the two treatment options?	Yes, I followed his/her recommendation □ Yes, but I chose the other treatment option □ My physician did not seem to have a preference □
Please add any additional comments here:	

13.4 ECOG Performance Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Note: As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.