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TITLE: A Phase II Study of Imatinib Mesylate in Children and Adults with Sclerotic Skin Changes of Chronic Graft-Versus-Host Disease

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PRÉCIS

Background:

- Chronic graft versus host disease (cGVHD) is a major complication of allogeneic stem cell transplant (alloHSCT). The sclerotic skin manifestations of chronic cutaneous GVHD (ScGVHD) can lead to significant functional impairment and no satisfactory therapy exists to adequately treat this form of cGVHD.
- Imatinib mesylate is a small molecule tyrosine kinase inhibitor with potent activity against platelet derived growth factor receptor (PDGFR) signaling, a key cytokine pathway which has been implicated in fibrotic disease in general, and in extensive cGVHD in particular.
- We hypothesize that treatment with imatinib mesylate will reduce the sclerotic manifestations of cGVHD as assessed by quantitative range of motion assessment of an affected joint.

Objectives:

- Primary Objective:
    - To investigate whether imatinib mesylate results in clinical improvement in skin fibrosis in children and adults with ScGVHD using range of motion assessment of affected joints.
    - To determine if imatinib mesylate 200 mg daily is tolerated by patients with cGVHD.

- Secondary Objectives:
    - To assess toxicity associated with imatinib mesylate in patients with cGVHD.
    - To establish outcome criteria for the evaluation of ScGVHD using multi-modality objective and subjective assessments, including magnetic resonance imaging, skin scoring, and patient self-reported measures.
    - To evaluate biomarkers of disease activity and correlative response measures to treatment with imatinib mesylate.
    - To assess quality of life and functional measures of disease activity and to evaluate changes through the course of therapy.
    - To evaluate the response of other organ manifestations affected by cGVHD to treatment with imatinib mesylate.
    - To evaluate steady-state pharmacokinetics of imatinib mesylate in the cGVHD patient population.

Eligibility:

- Patients age 4 years of age or older with the diagnosis of ScGVHD.

Design:

- This is an open-label, pilot study of imatinib mesylate.
- Treatment cycles are 28-day cycles with no rest period between cycles.
- A target of 10 evaluable patients will be enrolled on this trial.

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1 OBJECTIVES

1.1 Primary Objectives

- To investigate whether imatinib mesylate results in clinical improvement in skin fibrosis in children and adults with ScGVHD using range of motion assessment of affected joints.
- To determine if imatinib mesylate 200mg daily is tolerated by patients with cGVHD.

1.2 Secondary Objectives

- To assess toxicity associated with imatinib mesylate in patients with cGVHD.
- To establish outcome criteria for the evaluation of ScGVHD using multi-modality objective and subjective assessments, including magnetic resonance imaging, skin scoring, and patient self-reported measures.
- To evaluate biomarkers of disease activity and correlative response measures to treatment with imatinib mesylate.
- To assess quality of life and functional measures of disease activity and to evaluate changes through the course of therapy.
- To evaluate the response of other organ manifestations affected by cGVHD to treatment with imatinib mesylate.
- To evaluate steady-state pharmacokinetics of imatinib mesylate in the cGVHD patient population

2 BACKGROUND

2.1 Imatinib mesylate

Imatinib mesylate is a tyrosine kinase inhibitor that was specifically developed to target inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction. It additionally has a high degree of specificity and biological activity against both platelet-derived growth factor (PDGF) and transforming growth factor-ß (TGF-ß) signaling pathways, cytokines strongly implicated in the fibrogenesis process.

The FDA-approved imatinib mesylate dosing for CML, gastrointestinal stromal tumors, eosinophilic leukemia, dermatofibrosarcoma protuberans ranges from 400 mg – 800 mg daily for adults and 260 mg/m^2 – 340 mg/m^2 in children. The dosing schedule of 400 mg daily for adults and 260 mg/m^2 daily for children will be used on this protocol. This dosing regimen is based on data that the inhibitory effect of imatinib on the PDGFR is quite potent and equals inhibition of BCR-ABL with a similar IC_{50} ~0.1-0.3µM [1-5]. Patients achieve mean steady state serum peak

levels of ~4.6 μM and mean trough levels of ~ 1.46μM at a once daily dose of 400mg.[1] A pediatric phase 1 study looking at the use of imatinib mesylate in children with chronic myelogenous leukemia (CML) found biologic efficacy at a dose of 260mg/m^2 with PKs equivalent to the adult dose of 400mg daily. No maximum tolerated does (MTD) was established with doses up to 570mg/m^2.[6] A dose de-escalation study for FIP1L1/PDGFRA-positive chronic eosinophilic leukemia showed effective PDGFR inhibition at doses below 400mg, and as low as 100 mg daily in adult patients [7]. Additionally, although in both pediatric and phase I studies no MTD's were identified, side effect profiles are related to dose intensity.[1,8] In this patient population, likely entering the study on multiple medications with potential multi-organ system involvement of disease, doses above 400mg daily are likely to be unnecessary and less well tolerated.

2.1.1 Major route of elimination

The oral capsule is 98% bioavailable. It is highly protein bound (95%) to alpha-1 acid glycoprotein and albumin. It is extensively metabolized by the liver and 13% is excreted by the kidneys (5% of oral dose appears unchanged in urine). Approximately 70% is excreted in the feces, 20% is eliminated unchanged. Elimination half –life is 13-18 hours. [Prod Info Gleevec(TM), 2001a]

2.1.2 Metabolism

Extensive liver metabolism, primarily by cytochrome P450-3A4 enzymes; other cytochrome P450 enzymes play a minor role. An N-demethylated piperazine derivative is the main circulating metabolite, which has in vitro activity similar to the parent compound [Prod Info Gleevec(TM), 2001a].

2.1.3 Drug interaction

In vitro studies showed that CYP3A4 was the major human isozyme catalyzing the biotransformation of imatinib. Thus, drugs such as ketoconazole that inhibit CYP3A4 activity could increase imatinib exposure and drugs that induce CYP3A4 (e.g. rifampin, dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St. John's Wort) may reduce imatinib exposure. In two published studies, concomitant administration of imatinib and a product containing St. John's Wort led to a 30-32% reduction in the AUC of imatinib.

Imatinib was also shown to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5, with K_i values in human liver microsomes being 27, 7.5 and 7.9 μmol/L, respectively. Thus, drugs which are substrates of CYP2C9, CYP2D6 and CYP3A4/5 could have their exposure affected by imatinib [Investigator Brochure, Ed. 9, 2006].

2.2 Graft-versus-Host disease

Approximately 7,000 allogeneic hematopoietic stem cell transplants are performed each year in North America for patients with malignant and non-malignant diseases. Approximately one-half of allogeneic transplant recipients develop cGVHD, a serious and potentially life threatening long-term complication of alloHSCT. cGVHD is a multi-system alloimmune and autoimmune

disorder characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival. cGVHD may manifest with cutaneous, gastrointestinal, hepatic, ocular, oral, and/or pulmonary involvement and is often characterized by the development of features resembling autoimmune or immunologic disease, including scleroderma, Sjogren's syndrome, chronic immunodeficiency, and bronchiolitis obliterans. cGVHD leads to impaired performance status, diminished quality of life and an increased risk of mortality. Five-year survival rates for patients who develop cGVHD range from 40% for poor prognosis or "high-risk" cGVHD to 70% for "standard-risk" cGVHD. Due to improvements in supportive care and decreases in early posttransplant-related mortality there are an increasing number of long-term survivors after transplantation who develop cGVHD. The incidence of cGVHD is as high as 80% in some patient populations, including recipients of peripheral blood or unrelated donor alloHSCT. Standard front-line therapy for cGVHD consists of cyclosporine with high-dose systemic corticosteroids. Approximately 70% patients respond to front line therapy within three months, however, one-half of patients require second-line treatments. Even in patients who do respond to treatment, significant side effects often occur, including serious infections. The list of immunosuppressants and other drugs attempted for salvage therapy of cGVHD is long and there is no standard approach to salvage treatment. The average response rate to salvage agents is approximately 35% and responses achieved with these agents are often incomplete and short-lived [9,10].

There are several cutaneous manifestations of cGVHD, including dyspigmentation, erythema, maculopapular rash, pruritus, lichenoid changes, and superficial and deep sclerosis. The most severe and difficult-to-treat skin manifestation is ScGVHD. Extensive, sclerotic skin changes with superficial or deep subcutaneous or fascial involvement develops in approximately 3-4% of patients with cGVHD and can be a life-threatening manifestation [11]. The process is characterized by fibrosis of the skin or subcutaneous tissues and may result in joint contractures, severe wasting, and chest wall restriction. The mean onset of sclerotic skin changes following transplant is late (529 days in one study [12]). The natural history of this process is unknown and there are no large, published series of patients that describe the clinical, histological, and natural history of ScGVHD. In addition, there is currently no standardized assessment for ScGVHD. Many therapies have been used including calcineurin inhibitors, systemic corticosteroids, antimetabolites, antibodies, hydroxychloroquine and extracorporeal photopheresis. Reported responses are mixed and slow to occur and no therapy has demonstrated significant, sustained responses.

Patients for this trial will be recruited nationwide and treated and evaluated in the cGVHD Multidisciplinary Program at the National Cancer Institute/National Institutes of Health. In evaluating an exceedingly complex disease with a diverse patient population, cGVHD clinical trials suffer from poor standardization of entry and response-assessment criteria. This has resulted in difficulties in clinical trial data interpretation. Diagnosis and response assessment will be based on the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease criteria [10,13]. We propose a study of imatinib mesylate in cGVHD focused primarily on well-defined cGVHD organ manifestations with clearly defined entry, concurrent treatment, and evaluation criteria.

2.3 Rationale

As noted in section 2.1, both platelet-derived growth factor (PDGF) and transforming growth factor-ß (TGF-ß) cytokines have been implicated in the pathogenesis of fibrosing diseases, including hepatic fibrosis, renal fibrosis, idiopathic pulmonary fibrosis, and systemic sclerosis (scleroderma), a disease which clinically resembles ScGVHD[14-26].

Furthermore, in the last year, stimulatory antibodies specific for the PDGF receptor (PDGFR) were identified in a series of 39 patients with extensive cGVHD. Higher levels were detected in patients with skin involvement[15]. Similar stimulatory antibodies targeting PDGFR have also been reported in patients with systemic sclerosis, suggesting a common therapeutic target for these fibrosing skin diseases [16,17]. Imatinib mesylate has particularly potent activity against PDGFR and is FDA-approved for the treatment of several disorders associated with aberrant PDGFR signaling, including myelodysplastic disease, hypereosinophilic syndrome, chronic eosinophilic leukemia, and dermatofibrosarcoma protuberans [27-30]. The side effect profile of the drug is well established, which is an important factor in the setting of a therapy for allo-HSCT patients, many of whom have multi-organ disease and are maintained on chronic immunosuppressive therapy[27,28,30].

Imatinib mesylate has demonstrated pre-clinical and clinical activity in several non-malignant fibrosing conditions, including rheumatoid arthritis, renal fibrosis, dermal sclerosis, and pulmonary fibrosis[18,24,26]. There are currently six phase II studies evaluating the use of imatinib mesylate for systemic sclerosis. In addition, there is a report of improved pulmonary function in an alloHSCT recipient with pulmonary fibrosis treated with imatinib mesylate for recurrent CML[31] as well as a case series reporting lower GVHD incidence in post transplant patients receiving Imatinib mesylate [32].

More recently, the GITMO multi-center consortium has reported results of a pilot study evaluating low dose imatinib for the treatment of refractory sclerotic cGvHD. Patients received imatinib mesylate starting at a dose of 100 mg/day, increasing to 200 mg/day in absence of severe adverse reactions. A total of 15 patients were treated. The authors report minimal toxicity with four patients experiencing minor, non-hematologic toxicity with one grade 3-4 toxicity. There was no significant hematalogic toxicity and no treatment related mortality. No TRD were observed and treatment was interrupted in one patient. They report an overall response rate of 86% with a median follow up of 8 months [33]. When compared to other salvage therapy regimens in refractory cGVHD, these response rates are quite encouraging.

2.4 Correlative Studies Background

2.4.1 PDGFR Studies (Mark Raffeld, NCI)

PDGFR activity has been implicated in the development of several fibrosing conditions. Stimulatory antibodies targeting PDGFR have also been reported in patients with systemic sclerosis, suggesting an important therapeutic target for these fibrosing conditions. Within the last year, stimulatory antibodies specific for the PDGF receptor were identified in a series of 39 patients with extensive cGVHD. Furthermore, higher levels were detected in patients with skin

involvement.

2.4.1.1 Rationale for PDGFR Studies
Understanding PDGFR status in patients with ScGVHD will help elucidate the pathophysiology of this disease manifestation and may lead to improvements in the prevention and treatment of this complication.

2.4.1.2 Objectives / Specific Aims for PDGFR Studies

- To evaluate the functional activation status of PDGFR alpha and beta subunits and to correlate these findings to disease activity and response to imatinib therapy.

2.4.2 Immune Function Studies (Fran Hakim, ETIB, NCI)
The pathophysiological basis for ScGVHD is poorly understood. A critical issue in cGVHD immunology is the characterization of the Tcells which mediate it. It is not known whether the effector T cells in the autoimmune symptomatology of cGVHD are derived from mature T cells in the donor inoculum (hence are a failure of peripheral tolerance), or arise secondarily from failures of thymic maturation/negative selection (hence a failure of central tolerance). Part of the problem in analyzing cGVHD is that information based on studies of peripheral blood is conflicting. Even the role of type I vs. type II cytokines is unclear.

2.4.2.1 Rationale for Immune Function Studies
We believe analysis of T cells infiltrating the site of cGVHD in the skin will further our understanding of the immunologic nature of this manifestation.

2.4.2.2 Objectives for Immune Function Studies

- To characterize the T cell subsets in the peripheral blood for markers indicative of naïve/memory/effector/regulatory T cell status before and after therapy.

- To characterize the T cell subsets specifically involved in affected skin by fluorescence immunohistochemistry using confocal microscopy, and to assess changes in frequency of subsets following treatment.

2.4.3 **TGF-β studies (Kathy Flanders, Lalage Wakefield, Fran Hakim, NCI)**
2.4.3.1 Background
Previous studies have suggested that patients with cGVHD complications have higher circulating levels of TGF-β, but the form (active vs. latent) and cellular source leading to an increased circulating level of this cytokine are not known. Several studies have linked specific gene polymorphisms to increased synthesis and secretion of TGF-β and have demonstrated an association between these polymorphisms and the severity of GVHD complications.

2.4.3.2 Rationale for TGF-β studies
To determine the role TGF-β in ScGVHD, including the source of TGF-β production, and the function of the TGF-β signaling pathway in immune cells in patients with ScGVHD.

2.4.3.3 Objectives/Specific Aims of TGF-β studies

- Determine the status of circulating TGF-β in patients with chronic GVHD.

- Determine whether expression of TGF-β ligands are increased in fibrotic tissues in GVHD, and whether the immunohistochemical detection of phosphorylated, receptor activated Smads (rSmads) can be used as a biochemical marker of active TGF-β signaling in tissues.

- Determine whether activated immune cells or regulatory T cells are the source of high systemic TGF-β by performing FACS analysis for intracellular TGF-β expression.

2.4.4 IL-13 and IL-13 Receptor Studies (Thomas A. Wynn, NIAID)

2.4.4.1 Background

Th2 cytokines such as IL-4, IL-10, and IL-13 have been implicated in the chronic manifestations of GVHD, including the fibrosis that develops in skin and other organs. Studies in multiple experimental models recently identified IL-13 as a major mediator of tissue remodeling and fibrosis. Although each of the Th2-associated cytokines has a distinct role in fibrosis, IL-13 was identified as the master regulator, likely because the cytokine is often over-produced relative to the other Th2-associated cytokines. *In vitro* studies conducted with purified human fibroblasts showed potent collagen-inducing activity for IL-4, IL-13, and TGF-beta, suggesting that Th2-associated cytokines might directly activate collagen deposition by fibroblasts. In fact, some studies have suggested that IL-13 is nearly twice as efficient as TGF-β in mediating fibrosis. Previous studies have suggested that patients with chronic GVHD have higher circulating levels of Th2-associated cytokines, however no studies have carefully monitored the levels of IL-13 or its receptors. The receptors that bind IL-13 include the signaling IL-13Rα1 chain and the non-signaling decoy receptor, IL-13Rα2. High circulating levels of IL-13Rα2 were recently shown to neutralize the activity IL-13 *in vivo*, suggesting that the activity of IL-13 is tightly controlled by the amount of 'free' versus 'IL-13Rα2-bound' protein. To date, however, there has been no attempt to monitor the levels of IL-13 or its decoy receptor in GVHD patients or to link IL-13 activity with the severity of GVHD complications.

2.4.4.2 Rationale for IL-13 and IL-13 Receptor Studies

To study the role of IL-13 and IL-13 receptor in the fibrosis process in cGVHD

2.4.4.3 Objectives / Specific Aims for IL-13 and IL-13 Receptor Studies

- Determine the status of circulating IL-13 and IL-13Rα2 levels in patients with chronic GVHD and whether there is a correlation with sclerotic/fibrotic complications.

- Determine whether expression of IL-13 and IL-13Rα2 are increased in fibrotic tissues in GVHD, and whether the levels of cytokine or decoy receptor can be used as a biochemical marker of fibrosis progression.

- Determine the source of IL-13 and IL-13Rα2 by performing FACS analysis for intracellular IL-13 and IL-13Rα2 expression.
- Determine whether IL-13 has inhibitory effects Th1 cytokine gene expression and lymphocyte activation in leukocyte populations in patients with chronic GVHD.

2.5 Interim Study Background

To date, we have enrolled and treated 8 patients. Of these, 1 patient withdrew from study prior to the 3 month time point (patient choice), 1 patient came off study for disease progression at 3 months, and 2 patients came off study early for inability to tolerate drug due to exacerbation of pre-existing conditions (CPK elevation and tinnitus) which did not adequately improve despite dose reduction or holding therapy. Furthermore, all patients enrolled to date have required dose reduction per protocol guidelines due to limited tolerability in the setting of cGVHD

As a result, it appears that the cGVHD patient population, characterized by significant cutaneous fibrosis and often multiple additional co-morbidities, does not tolerate the standard dosing of imatinib mesylate as is typically employed for CML and other conditions. In our experience, many of the adverse events in our initial cohort were worsening manifestations of pre-existing conditions including fatigue, CPK elevations, and myalgias. We therefore propose treating this population at a reduced dose of 200 mg daily following a one-month lead in of 100 mg daily, during which time tolerability will be closely monitored. Furthermore, we will begin evaluating steady-state serum concentrations of imatinib mesylate at baseline, 1 month, and 3 month time points.

Because of the number of patients who have required temporary cessation of therapy for adverse events, we are not yet able to determine the therapeutic benefit of imatinib based on our pilot study data. However, the patient who has been treated for the longest duration on our study (10 months, current dose 300 mg daily) has sustained continued improvement at each time interval, has tolerated tapering of his steroids, and continues to tolerate the drug well. Furthermore, other reports have described efficacy in cGVHD treatment at doses lower than the 400mg daily dose, and therefore, we believe the proposed dose reduction will be better tolerated and remain potentially efficacious.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 ScGVHD manifesting after at least 100 days following allogeneic hematopoietic stem cell transplantation is considered diagnostic for cGVHD according to NIH cGVHD Consensus Statement diagnostic criteria [10,13]. The diagnosis can be made clinically or by histopathology. The diagnosis must be confirmed by the principal investigator (PI), or lead associate investigator (LAI). Skin biopsies will be reviewed by the NCI Laboratory of Pathology to confirm the diagnosis of ScGVHD.

3.1.2 Patients must have measurable limitation in range of motion, defined as ScGVHD with or without fasciitis, restricting range of motion (ROM) of at least one joint with a minimum deficit of 25%. See Section 11 for the evaluation of measurable disease.

3.1.3 Prior therapy: Patients must have cGVHD refractory to at least one treatment regimen for cGVHD. One prior regimen must have included systemic corticosteroids at the equivalent prednisone dosing of 1mg/kg/day x 14 days. Patients in whom calcineurin inhibitors or

corticosteroids are medically contraindicated may also be eligible for enrollment. Patients who have had stabilization of disease on calcineurin inhibitors or steroids, but in whom these medications cannot be tapered without disease flare are also eligible. Patient must be on stable or tapering immunosuppressive regimen for at least one month.

3.1.4 Age: 4 years of age or older at the time of enrollment. Lower age limit set by lower established age limit norms of ROM scores for measurement criteria.

3.1.5 Life expectancy of greater than 6 months.

3.1.6 Karnofsky $\geq$60%; see Appendix A.

3.1.7 Patients must be platelet transfusion and growth factor independent at the time of study entry. Patients must have adequate organ and marrow function as defined below. Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin. (Gilbert syndrome is found in 3-10% of the general population, and is characterized by mild, chronic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis).

X	absolute neutrophil count	$\geq$1,000/mcL
X	platelets	$\geq$50,000/mcL
X	total bilirubin	< 3x upper limit of normal
X	AST(SGOT)/ALT(SGPT)	<5 x upper limit of normal
X	creatinine	age-adjusted within normal limits
	OR	
		creatinine clearance $\geq$ 30 mL/min/1.73 m^2 for adults and pediatric patients with BSA $\geq$ 0.97 m^2 with creatinine levels above institutional normals and $\geq$40 mL/min/1.73 m^2 for pediatric patients with BSA < 0.97 m^2

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

3.1.8 Normal cardiac function for age as determined by ECHO or MUGA (normal LV function as measured by ejection fraction or shortening fraction).

3.1.9 The effects of imatinib mesylate 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, for the duration of study participation, and for six months following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document. All patients or their legal guardian (for patients <18 years old) must sign an IRB approved document of informed consent (cGVHD natural history or any NCI protocol allowing for screening procedures) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardian must sign the protocol-specific informed consent. Pediatric patients will be included in age appropriate discussions and age appropriate assent will be obtained in accordance with NIH guidelines.

3.1.11 Durable Power of Attorney (DPA): All patients 18 years of age at the time of enrollment will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy, radiotherapy, or immunotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents, including extracorporeal photopheresis. Patients may not have received monoclonal antibody therapy within 6 weeks.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to imatinib mesylate.

3.2.5 Patients receiving any of the following medications or substances that are inhibitors or inducers of P450 3A4 are ineligible. Use of the following medications must be discontinued at least two weeks prior to starting therapy:

1. Alfuzosin

2. Aprepitant
3. Carbamazepine
4. Clarithromycin
5. Eletriptan
6. Erythromycin
7. Pimozide
8. St John's Wort
9. Warfarin

A list of medications and substances known or with the potential to interact with the P450 3A4 isoenzyme is provided in Section 8. Imatinib mesylate is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. Close monitoring is warranted when using agents metabolized by these enzymes. Grapefruit juice should not be consumed while on therapy.

3.2.6 Prior treatment with imatinib mesylate or other tyrosine kinase inhibitor after the date of transplant.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, pulmonary, hepatic, or other organ dysfunction, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the patient's ability to tolerate protocol therapy.

3.2.8 Pregnant women are excluded from this study because imatinib mesylate is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with imatinib mesylate, breastfeeding should be discontinued if the mother is treated with imatinib mesylate.

3.2.9 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with imatinib mesylate and the possibility of associated severe immunosuppression.

3.2.10 Patients with active hepatitis C or hepatitis B infection as defined by seropositivity for hepatitis C or hepatitis B (HepBSAg) and elevated transaminases, as GVHD manifestations involving the liver will be indistinguishable and drug-toxicity uninterpretable.

3.2.11 Persistent malignancy, requiring ongoing therapy.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours. Also, the CRO will be notified for removal of patients from study as defined in section **5.5**.

5 TREATMENT PLAN

5.1 Imatinib Mesylate Administration

This is an open-label pilot study of oral imatinib mesylate for ScGVHD. Adult patients will receive 100 mg imatinib mesylate daily and pediatric patients will be dosed at 65 mg/m2 daily (100 mg maximum) for 28 days. If tolerated, after 28 days, adult patients will be increased to 200 mg daily and pediatric patients will be increased to 130 mg/m2 (200 mg maximum). If the 100mg (or 65mg/m2) dose is not tolerated due to unacceptable toxicity within the first 28 days despite following the dosing delay guidelines (section 6.0), the drug will be discontinued, except for patients taking 100mg daily who are also on potent CYP3A4 inhibitors. This group will be allowed dose reduction to 50mg. Children with a BSA < 0.97 (starting dose 50mg) who do not tolerate the drug during the first 28 days will be taken off study because dose reduction below 50mg is not possible with the 100mg tablets. Treatment cycles are continuous 28-day cycles with no rest period between cycles.

Imatinib mesylate is supplied as 100 mg tablets. Adult patients will initially receive 100 mg imatinib mesylate daily and pediatric patients will be dosed at 65 mg/m^2 daily (100 mg maximum, see nomogram below). After 1 month, adult patients will increase to 200 mg daily and pediatric patients will receive 130 mg/m2 daily. Individual patient dosages will be rounded to the nearest 50 mg increment. Tablets are scored and the 100 mg tablets may be cut into achieve 50 mg dosing. According to the package insert, tablets may be dispersed in a glass of water or apple juice, stir until disintegrated and administer immediately. Since no long-term stability data are available, the administration of imatinib suspension should not be delayed. Patient should take drug with a meal and a large glass of water (patients who dissolve their tablets in liquid do not need to drink additional water). See Appendix Q for patient instructions.

The product labeling for imatinib mesylate provides dosing guidelines for patients with renal dysfunction, as defined by the following criteria (Prod Info GLEEVEC® oral tablets, 2010).:

Renal Dysfunction Definitions (based on Product labeling)
Mild CrCL = 40-59 mL/min
Moderate CrCL = 20-39 mL/min
Severe CrCL = <20 mL/min

Mild renal dysfunction

The product labeling cautions that dose reduction may be needed at higher dosages of imatinib mesylate for patients with mild renal dysfunction. However, because patients on this protocol receive a low starting dose (100mg), dose adjustment will not be made for patients with mild renal dysfunction (creatinine clearance $\geq$ 40ml/min).

Moderate renal dysfunction

As recommended by the product labeling guidelines (Prod Info GLEEVEC® oral tablets, 2010), patients with moderate renal dysfunction will decrease the starting dose by 50% Therefore, adult patients and pediatric patients with BSA $\geq$ 0.97 will initially receive 50mg imatinib mesylate daily. After 1 month, adult patients and pediatric patients with BSA $\geq$ 0.97 and moderate renal dysfunction will increase to 100 mg daily if tolerated. Treatment and dose reductions will be based on estimated glomerular filtration rate (eGFR) and not on serum creatinine for patients with moderate renal dysfunction.

Children with a BSA < 0.97 (normal starting dose 50mg) with moderate renal dysfunction (creatinine clearance 30 -39ml/min) are ineligible because dose reduction is not possible below 50 mg.

Adult and pediatric patients with renal dysfunction between 20-30ml/min and with severe dysfunction (<20 ml/min) are not eligible for treatment.

Dose Nomogram for Pediatric Patients

65 mg/m^2/d		**130 mg/m^2/d**	
BSA [m^2]	Dose [mg]	BSA [m^2]	Dose [mg]
		0.38 – 0.57	50
0.58 – 0.96	50	0.58 – 0.96	100
$\geq$ 0.97	100	0.97 – 1.34	150
		$\geq$1.35	200

Patients receiving concomitant CYP3A4 inducers will have the starting dose of imatinib increased by 50%. The starting dosing of imatinib will be 150 mg/day for adult patients and 100 mg/m2/day for pediatric patients on concomitant CYP3A4 inducers. According to the package insert, tablets may be dispersed in a glass of water or apple juice, stir until disintegrated and administer immediately. Patients receiving concomitant CYP3A4 inhibitors (itraconazole, ketoconazole, posaconazole, voriconazole and fluconazole) will be monitored closely for toxicity, but routine dose reduction will not be employed.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for imatinib mesylate 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 cGVHD.

Patient Instructions (See **Appendix Q: Patient Instructions**)

It is best to take this medicine with food and a large glass of water. If the patient is not able to swallow the tablet, he/she may dissolve the tablet in a glass of water or apple juice. If taking ½ tablet (50 mg), it should be dissolved in 1 ounce (1/8 cup) of water or juice. If taking 100 mg (1 tablet), it should be dissolve in 2 ounces (1/4 cup) of water or juice. If taking 200 mg (2 tablets), it should be dissolved in 4 ounces of water or juice. If you are taking 300 mg (3 tablets), dissolve it in 6 ounces (about 3/4 cup) of water or juice. Stir with a spoon and drink immediately after the tablet has dissolved.

Patients that require a ½ tablet (50 mg) dose will be required to split the scored tablets. Parents will be taught the proper technique for breaking tablets according to standard procedure. Do not handle broken tablets with unprotected hands. Patients should wear gloves when handling broken or cut tablets.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

If a dose is missed, it should be taken as soon as possible. If it is almost time for the next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

Grapefruit juice should be avoided.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Steroid therapy.

For patients on systemic steroids, a steroid taper will be attempted 6 to 8 weeks after starting on protocol for those patients responding to therapy. Steroid taper will be performed at a maximal approximate rate of 10% (of starting dose) decrease per week. Once patients are on the equivalent prednisone dose of 0.5 mg/kg/day, taper will consist of decreasing the dose on an every other day schedule. The total decrease should remain equivalent to a maximum of approximately 10% decrease per week as tolerated. For worsening of cGVHD symptoms during steroid taper, a steroid pulse and dose increase will be allowed and subsequent taper attempted. For example, a typical steroid pulse of the equivalent to 1-2 mg/kg for 5-7 days with subsequent taper is acceptable. Steroid pulses require PI or LAI approval. Greater than 1 steroid pulse per 3 month period is considered disease progression. For patients on corticosteroids, consideration will be given to H2 blockade or other gastrointestinal protective agents.

5.2.2 Other immunosuppressants

Patients on a stable dose of calcineurin inhibitors (e.g. tacrolimus or cyclosporine) or other immunosuppressants (e.g. mycophenolate or sirolimus) will continue on these agents with the intent to wean if possible after steroids are tapered.

5.2.3 Infectious disease guidelines

Infection Prophylaxis: Routine measures to prevent infection in accordance with NIH Allogeneic Stem Cell Transplantation guidelines should be employed (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml).

5.2.4 Concomitant drug interactions

Because there is a potential for interaction of imatinib mesylate with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Use of the following concurrent medications is prohibited and must be discontinued at least two weeks prior to starting therapy (recommendations adapted from Thomson Reuters Micromedex®:

a) 1. AlfuzosinInteraction: an increase in alfuzosin exposure
b) Summary: Alfuzosin should not be coadministered with potent inhibitors of cytochrome P450 3A4, such as imatinib, because alfuzosin exposure may be increased, (2008; Prod Info GLEEVEC(R) oral tablets, 2007).
c) Severity: moderate
d) Clinical Management: The concomitant use of alfuzosin and imatinib is not recommended. Pulse and blood pressure monitoring may be necessary.
e) Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of alfuzosin by imatinib

2. Aprepitant

a. Interaction: elevated imatinib plasma levels
b. Summary: Aprepitant is a weak-to-moderate (dose-dependent) inhibitor cytochrome P450 3A4 and could moderately inhibit the metabolism of imatinib, resulting in elevated plasma concentrations of imatinib and potentially increased imatinib side effects.
c. Severity: major
d. Clinical Management: If coadministered, consider monitoring the patient for the following imatinib-related adverse effects: delayed myelosuppression, nausea, vomiting, and diarrhea.
e. Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of imatinib by aprepitant

3. Carbamazepine

a) Interaction: decreased plasma levels of imatinib
b) Summary: Concurrent administration of imatinib and carbamazepine may result in a significant decrease in exposure to imatinib due to induction of CYP3A4-mediated imatinib metabolism. Caution is advised when these two agents are coadministered. Alternatives to carbamazepine, with less enzyme induction potential, should be considered. When imatinib is used concurrently with carbamazepine, consider an increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response closely (Prod Info GLEEVEC(R) oral tablets, 2005).

c) Severity: major
d) Clinical Management: Consider using alternatives to carbamazepine with less enzyme induction potential. However, if imatinib is used concurrently with carbamazepine, consider an increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response closely.
e) Mechanism: induction of cytochrome P450 3A4-mediated metabolism of imatinib by carbamazepine

a) 4. ClarithromycinInteraction: increased plasma levels of imatinib
b) Summary: Caution is recommended when administering imatinib with cytochrome P450 3A4 inhibitors such as clarithromycin as they may decrease the metabolism and increase concentrations of imatinib (Prod Info GLEEVEC(R) oral tablets, 2005). Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia).
c) Severity: moderate
d) Clinical Management: Caution is recommended when administering imatinib with inhibitors of the cytochrome P450 3A4 family, such as clarithromycin. Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia).
e) Mechanism: inhibition of cytochrome P450 3A4 metabolism of imatinib by clarithromycin

5. Eletriptan
a) Interaction: increased eletriptan exposure
b) Summary: Increased exposure to eletriptan may be expected when eletriptan is used concomitantly with imatinib. Eletriptan should not be used within 72 hours of drugs that have demonstrated potent cytochrome P450 3A4 inhibition, such as imatinib (Prod Info Relpax(R), 2002; Prod Info Gleevec(R), 2002).
c) Severity: moderate
d) Clinical Management: Eletriptan should not be used within at least 72 hours of treatment with imatinib, a potent cytochrome P450 3A4 inhibitor. Pulse, blood pressure, and ECG monitoring may be necessary.
e) Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of eletriptan by imatinib

6. Erythromycin
a) Interaction: increased plasma levels of imatinib
b) Summary: Caution is recommended when administering imatinib with cytochrome P450 3A4 inhibitors such as erythromycin as they may decrease the metabolism and increase concentrations of imatinib (Prod Info GLEEVEC(R) oral tablets, 2005). Monitor patients for signs of

imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia).

c) Severity: moderate
d) Clinical Management: Caution is recommended when administering imatinib with inhibitors of the cytochrome P450 3A4 family, such as erythromycin. Monitor patients for signs of imatinib dose-related adverse events (fluid retention/weight gain, nausea and vomiting, neutropenia).
e) Mechanism: inhibition of cytochrome P450 3A4 metabolism of imatinib by erythromycin

7. Pimozide
a) Interaction: increased plasma levels of pimozide
b) Summary: Plasma concentrations of pimozide may be altered when coadministration with imatinib. Caution should be utilized when administering imatinib with cytochrome P450 3A4 substrates, such as pimozide, that have narrow therapeutic windows (Prod Info Gleevec(TM), 2002).
c) Severity: moderate
d) Clinical Management: Caution is recommended when administering imatinib with pimozide, a cytochrome P450 3A4 substrate with a narrow therapeutic window.
e) Mechanism: inhibition of cytochrome P450 3A4 metabolism of pimozide by imatinib

8. St John's Wort
a) Interaction: increased imatinib clearance
b) Summary: In a pharmacokinetic study, concomitant use of imatinib and St. John's Wort resulted in significantly increased clearance of imatinib. Caution is advised when these two agents are coadministered. Alternatives to St. John's Wort, with less CYP450 enzyme induction potential, should be considered. However, if imatinib is used concurrently with St. John's Wort, consider an increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response closely (Prod Info GLEEVEC(R) oral tablets, 2005).
c) Severity: major
d) Clinical Management: Coadministration of imatinib and St. John's Wort, a CYP3A4 inducer, may result in a significant reduction in exposure to imatinib. Caution is advised when these two agents are coadministered. Consider using alternatives to St. John's Wort with less enzyme induction potential. However, if imatinib is used concurrently with St. John's Wort, consider an increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response closely.
e) Mechanism: induction of cytochrome P450 3A4 metabolism of

imatinib by St. John's Wort

9. Warfarin
   a) Interaction: increased risk of bleeding
   b) Summary: Imatinib is a moderately potent inhibitor of the cytochrome P450 isoenzymes CYP2C9, CYP2D6 and CYP3A4, for which warfarin is a substrate. Concurrent treatment with imatinib and warfarin may increase the bioavailability of warfarin, thereby increasing the risk of bleeding (Prod Info GLEEVEC(R) oral tablet, 2005). Low molecular weight heparins or standard heparin may be considered as thromboprophylactic alternative, due an apparent absence of interaction between imatinib and these agents. Since thrombocytopenia is an adverse event consistently associated with imatinib therapy, caution is advised with any concomitant anticoagulant/antithrombotic therapy given with imatinib.
   c) Severity: major
   d) Clinical Management: Patients requiring anticoagulant therapy during treatment with imatinib should receive a low-molecular weight or standard heparin. If warfarin is used, closely monitor coagulation parameters (International Normalized Ratio, activated clotting time) for any patient receiving concurrent treatment with imatinib.
   e) Mechanism: competitive inhibition of isoenzyme CYP3A4 and imatinib-provoked inhibition of CYP2C9 and CYP2D6-mediated warfarin metabolism

Secondary to P450 3A4-mediated interaction, use of the following concurrent medications is allowable, with the following precautions:

1. P450 3A4 inducers: Induction of cytochrome P450 3A4-mediated metabolism of imatinib by potent inducers causes decreased exposure to imatinib. When imatinib is used concurrently with potent P450 3A4 inducers, imatinib dose will be increased by 50% to maintain therapeutic efficacy. Patients will be monitored closely for toxicity. The following medications are considered potent inducers of P450 3A4: Phenobarbital, Phenytoin, and Rifampin.

2. P450 3A4 inhibitors: Inhibition of cytochrome P450 3A4 affects the metabolism of imatinib causing increased plasma levels of imatinib. Patients will be monitored carefully while on the following medications: itraconazole, ketoconazole, posaconazole, voriconazole and fluconazole. However, routine dose reduction will not be employed due to the lower dosing (100-200mg daily) compared with typical imatinib therapy (400mg daily). Grapefruit juice should not be consumed while on therapy.

3. Other drug–drug interactions: Imatinib mesylate is an inhibitor of CYP3A4, therefore the following precautions should be followed:

a. Cyclosporine – interaction effect caused by inhibition of CYP3A4-mediated metabolism of cyclosporine by imatinib, leads to increased plasma levels of cyclosporine. Must closely monitor CSA levels on imatinib and when imatinib is discontinued, adjust dosing to therapeutic window as indicated.

b. Levothyroxine – imatinib causes decreased levothyroxine effectiveness and worsening of hypothyroidism. Closely monitor thyroid hormone levels while receiving imatinib and when discontinued, adjust as indicated.

c. Simvastatin - Concurrent administration of simvastatin and imatinib resulted in 2- and 3.5-fold mean increases in Cmax and AUC values of simvastatin, respectively (Prod Info GLEEVEC(R) oral tablets, 2005). Caution is advised when these two agents are coadministered. Monitor patients for increased simvastatin side effects (rhabdomyolysis, myopathy).

d. Patients using other CYP3A4 substrates including sirolimus and tacrolimus should be monitored closely for toxicity while on imatinib mesylate therapy and levels closely followed.

5.2.5 Supportive care

Supportive care will include standard infection prophylaxis, anti-emetics, CMV surveillance at follow-up, topical care, pulmonary toilette with inhalers, physical therapy, nutritional, and psychosocial support. Anti-emetic therapy should not include dexamethasone or other corticosteroids. Support care as per recommendations in the NIH Consensus Project Report by the Ancillary Therapy and Supportive Care Working Group [34].

5.3 Duration of Therapy

Patients will be evaluated weekly for side effects for a minimum of one month or until stable dose is achieved. Patients will be evaluated monthly thereafter for safety monitoring and every 3 months for disease response. The primary endpoint assessment will occur at 6 months. Responsive patients will be provided continued treatment for up to 6 months following maximal response up to a maximum of 24 months. While on study, patients will need to return to the clinical center for evaluations at the 1 month, 3 month and 6 month time points, and every 6 months thereafter. Interim evaluations may be done by their primary physician. Patients who progress on treatment will be removed from the study.

In the absence of treatment delays due to adverse event(s), treatment will continue until the primary endpoint (6 months). Patients who are continuing to show a response will be treated up to 2 years or until one of the following criteria applies:

- Disease progression after 8 weeks, or no evidence of response at 6 months,

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Recurrent malignancy
- Inability to comply with study requirements or PI discretion
- Patients requiring additional systemic therapy for control of GVHD will be taken off study after discussion with the PI or LAI.

5.4 Duration of Follow Up

Patients will be followed every three months for 1 year by telephone interview after discontinuing treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Once there is resolution of adverse events, patients will be removed from study.

5.5 Criteria for Removal from Study

Patients will be evaluated weekly for side effects for a minimum of one month after a stable dose is achieved. Patients will be evaluated monthly thereafter for safety monitoring and every 3 months for response. Patients will be removed from study when any of the criteria listed in Section 5.3 applies. Primary endpoint assessment will occur at 6 months. Patients will be treated for 6 months following maximal response up to a maximum of 24 months. Patients will be followed for 1 year after discontinuing study treatment. Therefore the maximum a patient will remain on study is 3 years. The reason for study removal and the date the patient will be documented in the Case Report Form.

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

6 DOSING DELAYS/DOSE MODIFICATIONS

Treatment modifications: All dose modifications must be discussed with the PI or LAI. This study will utilize version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) (http://ctep.cancer.gov/reporting/ctc.html) for toxicity and adverse event reporting.

Only those adverse events deemed possibly, probably, or definitely related to imatinib mesylate will be used in the definition of DLT. Events that are considered disease related will not be considered dose limiting. Expected pre-existing or concurrent manifestations of cGVHD or systemic steroid therapy may include the following examples: fatigue, colitis, cushingoid appearance, anorexia, xerostomia, nausea, taste alteration, arthritis, fibrosis, myositis, osteonecrosis, osteopenia, dry eye, watery eye, pain, dyspnea, vaginal dryness, skin atrophy, alopecia, hyperpigmentation, skin dryness, hypopigmentation, nail changes, photosensitivity, pruritus, rash, and ulcers. Any of the above symptoms newly presenting after initiation of imatinib mesylate must be carefully evaluated for attribution, i.e. new skin rash will be biopsied to determine drug reaction versus GVHD.

6.1 Dose reduction for adverse events

Adult patients receiving 200 mg daily or pediatric patients receiving 130 mg/m2 who require dose reduction for adverse events will have their dose reduced to 100 mg (or 65 mg/m2). A second dose reduction to 50 mg daily is allowed for patients on potent CYP3A4 inhibitors. Patients with impaired renal function receiving 100mg daily who require a dose reduction for adverse events will have their dose reduced to 50mg daily. Treatment and dose reductions will be based on eGFR and not on serum creatinine for patients with moderate renal dysfunction.

Dose Modification Table for Non-hematologic and Hematologic Toxicities

Adverse Event	**CTCAE 4.0 Grade/Attribution**	**Protocol Action**
Non-hematologic toxicity (LFTs and eGFR^ excluded)	Grade 2 >7 days that is probably or definitely related to imatinib.	Hold study drug; *If toxicity resolves to ≤ grade 1 or baseline within 14 day days: restart drug at same dose level.
Non-hematologic toxicity (LFTs and eGFR^ excluded)	Same grade 2 recurs that is probably or definitely related to imatinib.	Hold study drug; *If toxicity resolves to ≤ grade 1 or baseline within 14 day days: decrease dose by 1 dose level. **If toxicity does NOT resolve to ≤ Grade 1 or baseline within 14 day days: patient comes off study.
Non-hematologic toxicity (LFTs and eGFR^ excluded)	Same grade 2 recurs after dose reduction that is probably or definitely related to imatinib.	Patient comes off study. **Exception:** patients on a CYP3A4 inhibitor [which allows a second dose reduction].

Adverse Event	**CTCAE 4.0 Grade/Attribution**	**Protocol Action**
Non-hematologic toxicity (LFTs and eGFR^ excluded)	Grade 3 that is probably or definitely related to imatinib.	Hold study drug; *If toxicity resolves to ≤ grade 1 or baseline within 14 day days: decrease dose by 1 dose level. **If toxicity persists >14 days or if Grade 3 recurs after dose reduction: patient comes off study.
Non-hematologic toxicity (LFTs and eGFR^ excluded)	Grade 4 that is probably or definitely related to imatinib.	Patient comes off study
Non-hematologic toxicity: LFTs ; eGFR^	Grade 2	No dose adjustment.
Non-hematologic toxicity: LFTs; eGFR^	Grade 3 >7 days that is probably or definitely related to imatinib.	Hold study drug; *If toxicity resolves to baseline within 14 day days: restart drug at same dose level.
Non-hematologic toxicity: LFTs; eGFR^	Same grade 3 recurs that is probably or definitely related to imatinib.	Hold study drug; *If toxicity resolves to baseline within 14 day days: decrease dose by 1 dose level. **If toxicity does NOT resolve to baseline within 14 day days: patient comes off study.
Non-hematologic toxicity: LFTs; eGFR^	Grade 4 that is probably or definitely related to imatinib.	Patient comes off study
Hematologic: Cytopenias	Grade 2	No dose adjustment.
Hematologic: Neutrophil or Platelet toxicity	Grade 3 on two sequential evaluations within 7 days that is probably or definitely related to imatinib.	Hold study drug; *Until counts recover to a grade 2 then restart at same dose level.

Adverse Event	CTCAE 4.0 Grade/Attribution	Protocol Action
Hematologic: Neutrophil or Platelet toxicity	Same grade 3 recurs that is probably or definitely related to imatinib.	Hold study drug; *Until counts recover to a grade 2 then decrease dose by 1 dose level.
Hematologic: Neutrophil or Platelet toxicity	Same grade 3 recurs after dose reduction that is probably or definitely related to imatinib.	Patient comes off tudy.
Hematologic: Neutrophil or Platelet toxicity	Grade 4	*If toxicity resolves to < Grade 2 within 14 day days: Decrease dose by 1 dose level. **If toxicity does NOT resolve to < grade2 within 14 day days: Patient comes off study.
Hematologic: Neutrophil or Platelet toxicity	Same grade 4 recurs	Patient comes off study.

^ = **Patients with moderate renal dysfunction.** Patient with mild renal dysfunction or normal renal function at baseline will receive dose adjustment based on the standard guidelines for other non-hematologic provided in Table 1.

Exceptions to the above treatment modifications:

1. Alopecia.
2. Grade 2 or 3 low electrolyte levels in patients with chronic low levels of the same electrolyte. Such individuals should receive supplementation and any worsening of levels should be discussed with the PI to determine whether to consider dose limiting.
3. Hypocalcemia toxicity grade should be assigned based on the calcium level corrected for degree of hypoalbuminemia according to the following formula: albumin ↓ 1 gram/dL: total calcium ↑ 0.2 mmol/L. Ionized calcium can also be used to assess toxicity.
4. Grade 3 fever.
5. Infection or neutropenic fever unless attributed to imatinib mesylate.
6. Lymphopenia any grade
7. Grade 3 hypertriglyceridemia or hypercholesterolemia.
8. Grade 3 non-life-threatening basal or squamous cell carcinoma of the skin. This patient population is predisposed to non-melanoma skin cancer due to chronic immunosuppression associated with cGVHD treatment.
9. Grade 2 fatigue

10. Grade 2 dry skin
11. Grade 2 albumin
12. Grade 2 or 3 asymptomatic CPK elevation with no evidence of rhabdomyolysis or cardiac myositis.
13. Grade 2 proteinuria
14. Grade 2 tinnitus
15. Grade 2 insomnia
16. Grade 2 rash
17. Grade 2 anorexia

Each treatment cycle should be no longer than 28 days. Doses withheld while recovering from toxicity should not be made up.

6.2 Dose adjustment for patients starting CYP3A4 inducers

Patients on inducers will start at a 50% higher dose as stated in sections 5.1 and 5.2.4.1.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 Definitions

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

A protocol deviation is any change, divergence, or departure from the IRB approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB Reporting

7.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.3 Data and Safety Monitoring Plan

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 8.1) and the characteristics of an observed AE (Section 8.2) will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine reporting.

8.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Imatinib Mesylate (STI571, NSC 716051)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the

Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 5169 patients.* Below is the CAEPR for imatinib mesylate (STI571).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, November 9, 2011[1]

Adverse Events with Possible Relationship to Imatinib Mesylate (STI571) (CTCAE 4.0 Term) [n= 5169]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
	Pericardial effusion		***Pericardial effusion (Gr 2)***
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Ascites		***Ascites (Gr 2)***
Diarrhea	Constipation		***Constipation (Gr 3)*** ***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 3)***
	Flatulence		***Flatulence (Gr 2)***
	Gastrointestinal hemorrhage[2]		***Gastrointestinal hemorrhage[2] (Gr 3)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema face		
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	General disorders and administration site conditions - Other (superficial edema)		***General disorders and administration site conditions - Other (superficial edema) (Gr 2)***
INFECTIONS AND INFESTATIONS			

	Infection[3]		***Infection[3] (Gr 4)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 4)***
	Creatinine increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
	Weight gain		***Weight gain (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypokalemia		***Hypokalemia (Gr 3)***
	Hyponatremia		***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Arthritis		***Arthritis (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (muscle cramps)		***Musculoskeletal and connective tissue disorder - Other (muscle cramps) (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Pleural effusion		***Pleural effusion (Gr 3)***
	Pleuritic pain		
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Erythema multiforme		***Erythema multiforme (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin hyperpigmentation		***Skin hyperpigmentation (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
	Vascular disorders - Other (Intra-tumoral hemorrhage)		***Vascular disorders - Other (Intra-tumoral hemorrhage) (Gr 2)***
	Vascular disorders - Other (Hemorrhage with thrombocytopenia)		***Vascular disorders - Other (Hemorrhage with thrombocytopenia) (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

[5]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

Also reported on Imatinib Mesylate (STI571) trials but with the relationship to Imatinib Mesylate (STI571) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Heart failure; Myocardial infarction; Ventricular arrhythmia
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Papilledema; Photophobia; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Duodenal perforation; Esophageal fistula; Esophagitis; Gastritis; Gastrointestinal ulcer[4]; Ileus; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (Guillain-Barre syndrome); Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder
INVESTIGATIONS - CPK increased; GGT increased; Lipase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Back pain; Bone pain; Generalized muscle weakness; Pain in extremity
NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia;

Encephalopathy; Hydrocephalus; Intracranial hemorrhage; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal and urinary disorders - Other (kidney stones)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Hypoxia; Pharyngolaryngeal pain; Pneumonitis; Pulmonary hypertension; Respiratory hemorrhage[5]; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura
VASCULAR DISORDERS - Hypotension; Thromboembolic event; Vasculitis

Note: Imatinib Mesylate (STI571) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

In addition to the above, the investigators on this trial have found a case report in the literature of tinnitus occurring in a patient while receiving imatinib mesylate (53).

8.2 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 3.0 will be utilized for AE reporting until December 31, 2010. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **"Expectedness"**: AEs can be 'Unexpected' or 'Expected' (see Section 8.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 8.1).

- **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.

8.3 Expedited Adverse Event Reporting

8.3.1 Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event

Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

8.3.2 **Expedited Reporting Guidelines** – CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

Expedited AE reporting timelines defined:
"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-

specific expedited adverse event reporting exclusions.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

8.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, CTEP-AERS). The following AEs must be reported through the routine reporting mechanism (Section 7.4):

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Dermatology/skin	Alopecia	2	N/A	Yes or no	
Constitutional	Fever	3	No	no	
Infection	Febrile neutropenia	3		no	
Infection	Infection	2	No	no	
Blood/Bone Marrow	Lymphopenia	Any	No	Yes or no	
Metabolic/Laboratory	Hyperlipidemia	2,3	N/A	Yes or no	
Metabolic/Laboratory	Hypercholesterolemia	2,3	N/A	Yes or no	
Metabolic/Laboratory	Electrolyte abnormality	2,3	N/A	Yes or no	Patient with chronic low levels may be supplemented. Discuss with PI/LAI to see if dose limiting.
Secondary Malignancy	Non-life threatening basal or squamous cell skin carcinoma	3	No	Yes or no	This patient population is predisposed to non-melanoma skin cancer due to chronic immunosuppression associated with cGVHD treatment.
Constitutional	Fatigue	2	N/A	Yes or no	
Dermatology/skin	Dry Skin	2	N/A	Yes or no	

Metabolic/Laboratory	Albumin	2	N/A	Yes or no	
Metabolic/Laboratory	CPK	2,3	N/A	Yes or no	Asymptomatic CPK elevation with no evidence of rhabdomyolysis or cardiac myositis.
Metabolic/Laboratory	Proteinuria	2	N/A	Yes or no	
Auditory/Ear	Tinnitus	2	N/A	Yes or no	
Constitutional	Insommnia	2	N/A	Yes or no	
Dermatology/skin	Rash	2	N/A	Yes or no	
Gastrointestinal	Anorexia	2	N/A	Yes or no	

8.4 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions.

8.5 Secondary AML/MDS

AML/MDS events must be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

9 PHARMACEUTICAL INFORMATION

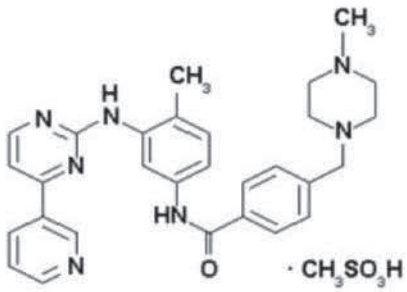
A list of the adverse events and potential risks associated with imatinib mesylate can be found in Section 7.1.

9.1 Imatinib mesylate (NSC 716051)

Imatinib mesylate: Synonyms - Imatinib, Gleevec®, STI571

Chemical Name: 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-[(4-3-pyridinyl)-2-pyrimidinyl)amino]-phenyl]-benzamide methanesulfonate

Chemical Structure:



Molecular Weight: 589.7

Formulation: Supplied as 100mg tablets.

Storage: At room temperature.

Stability: Very soluble in water and soluble in aqueous buffers (pH $\leq$ 5.5), with variable solubility in non-aqueous solvents. Very slightly soluble to insoluble in neutral/alkaline aqueous buffers.

Metabolism: Extensive liver metabolism. Metabolized primarily by cytochrome P450-3A4 enzymes; other cytochrome P450 enzymes play a minor role.

Route of administration: Oral. Tablets may be dispersed in a glass of water or apple juice (2 ounces for a 100-mg tablet; 4 ounces for a 200 mg dose, 2 tablets); stir until disintegrated and administer immediately. Take with a meal and a large glass of water.

Dose: Adults: 100mg imatinib mesylate p.o. daily for 28 days; if tolerated then dose will be increased to 200mg daily.
Pediatric: 65mg/m2 imatinib mesylate p.o. daily (100mg maximum) for 28 days; if tolerated then the dose will be increased to 130 mg/m2 (200 mg maximum).

Drug Interactions: Aprepitant (theoretical), Carbamazepine (theoretical) Dexamethasone (theoretical), Phenobarbital (theoretical), Phenytoin (probable), Rifampin (established), St John's Wort (established), Warfarin (probable), Ketoconazole (established), Levothyroxine (established), Pimozide (probable), Rifabutin (probable), Simvastatin (probable). Imatinib mesylate is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. Close monitoring is warranted when using agents metabolized by these enzymes.

9.2 Availability

Imatinib mesylate is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Imatinib mesylate is provided to the NCI under a Collaborative Agreement between Novartis and the DCTD, NCI (see Section 12.3).

9.3 Agent Ordering

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the Pharmaceutical Management Branch at (301) 480-4612. For questions about drug orders, transfers, returns, or accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.4 Agent Accountability

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

10 CORRELATIVE/SPECIAL STUDIES

Biologic studies: Research blood sample aliquot size will be minimized for patients < 10 years of age or < 30 kg and the total amount restricted to a maximum of 3 ml/kg per draw and 7 ml/kg per 6-week period. Patients > age 10 and > 30 kg will have no more than 450 ml blood drawn per 6-week period for research studies. In the event that blood draws are limited due to these restrictions, research studies will be performed in order of priority as listed below and in Appendix C.

10.1 Laboratory Studies

10.1.1 **PDGFR Studies** (Mark Raffeld, NCI)
Background: See section 2.4.1.

Methodology: Whole blood samples will be collected in 4 mL red/yellow rimmed collection tubes at pre-determined patient visits. After clot formation, samples will be centrifuged at 3000 rpm x 10 minutes at 4ºC, and the supernatant will be stored in aliquots at -80ºC until assayed. A numerical assignment will be used in a master database to anonymize patient samples.

Human fibroblasts expressing PDGFR alpha and beta subunits will be exposed to immunopurified IgG from patients and appropriate controls. For each patient and control, 250 uL of serum will be used to derive immunopurified IgG. The expected quantity of IgG is 5-10 ug/uL of serum and each experiment will require 200 ug of purified IgG. All experiments will be performed in duplicate. Using FACS analysis, antibody binding and functional activation will be determined using commercially available mouse anti-human antibodies to a variety of target antigens (assay under development).

Tissue inhibition of PDGFR with imatinib mesylate will be performed by immunohistochemical analysis of phosphorylated PDGFR under the direction of Mark Raffeld in the Laboratory of Pathology, NCI, or through a laboratory contractor utilizing an assay protocol optimized by Dr. Raffeld. Skin biopsies will be taken before starting therapy and at the sixth month time points in patients 18 years and older. Tissue specimens obtained in patients less than 18 years of age for diagnostic or clinical purposes may be used for PDGFR analysis, but skin biopsies will not be performed solely for research purposes.

10.1.2 Immune Function Studies (Fran Hakim, , ETIB, NCI)
Background: **See section 2.4.2.**

Methods
Coordinated analysis of samples of peripheral blood and GVHD-affected skin will be performed. Flow cytometry will examine the expression of relevant cytokine and chemokine receptors, including TGFbRII, in the context of markers of naïve, memory, effector and regulatory CD4 and CD8 T cells. Sections (4 or 5 sections cut from blocks of tissues fixed in formalin) will be analyzed by immunohistochemical staining. Confocal microscopy for T cell subsets and transcription factors (TBet, FoxP3, CD4, CD8) will be done on paraffin sections from tissue biopsies in order to characterize the T cell subsets specifically involved in disease pathology.

10.1.3 TGF-β studies (Kathy Flanders, Lalage Wakefield, Fran Hakim, NCI)
Background: **See section 2.4.3.**

Methodology

Plasma: quantity (1ml) for analysis of circulating TGF-β levels (active and latent by ELISA and bioassay). NOTE: we will not use serum for this as platelet degranulation drastically elevates the background level.

Peripheral Blood: quantity (10ml) for FACS analysis of leukocyte (T / B cell) expression of TGF-β1 / TGF-β receptors / phospho-rSmad, and TGF-β response.

Tissue Biopsy: Skin. Sections (4 or 5 sections cut from blocks of tissues fixed in formalin) will be analyzed by immunohistochemical staining for the TGF-β ligands and for receptor-activated Smads (rSmads). Antibodies specific for phosphorylated Smad proteins will be used as a biochemical marker for active signaling.

10.1.4 IL-13 and IL-13 Receptor Studies (Thomas A. Wynn, NIAID)
Background: See section 2.4.4.

Methodology
Plasma: quantity (0.5 ml) for analysis of circulating IL-13 and IL-13Rα2 levels by ELISA.

Peripheral Blood: quantity (10ml) for ELISA and FACS analysis of leukocyte (T / B cell) production of IL-13 and IL-13Rα2.

Tissue Biopsy: Skin. Sections (4 or 5 sections cut from blocks of tissues fixed in formalin) will be analyzed by immunohistochemical staining for IL-13, IL-13Rα1, and IL-13Rα2. Fresh biopsies may also be used to prepare mRNA for real-time PCR analysis of IL-13, IL-13Rα1, and IL-13Rα2.

10.1.5 Pharmacokinetic Studies (Erin Gardner/Douglas Figg, MOB)
Background: See section 2.4.4. and section 2.5.

Steady state plasma concentrations of imatinib will be assessed prior to the start of treatment (to ensure no interfering concomitant medications), and after 1 and 3 months on study.

10.1.5.1 Specimen Collection

Venous blood will be collected in a 4 mL heparin-containing (green top) tube at each of the following time points:

- Prior to treatment
- After 1 month on treatment
- After 3 months on treatment

Immediately place specimens on wet ice and refrigerate until pick-up. The date and **exact** time of each blood draw should be recorded on the sample tube. In addition, the time and dose of the last drug administration should be provided (i.e. 200 mg 1/10/10 21:30).

Please page 102-11964 (Gareth Peters or alternate tech) for immediate pick-up. (Contact the Clinical Pharmacology Program (CPP – Dr. Figg's Lab) processing group in 10/5A09 at 301-594-6131 or 301-402-3622 with any questions).

10.1.5.2 Sample processing

Blood samples should be centrifuged for 5 minutes at 1200 x *g* at 4°C. Plasma will be transferred into 2 cryovials and stored at –80° C until the time of analysis.

10.1.5.3 Sample Data Collection

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

10.1.5.4 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the

PSDMS. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

10.1.5.5 Sample analysis

Imatinib concentration will be measured in plasma, using liquid chromatography coupled with mass spectrometric detection (LC-MS). An assay has been developed by the CPP and validated following the FDA Guidance for Bioanalytical Method Validation.

10.2 Special Studies

10.2.1 MRI imaging of sclerotic cGVHD (Lawrence Yao, CC/DRD)

Objective: To establish the role of MRI in the detection of sclerotic skin changes in patients with cGVHD.

Rationale: Development of objective imaging evaluations will aid better diagnosis, staging, subclassification and clinical response assessment in cGVHD.

Methods: Contrast enhanced MRI of muscle and fascia will be performed in cGVHD patients. The MRI will gather information about anatomic disease extent and depth, and investigate features of disease on enhanced imaging that may potentially reflect disease activity. An affected joint under evaluation as a primary endpoint for range of motion evaluation will be preferentially imaged in a 1.5 or 3.0 Tesla clinical MRI unit, with the aid of a surface coil. Scans will encompass a representative region of cutaneous/subcutaneous disease, and will include: STIR, T1 spin echo, and 3D field echo scan. After intravenous injection of a standard, weight-adjusted dose of an FDA approved gadolinium chelate (0.1mmol/kg), high resolution post contrast field echo scans will be obtained. Additional, higher resolution imaging may be performed at 3T using a microscopy coil adapted for detailed assessment of skin and subcutis in selected cGVHD patients. Non-FDA approved MRI sequences may be performed on these patients under protocol 87C0091, PI: John Butman.

Scoring: MR findings will be scored for the following anatomic areas, with respect to the listed features:

1. Skin: thickening, edema
2. Subcut tissue: septal thickening, compartment narrowing, edema
3. Deep fascia: edema, thickening
4. Muscle: edema
5. Epimysium: edema

10.2.2 Occupational Therapy Assessment

Objective: To examine the self-reports on manual ability and functional performance, compare these with observational based measures of the same construct, and to compare these assessments to primary outcome measures.

Rationale: These batteries of assessments are designed to study the value of these measures of functional capacity, performance skills, and manual abilities. There are four assessments of manual ability, one observation-based assessment of functional performance and two quality of life (QOL) measures will be administered by the Occupational Therapy Section of the Rehabilitation Medicine Department of the National Institutes of Health. [36]

Methods: See Appendix S for detailed explanation of assessment.

1. 36 item Manual Ability Measure (MAM-36)-self report [39-41]
2. Jebsen-Taylor Hand Function Test [42-44]
3. Disabilities of the Arm, Shoulder and Hand (DASH) [45-47]
4. Grooved Pegboard [48, 49]
5. Assessment of Motor and Process Skills (AMPS) [50]
6. Short Form -36 Health Survey (SF-36) [51]
7. Human Activity Profile (HAP) [52]

10.3 Research Specimen Handling

Storage/Tracking: Patient blood samples, collected for the purpose of research, will be archived by the Experimental Transplantation and Immunology Branch (ETIB) Preclinical Service. All data associated with archived clinical research samples is entered into the ETIB Preclinical Services' Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB Preclinical Service folder. Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory receive annually updated NIH/CIT training and maintain standards of computer security. Patient tissue samples will be processed by the Laboratory of Pathology.

All samples will receive a unique bar code number, which will be added to the sample Preclinical Service database. Only this bar code will be recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the Preclinical Service database. The data recorded for each sample includes the trial name/protocol number, date drawn, treatment cycle/post transplant time point, cell source (e. g. peripheral blood, lymphapheresis) as well as box and freezer location. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.

Samples are stored in locked freezers at -85°C (sera and plasma) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the Preclinical Service laboratory (12C216) (-85° freezer) or in ETIB common equipment space (CRC/3-3273). Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol or through his/her submission and IRB approval stipulating whether IRB review is not necessary or IRB approval is granted for the pursuit of this new research activity. All research samples are only to be used for research purposes associated with objectives of the original protocol for which the samples were collected, or (using only unlinked

or coded samples) for an IRB approved protocol as stipulated on the IRB Authorization Form, and that any unused samples must be returned to the Preclinical Service laboratory.

Protocol Completion/Sample Destruction: Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples providing they have an IRB approved protocol and patient consent. Samples, and associated data, will be stored permanently in those patients that give consent unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the Preclinical Service laboratory.

The Preclinical Service staff will report to the Principal Investigator any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher. The Principal Investigators will annually report this information to the IRB.

11 STUDY CALENDAR

See Appendix B for study evaluation calendar.

11.1 On Study Protocol Evaluation

11.1.1 Pre-treatment Evaluation: Pre-treatment tests should be performed within 8 weeks prior to enrollment on the trial unless otherwise stated. The evaluation required prior to starting treatment is listed in table form in Appendix B. The evaluation may be performed as part of enrollment onto NIH Protocol #04-C-0281 entitled: "Prospective Assessment of Clinical and Biological Factors Determining Outcomes in Patients with Chronic Graft-Versus-Host Disease". Attempts will be made to enroll patients on this study.

1. History and Physical Examination: All patients should have a complete history (including prior and concurrent therapy) and physical examination including documentation and scoring of cGVHD, performance status, and signs and symptoms. Height, weight and body surface area must be recorded. All physical exam and cGVHD findings should be recorded and documented as per Appendices D-H. This evaluation should be within 2 weeks of starting therapy.
2. Hematology: PT/PTT, fibrinogen, complete blood counts, with differential and platelet count. To be performed within 72 hours prior to starting therapy. If there is significant change in clinical status, all eligibility labs will be repeated prior to starting therapy.
3. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, and bilirubin. Serum iron studies (Fe, ferritin, and transferrin). To be performed within 72 hours prior to starting therapy. If there is significant change in clinical status, all eligibility labs will be repeated prior to starting therapy. For patients with serum creatinine levels above the age-adjusted normal limits, a 24 hour urine collection for creatinine clearance and eGFR will be performed.

4. Other lab tests: Infectious disease screening for CMV, HSV, EBV, HIV, HTLV, HBV, HCV, VZV, Lymphocyte Phenotyping TBNK and immunoglobulin levels. Research labs as defined in section 9.1.
5. Urine or Serum Pregnancy test: For all females of childbearing potential. This test is to be performed within 7 days prior to enrollment on the trial.
6. Pulmonary Function Tests (PFTs): All patients. Patients requiring a pediatric PFT lab will be evaluated by Children's National Medical Center (CNMC) Department of Pulmonology. Calculate lung function score (LFS) based on findings (Appendix O),
7. Radiographic Evaluation:
   a. An MRI scan of one involved sclerotic skin area will be performed. The area will be determined based on severity of involvement and ability to adequately image after discussion between relevant study investigators. MRI will not be required for patients with contraindications to MRI procedure. (See section 3.5.4). Children who require sedation for MRI will be excluded.
   b. All patients: High resolution CT scan of the chest following NIH Department of Radiology protocol for evaluation of bronchiolitis obliterans.
8. Evaluation by Ophthalmology for ocular cGVHD assessment, if indicated.
9. Evaluation by Dental Clinic for oral cGVHD assessment, if indicated.
10. Evaluation by Physiatry for ROM and functional status, includes occupational therapy (OT) assessment (Appendix S) will be performed within 2 weeks of starting therapy.
11. Evaluation by Dermatology for GVHD assessment of the skin will be performed within 2 weeks of starting therapy. A 6mm skin biopsy will be performed from an area of clinically affected skin in patients 18 years and older. This specimen will be divided for histological analysis and phospho-PDGFR studies.
12. Cardiac Evaluation: Baseline ECG and an echocardiogram or MUGA scan should be performed on all patients.
13. Quality of Life (QOL) and Functional Assessment (Appendices J-L, S): Patient-reported functional status measures include the Lee Symptom scale (Appendix K) and GVHD symptom self-assessment (Appendix L).
14. Leukapheresis (Optional): Collection of blood cells for research purpose only by a leukapheresis procedure - patient will have a consent option to decline. One pass leukapheresis will be performed in the Department of Transfusion Medicine (DTM) using standard procedure. Approximately 2-5 liters will be processed, with the goal to obtain approximately 2 x 109 cells per procedure. Leukopheresis will be offered only to subjects older than 18 years of age. The cells collected during this procedure will be used for Immune function, TGF-β, and IL-13 studies, as described in section 9.1.

11.1.2 On Study Evaluation:

1. History and physical examination, performance status at least once every other week for one month and once monthly while on treatment.
2. Laboratory Assessment (weekly for one month, every other week for 6 months and then approximately monthly thereafter): Complete blood count, differential and platelet count, electrolytes, creatinine, calcium, magnesium, phosphorus, SGPT, SGOT, bilirubin,

and routine infectious disease surveillance as clinically indicated. For patients with serum creatinine levels above the age-adjusted normal limits, an eGFR will be performed.
3. Urinalysis and Lymphocyte Phenotyping TBNK will be performed every 3 months.
4. Complete GVHD evaluation at the NIH will be performed every 3 months. This includes eye evaluation, dermatology assessment, oral assessment, ROM physiatry evaluation, pulmonary function tests (PFTs) if indicated, quality-of-life scales and functional assessment evaluation (including OT evaluation). NIH subspecialty exam (ie. ophthalmology, dentistry) will be employed if clinically indicated. ROM evaluation constitutes the primary study endpoint.
5. Research labs as per appendix C.

11.1.3 End of Study Evaluation:

The following tests and procedures should be performed, if possible, at the time a patient comes off treatment regardless of the reason for coming off treatment, unless the test or procedure has been performed in the last 4 weeks (2 weeks for physical examination and laboratory assessment). This evaluation should be at the NIH.

1. History and physical examination, performance status, ROM and functional assessment, and complete assessment of cGVHD including evaluation by Dermatology, Physiatry, and OT. Other evaluations such as Ophthalmology and Dental if indicated.
2. Laboratory Assessment: Complete blood count, differential and platelet count, Electrolytes, creatinine, calcium, magnesium, phosphorus, SGPT, bilirubin, and urinalysis.
3. MRI of the skin.
4. Pulmonary function tests (if indicated).
5. High resolution CT scan of the chest for patients with BO.
6. Quality-of-Life Scale.
7. Apheresis. (Optional)

At the physician's discretion, patients may be asked to return to the NIH for a one year off treatment evaluation prior to their removal from this study.

12 MEASUREMENT OF EFFECT

12.1 Response Criteria

The primary endpoint for evaluation of response is established at the 6-month time point. Patients will be evaluated for response based on their ScGVHD evaluation. For the secondary endpoints, other involved organs will be evaluated, but not used in scoring for response to therapy (see appendix P).

12.1.1 ScGVHD will be measured and scored at baseline and every three months from beginning protocol treatment and will be measured by Physiatry. The ROM score will be

based on the composite joint ROM from the three most affected joints for patients with 3 or more affected joints (Appendix M, N). For those patients with fewer than 3 affected joints, the 2 most affected joints or the change in the overall ROM if only a single joint is affected. As there is not currently standardized assessment for ScGVHD, in our experience ROM assessments provide the most reproducible measure of disease progression or improvement in patients with involvement of skin and subcutaneous tissue involving joints. ROM will be measured using the American Academy of Orthopaedic Surgeons Criteria (AAOS, Chicago 1965). Percent change is based on percent change of deficit as compared to baseline. This scoring system has been successfully used in several recently published studies from the NCI evaluating the effects of anti-fibrotic agents on radiation-induced fibrosis[36,37].

As mentioned above, range of motion has been used in other clinical trials as a primary outcome measure, including trials conducted at the NIH Clinical Center studying pentoxyphylline [37] and pirfenidone [36] for the treatment of radiation-induced fibrosis. There are several criteria by which ROM may be performed. Our physiatrist will perform the ROM measurements using the American Academy of Orthopaedic Surgeons Criteria (AAOS), which has been used extensively for several decades. However, reproducibility is a potential concern, and we will attempt to minimize this by the use of a single clinician who is experienced in ROM measurement. It is also important to recognize that there are no alternative validated measures of skin fibrosis in ScGVHD [32]. This emphasizes the value of the secondary objective to "establish outcome criteria for the evaluation of ScGVHD using multi-modality objective and subjective assessments, including magnetic resonance imaging, skin scoring, and patient self-reported measures".

To our knowledge, there is no data on the decrease in ROM typically found in individuals with ScGVHD, but it is dependent on the severity and extent of disease.

12.1.2 **Progression:** defined as one of the following:

12.1.2.1 Joint ROM: decrease of >25% in composite ROM score on 2 consecutive evaluations at least 2 weeks apart, but not greater than 4 weeks apart.

11.1.2.2: Steroid pulse: > 1 steroid pulse per 3 month period (see section for acceptable steroid pulsing guidelines) if administered for ScGVHD.

12.1.3 **Response:** defined one of the following:

12.1.3.1 Joint ROM: increase of >25% in composite ROM score.

12.1.4 **Maximal Response**: Defined as a response with no further improvement over 2 sequential 3-month evaluations.

12.1.5 **Stable Disease:** Does not meet above criteria for progression, response, or maximal response.

13 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

13.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

13.2 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s)@) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed

combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14 STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

The primary objectives of this trial are to be a pilot study to explore the potential benefit of using imatinib mesylate in patients with cGVHD manifesting as sclerotic skin changes (ScGVHD), as well as to determine if the use of 200 mg imatinib mesylate will be tolerated by patients enrolled on the trial.

The primary endpoint for ScGVHD will be as follows: percent change in absolute ROM from baseline to 6 months.

With one primary endpoint, 10 patients will be adequate to have 80% power for a two-tailed 0.05 alpha level test to detect 1.0 SD change from baseline to 6 months for this endpoint. A paired t-test will be used to evaluate the change if the data are normally distributed. If the data are not normally distributed ($p<0.05$ by a Shapiro-Wilks test), then a Wilcoxon signed rank test will be used instead.

In addition, as patients will be evaluated every three months, a slope parameter for the change in ROM over time will be measured. The slope (ROM vs. time) from linear regression will be computed for each patient, and with 10 patients' slopes, there will be 80% power to determine if the slopes differ from zero, using a two-sided, one sample t-test and a 1 standard deviation effect size. That is, for each patient, the slope of ROM over all of the available measurements after starting treatment will be determined, and testing will be done to see if the mean slope differs from zero; with 10 patients a mean slope greater than the standard deviation of the 10 slopes should be identifiable with a 0.05 significance level, with 80% power. In practice, if the slopes are not consistent with normality ($p<0.05$ by a Shapiro-Wilks test), then a Wilcoxon signed rank test will be used.

Patients may drop out due to disease progression, recurrent malignancy, inability to comply with study requirements, unacceptable toxicity, or need for additional systemic therapy for cGVHD, prior to the 6-month evaluation. It is expected that this will be the case in no more than 10-20 percent of patients. In order to allow for this, up to 13 patients will be permitted to be enrolled, but accrual will stop when 10 are evaluable. Patients will only be replaced if they are not evaluable for the ROM evaluation at the 3 month time point for any reason, since this would make the slope estimate impossible to determine (in the absence of intermediate time points, which are not useful to obtain since anti-fibrotic responses are likely to be slow and thus not reflective of any benefit when possible to be identified.

There could be bias due to drop out because of progression, but this is expected to be very limited. In addition to 6-month values, the trial will also obtain intermediate values at 3 months. By having these intermediate values available, estimates from fitting a regression line or from a

'last observation carried forward' technique may be used to try to obtain reasonable substitutes for values not available from those who do not complete 6 months of observation. This type of procedure will be done with appropriate caveats if implemented.

A stopping rule based on the appearance of unresolved grade 3 or any grade 4 toxicity attributable to imatinib will be as follows: of at any time during the trial, a cumulative total of 2 patients experience this level of toxicity, no further patients will be enrolled. This is because the upper one-sided 80% confidence bound on fractions between 2 of 3 and 2 of 10 patients with toxicity extends from 0.38 to 0.93, and as such, this level of toxicity would be consistent with levels clearly considered excessive and which outweigh the potential benefit of the agent in this population.

As this is a one-arm pilot study, there is no control for natural history or regression to the mean, but improvements without the use of treatment are unlikely since this manifestation of GVHD is typically static or progressive and does not remit or improve spontaneously. Nonetheless, if results from this trial look promising, then a randomized study is indicated as the next evaluation.

14.1.1 Updated Statistics Amendment E

After enrolling 8 patients on the trial at the 400 mg dose initially, none of the patients were able to tolerate this dose and all required dose reduction. The five of these 8 who have been evaluable for efficacy following dose reduction will have their outcomes described when the study is reported.

Amendment E will seek to determine the tolerability of the agent at 200 mg (130 mg/m2 pediatric) after initially starting at 100 mg (65 mg/m2 pediatric), and to seek the same determination of level of efficacy as was intended for the original cohort. To evaluate tolerability, the study will evaluate the fraction of the first 10 patients who start at 100 mg and escalate to 200 and who are able to tolerate the drug long enough to have a 3 month efficacy evaluation. It would be desirable if a fraction consistent with 90% would be able to tolerate the agent at this dose level and not acceptable if it were consistent with 50% or lower. If among the first 10 patients enrolled, 8 or more can tolerate the drug at 200 mg, this has 93.0% probability of occurring if the true fraction tolerating the drug were 90% and only 5.5% probability of occurring if the true fraction tolerating the drug were only 50%. Thus, it would be considered acceptable tolerability if 8 or more of the first 10 enrolled in the new cohort would tolerate the 200 mg dose.

Efficacy in the 200 mg cohort would be determined using the original specifications based on the initial evaluation intended for 400 mg. Thus, up to 13 patients will enrolled in the 200 mg cohort in order to try to obtain 10 who can be evaluated for the change in their range of motion as specified above. If appropriate based on similarity of results, the findings from the two cohorts may be combined as well as presented individually in publications resulting from the study. The study will end accrual when there are 10 who are evaluable for ROM evaluation in this cohort.

A total of 8 patients were enrolled in the first cohort. With a new requirement of up to 13 additional patients in the 200 mg cohort, the study will have an accrual ceiling of 21 patients. It

is anticipated that the maximum of 13 unique individuals who may be required to be enrolled onto this second cohort of the trial will be accrued within 2 years or sooner.

14.2 Sample Size/Accrual Rate

Up to 28 patients will be permitted to be enrolled, but accrual will stop when 10 are evaluable from the second cohort (plus the 8 enrolled from the initial cohort). Subjects of both genders, from all racial and ethnic groups are eligible for this trial. To date, there is no information that suggests differences in disease response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. Efforts will be made to extend the accrual to a representative population, but in a pilot study with limited accrual, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, age, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Expected accrual is 1-2 patients per month. The natural history cGVHD protocol will serve as the primary screening method for new study participants. 1-2 new participants are currently evaluated on this protocol each week. The protocol has been drawing participants from throughout the country and new appointments are currently being booked several months in advance.

14.3 Stratification Factors

Not applicable

14.4 Analysis of Secondary Endpoints

Secondary endpoints are also important as described elsewhere in the protocol. These include evaluations for toxicity, lung manifestations, percent of patients who are considered as responding or stable from the use of imatinib mesylate, time to progression and time to response, evaluations of tissue or blood samples, MRI results, quality of life, rehabilitative and functional changes. Since this is a pilot study, all secondary endpoints will be evaluated with exploratory intent, using non-parametric techniques and will use data on however many patients are able to provide the necessary information. No patients will be enrolled for the sole purpose of increasing the accrual for evaluation of secondary endpoints. A set of several occupational therapy assessments will also be performed at baseline and at three month time points. Differences from baseline to subsequent time points will be obtained, and these changes will be tested for statistical significance in an exploratory manner most likely using paired non-parametric tests. The changes in assessments will be correlated with clinical measurements as well. Given the limited number of patients to be enrolled on the study, and the fact that these evaluations will all be considered exploratory and secondary, the results will be reported without formal adjustment for multiple comparisons. The results will be noted to be exploratory in any publications in which they are incorporated. Should any interesting findings be identified in this manner, this information may be used to help design future studies for patients with cGVHD.

14.5 Reporting and Exclusions

14.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with imatinib mesylate regardless of inclusion in primary response evaluation.

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16 Appendix A: Performance Scales

%	Karnofsky†	Status	Lansky Scale#
100	Normal; no complaints/ no evidence of disease	**100**	Fully Active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restrictions in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
70	Cares for self; unable to carry on normal activity or do active work	**70**	Both greater restrictions of and less time spent in active play
60	Requires occasional assistance but is able to care for most of his needs	**60**	Ambulatory up to 50% of time, limited active play with assistance / supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play; fully able to engage in quiet play
40	Disabled, requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled; hospitalization is indicated though death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick; hospitalization is necessary	**20**	Limited to very passive activity initiated by others e.g. TV
10	Moribund; fatal process progressing rapidly	**10**	Completely disabled, not even passive play
		0	Unresponsive, coma

† **Karnofsky = D.A., et al., Cancer 1: 634-656, 1948**

Lansky Scale = Lansky, et. al., Cancer Oct 1; 60(7): 1651-1656, 1987

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17 Appendix B: Required Study Evaluations

Observation	Eligibility	Pretreatment	Labs: weekly x 1 mos; every other week x 6 mos; then monthly	H &P: every other week x 1 mos; then monthly	Q 3 mos	6 Month	Post Study
History & physical exam[t]	X	X		X	X	X	X
Performance status	X	X	X		X	X	X
Body surface area		X			X	X	
CBC, platelets, differential	X	X	X		X	X	X
PT/PTT, fibrinogen, iron, ferritin, transferrin		X					
Chem 20 panel, For patients with serum creatinine levels above the age-adjusted normal limits, an eGFR will be performed.	X	X	X		X	X	X
Urine/serum pregnancy test (females)		X	X		X	X	
Urinalysis		X			X	X	
Research Labs		X			X	X	
Infectious surveillance- CMV, HSV, HTLV, VZV, EBV		X					
Immunoglobulin levels		X					
Lymphocyte Phenotyping TBNK		X			X	X	X
CT Scan of chest		X					
MRI of skin (ScGVHD)		X[#]				X[#]	X[#]
Skin Biopsy (Skin GVHD)	X	X				X	
Physiatry: ROM & OT Examination	X**	X			X*	X*	X*
Pulmonary Function Tests		X			X[+]	X[+]	X[+]
Ophthalmology Evaluation		X[+]			X[+]	X[+]	X[+]
Dental Evaluation		X[+]			X[+]	X[+]	X[+]
QOL assessment (≥ 18 years)		X			X	X	X
ECHO or MUGA	X						
ECG		X					
HBV, HCV, HIV screening, 24 hour CrCL for patients with an elevated serum creatinine	X						
Apheresis (optional)		X					X

[t] H&P to include review of patient diaries to include compliance and toxicity monitoring [#] MRI will not be performed in children who require sedation * Patients with progressive disease will have a repeat evaluation in 2-4 weeks for confirmation of findings. ** Physiatry: ROM Examination only +Only for patients with organ involvement at screening, or otherwise clinically indicated.

18 Appendix C: Research Sample Procedures

Study	Responsible Investigator	Time points	Volume	Notes
PDGFR studies		Baseline, then Q 3 months (blood) Baseline, 6 months (skin biopsy)	See below.	All blood/plasma samples to be received and processed by Fran Hakim in the Pre-clinical Services Lab, Building 10 room 12C216., however, PDGRF studies hold the highest priority.
Immune function studies	Fran Hakim, PhD 301-402-3627	Baseline, then Q 3 months	Quantity and type of specimens to be approved by Dr. Hakim prior to draw.	All blood/plasma samples to be received and processed by Fran Hakim in the Pre-clinical Services Lab, Building 10 room 12C216. *Total samples to be collected include 9-10 CPT tubes, *5-10 mL x 2 in heparin (green top tube), *4ml SST tube (red/yellow rim) and *5-10 mL in EDTA. Samples to be distributed to Wynn, Flanders, and Udey Labs via Pre-clinical Lab.†
TGF-β studies	Kathy Flanders, PhD 301-496-5453	Baseline, then Q 3 months Baseline, then Q 3 months Baseline, (12 months opt.)	See above.	
IL-13 and IL-13 receptor studies	Thomas Wynn, MD 301-469-4758	Baseline, then Q 3 months Baseline, then Q 3 months Baseline, (12 months opt.)	See above.	
Imatinib mesylate Pharmacokinetic Studies	Erin Gardner, PhD 301-451-4980	Baseline, 1 month, 3 month	4mL heparin-containing (green top) tube	

†Research blood sample aliquot size will be minimized for patients < 10 years of age or < 30 kg and the total amount restricted to a maximum of 3 ml/kg per draw and 7 ml/kg per 6-week period. Patients > age 10 and > 30 kg will have no more than 450 ml blood drawn per 6-week period for research studies. In the event that blood draws are limited due to these restrictions, research studies will be performed in order of priority as listed above.

19 Appendix D: Initial H & P guidelines

1. Patient Demographic: age, gender, ethnicity, CMV status

2. Donor Demographic: age, relationship, degree of HLA match at A, B, C, DR, DQ, DP loci and type of match (allele or serologic), CMV status

4.Underlying Disease Characteristics: diagnosis, stage at transplant (complete response, minimal disease, recurrent or persistent disease) and stage at this presentation, number of failed therapies, post-transplant best response (CR, PR, SD, progression), post-transplant relapse and treatments (DLIs given?)

5. Stem Cell Characteristics: Marrow, peripheral blood, cord blood, CD34 cell dose

6. Conditioning Regimen characteristics: Myeloablative yes-no, TBI-based yes-no, quote the regimen. Non-myeloablative (quote)

7. GVHD prophylaxis: cyclosporine, tacrolimus, MMF, MTX, other drugs, ex vivo T-cell depletion, in vivo depletion with antibodies (which)

8. Early Post-Transplant Events: acute GVHD and grade (I-IV), organs involved and stage 1-4, steroid refractory acute GVHD yes-no, able to go off steroids prior to diagnosis of chronic GVHD for at least 2 months, able to go off all immunosuppression prior to diagnosis of cGVHD for at least 2 months, CMV disease/infection, major transplant-related toxicity yes-no (quote)

9. CGVHD Treatment history: date of cGVHD diagnosis, biopsy proven and which organ, initial organs involved, extensive or limited at onset, initial therapy, progressive-de novo-quiescent, subsequent therapies and approximate dates started, ever completely off immunosuppression for at least 3 months and approximate date (reason for stopping immunosuppression – successful cGVHD therapy or malignancy recurrence, other reasons), biopsy proven (yes-no), list all documented infections or infectious syndromes (such as sinusitis, cellulites etc.) since cGVHD diagnosis (Dr Banacloche's form).

10. CGVHD Characteristics at enrollment:
Prior DLIs – (yes-no, reason, number of administration, approximate dates), current cGVHD systemic and local therapy, organs involved (fill severity scale and all specialty-required data), skin %surface; Karnofsky or Lansky scores, weight and % change in last 3 mo, mild-moderate-severe (use IBMTR-form definitions), limited-extensive, platelet count, proximal muscle weakness, cramping, bilirubin, SGOT, SGPT, AP, GGT, eosinophils, list other clinical presentations or autoimmune phenomena suspicious for cGVHD such as myositis, myasthenia, polyneuropathy, serositis (pleural, pericardial, ascites), generalized edema, bilateral. LE edema, BOOP, other details from the H&P. Assessment of change from most recent evaluations: improving. Stable, progressing, cGVHD composite assessment scale (mark when biopsy proven organ), include all evaluation elements from the individual specialty sheets and manifestations as yes-no, indicate the primary severity organ per

physician assessment, indicate primary organ per patient assessment, biopsy (organ, date), photographs taken, date, albumen, BUN, creatinine, hypertension, albumen, HUS, other lab's from the MIS such as hemoglobin, reticulocyte count, autoantibodies, direct anti-globulin test etc (see clinical evaluation sheet).

11. Underlying disease characteristics at the time of enrollment
Underlying disease or second malignancy present at the time of cGVHD diagnosis (yes/no), if "yes": biopsy performed?, diagnosis, stage, proposed intervention.

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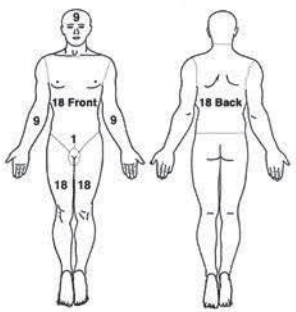
20 Appendix E: Chronic GVHD activity assessment

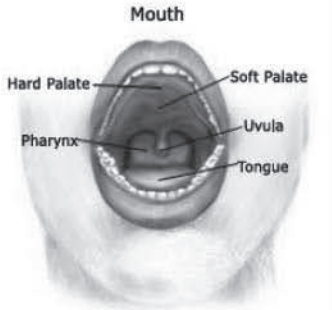
Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Component	Findings	Scoring (see skin score worksheet)
Skin 	Erythematous rash	% BSA (max 100%)
	Moveable sclerosis	% BSA (max 100%)
	Non-moveable sclerosis (hidebound/non-pinchable)	% BSA (max 100%)
	Subcutaneous sclerosis/fasciitis	% BSA (max 100%)
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer	Location: _____ Largest dimension: _____cm

Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting

Mouth



Mucosal change	No evidence of cGvHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

Blood Counts	Platelet Count K/uL	ULN K/uL	Total WBC K/uL	ULN K/uL	% Eosinophils %					
Liver Function Tests	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L				

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Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*		
Gastrointestinal-Esophageal • Dysphagia OR • Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*		
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*		
Lungs • Bronchiolitis Obliterans	Pulmonary Function Tests with Diffusing Capacity (attach report for person> 5 yrs old)	FEV-1 % Predicted	Single Breath DLCO (adjusted for hemoglobin) % Predicted

Health Care Provider Global Ratings: **In your opinion, do you think that this patient's chronic GvHD is mild, moderate or severe?** 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** **Most severe cGvHD symptoms possible**	**Over the past month would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Functional Performance (in persons >4 years old) • Walk Time • Grip Strength	Total Distance Walked in 2 Minutes: Number of laps: _____ (x 50 feet) + final partial lap: _____ feet = _____ feet walked in 2 minutes	Grip Strength (Dominant Hand) Trial #1 psi	Trial #2 psi	Trial #3 psi	Range of Motion: o Not performed o Physical Therapy Report Attached

Score	Lansky Performance Status Scale Definitions (circle from 0-100) (persons < 16 years old)	Karnofsky Performance Status Scale Definitions (circle from 0-100) (persons 16 years or older)
100	Fully active, normal	Normal no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of and less time spent in play activity	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most personal needs
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospital admission is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

21 Appendix F: Sign and symptoms of cGVHD

ORGAN OR SITE	***DIAGNOSTIC*** *(Sufficient to establish the diagnosis of chronic GVHD)*	***DISTINCTIVE*** *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)*	***OTHER FEATURES****	***COMMON*** *(Seen with both acute and chronic GVHD)*
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss** (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy) • Scaling, papulosquamous lesions	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), • Premature gray hair	
Mouth	• Lichen-type features • Hyperkeratotic plaques • Restriction of mouth opening from sclerosis	• Xerostomia • Mucocele • Mucosal Atrophy • Pseudomembranes** • Ulcers**		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes† • Cicatricial conjunctivitis • Keratoconjunctivitis sicca† • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	
Genitalia	• Lichen planus-like features • Vaginal scarring or stenosis	• Erosions** • Fissures** • Ulcers**		

GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus**		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children
Liver				• Total bilirubin, alkaline phosphatase > 2 x upper limit of normal† • ALT or AST > 2x upper limit of normal†
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy	• Bronchiolitis obliterans diagnosed with PFTs and radiology†		• BOOP
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to sclerosis	• Myositis or polymyositis †	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP)	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

*Can be acknowledged as part of the chronic GVHD symptomatology if diagnosis is confirmed
**In all cases, infection, drug effect, malignancy or other causes must be excluded.
†*Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer's test foreyes). GVHD (graft versus host disease); ALT (alanine aminotransferase); AST (aspartate aminotransferase); BOOP (bronchiolitis obliterans organizing pneumonia); PFTs (pulmonary function tests); AIHA (autoimmune hemolytic anemia)*

22 Appendix G: cGVHD score sheet

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ <5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops < 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN
LUNGS* **FEV1** ☐	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
DLCO ☐	☐ FEV1 > 80% **OR** LFS=2	☐ FEV1 60-79% **OR** LFS 3-5	☐ FEV1 40-59% **OR** LFS 6-9	☐ FEV1 <39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

* AP may be elevated in growing children, and not reflective of liver dysfunction

Other indicators, clinical manifestations or complications related to cGVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact (none – 0,mild -1, moderate -2, severe – 3)

ĺ Esophageal stricture or web___ ĺ Pericardial Effusion___ ĺ Pleural Effusion(s)___
ĺ Ascites (serositis)___ ĺ Nephrotic syndrome___ ĺ Peripheral Neuropathy___
ĺMyasthenia Gravis___ ĺ Cardiomyopathy___ ĺ Eosinophilia > 500µl___
ĺ Polymyositis___ ĺ Cardiac conduction defects___ ĺ Coronary artery involvement___
ĺ Platelets <100,000/µl ___ĺ Progressive onset
ĺ **OTHERS:** _____

23 Appendix H: Chronic GVHD Manifestations

Component	Items assessed	Measure	Assessor*
Skin	Erythematous and/or papular rash of any sort	% body surface area	C
	Superficial sclerosis (movable)	("rules of 9's)	C
	Deep sclerosis (non-moveable)		C
	Ulcers	largest dimension (cm) of the largest ulcer	C
	Pruritus or itching	0 – 10 scale	P
Eyes	Bilateral Schirmer's tear test scores without anesthesia	Mean of both eyes (mm)	C
	Chief ocular complaint at the time of the visit	0 – 10 scale	P
Mouth	Erythema	Total score 0 – 15	C
	Lichen-type Hyperkeratosis		C
	Ulcerations		C
	Mucoceles		C
	Symptoms of oral pain, dryness, sensitivity	0 – 10 scale	P
Hematology	Platelet count, eosinophils	number/μL	C
Gastrointestinal	Upper GI symptoms	0 – 3 score	C/P
	Esophageal symptoms	0 – 3 «	C/P
	Diarrhea	0 – 2 «	C/P
Liver	total serum bilirubin	mg/dL	C
	ALT, alkaline phosphatase	U/L	C
Lungs	Bronchiolitis obliterans syndrome	FEV1, DLCO	C
Chronic GVHD Symptom scale[37]	30 items, 7 subscales, 1 summary scale	1-100	P
Global activity rating	Severity of chronic GVHD symptoms	0 – 10	C/P
	Perception of change	+3 to -3	C/P
	Overall severity of chronic GVHD	Mild – Moderate-Severe	C/P

- Vulvar-vaginal symptoms (yes or no) and patient weight should be recorded at each visit. Range of motion of the most affected joints should be recorded, depending on the availability of a physical therapist.
*C=assessed by the clinician; P=reported by the patient

24 Appendix I: Core set of measures for assessing responses in chronic GVHD trials

Measure	Clinician Assessed	Patient Reported
I. Chronic GVHD specific measures		
Signs	Organ specific measures	N/A
Symptoms	Clinician assessed symptoms Patient reported measure	Patient reported symptoms Lee Symptom Scale
Global rating	Mild-moderate-severe 0-10 severity scale 7 point change scale	Mild-moderate-severe 0-10 severity scale 7 point change scale
II. Ancillary measures (chronic GVHD non-specific)		
Function	Grip Strength 2 min walk time MAM-36 DASH Jebsen-Taylor Hand Function Test AMPS SF-36	
Quality of Life	HAP	
Performance status	Karnofsky or Lansky	

25 Appendix J: QOL and Functional assessment scales

Scale	Time Points	Examiner
Performance status (Karnofsky or Lansky)	Entry	Evaluating MD/NP
Lee Symptom Scale	Entry, q 3 months	Evaluating MD/NP
cGVHD Patient Self Assessment Scale	Entry, q 3 months	Evaluating MD/NP
Functional Assessment:	Entry, q 3 months	
Grip Strength		Physiatry (Dr. Joe)
2 min walk time		Physiatry (Dr. Joe)
Occupational Therapy Assessment:	Entry, q 3 months	Occupational Therapy (L. Comis)
MAM-36	Entry, q 3 months	
DASH	Entry, q 3 months	
Jebsen-Taylor Hand Function Test	Entry, q 3 months	
AMPS	Entry, q 3 months	
SF-36	Entry, q 6 months	
HAP	Entry, q 6 months	

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26 Appendix K: Chronic GVHD patient symptom scale

APPENDIX

Please let us know whether you have been bothered by any of the following problems in the past month.

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

From Lee et al. BBMT, 8:444-452, 2002 [38]

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27 Appendix L: cGVHD activity assessment - patient self report

cGVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Today's Date: _____ MR#/Name: _____

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth dryness** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe is this eye symptom, between 0 (not at all severe) and 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10
Vulvovaginal Symptoms (females only)	Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia? **OR** Do you have any discomfort or pain with sexual intercourse?	o Yes o No o Not applicable

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
0= none
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe

Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

28 Appendix M: Functional Assessment: ROM, Walk Test, Grip Strength, Function Scales

Description:
There are standard ranges for all tests. Every joint has an established range of motion (ROM). For example, the normal ROM for shoulder flexion is 180 degrees, each quartile is 45 degrees. If the shoulder can be put through 125 degrees it is 75% of normal. Similar is for grip strength (in Kg or pounds of pressure) and for walk time. The velocity is established based on norms for age and sex. For example if 18 feet/second, if divided by 4 and gets quartiles.
The HAP has a standard scoring mechanism which determines normal activity. However, it has not been looked at with respect to disability. We have done this internally for several studies based on internal agreement. The maximum activity score (based on 94 questions) was divided into performance groups: top quartile are normal performers with scores of >81; next quartile with scores of 73-81; next quartile 61-72 and bottom quartile 60 and below.

ROM:
Active-assisted range of joint motion serves as very useful objective measure of chronic GVHD tissue response in patients whose large joints or trunk are involved by sclerotic skin changes. Norms are available for adults and for children more than 3 years of age.

Patients will be examined by a physiatrist upon enrollment and every 3 months while on study. Exam will consist of active-assisted ROM performed on all major joints. Based on the level of impairment (current degree/normal degree) and the clinical assessment (level of sclerotic tissue changes) the physiatrist will choose three signal joints (1-2 for patients with fewer involved joints) to be measured for primary endpoint evaluation. Physiatrist will determine percent change in impairment and record for all involved joints.

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29 Appendix N: Physiatry Evaluation ROM Assessment:

Patient Name_____ **MRN**_____**Date**

1) Active Assisted ROM Assess if patient≥4

	Actual Number	% of Predicted	Impairment Assessment			
			Normal=0	Mild=1	Moderate=2	Severe=3
Joint 1						
Joint 2						
Joint 3						

2) Other Musculoskeletal Findings

	Normal=0	**Mild=1**	**Moderate=2**	**Severe=3**
Grip Strength Assess if patient ≥6	**0-25%** ( )	**26-50%** ( )	**51-75%** ( )	**>75%** ( )
Walk velocity Assess if patient ≥6	**0-25%** ( )	**26-50%** ( )	**51-75%** ( )	**>75%** ( )
HAP Assess if patient ≥16	**>81** ( )	**73-81** ( )	**61-72** ( )	**<61** ( )

3) Grip Strength of the Dominant Hand

	Trial 1	**Trial**	**Trial 3**	**Average**	**% of Predicted**
R					
L					

4) Walk Velocity:

Total Distance Walked in 2 Minutes _____feet walked in 2 minutes, giving him/her velocity_____. % of predicted_____

5) HAP: _____AAS_____

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MRN:
AAROM:

Cervical spine:

Flexion	Extension	R SB	L SB	R Rotation	L Rotation

Shoulders:

	Abduction	Flexion	IR	ER
R				
L				

Elbows:

	Extension	Flexion
R		
L		

Wrists:

	Extension	Flexion
R		
L		

Hips:

	IR	ER
R		
L		

Knees:

	Extension	Flexion
R		
L		

Ankles:

	ADF	APF
R		
L		

Signature Printed Name Date

30 Appendix O: Lung Function Score

The Lung function score (LFS) is computed by the extent of FEV_1 and DLCO compromise (>80% = 1, 70 – 79% = 2, 60 – 69% = 3, 50 – 59% = 4, 40 – 49% = 5, <40% = 6). The scores for FEV_1 and DLCO are then added together, and the sum is reduced to an overall category according to the following table.

Category	30.1.1 Lung function	30.1.2 LF score
I	Normal	2
II	Mild decrease	3 – 5
III	Moderate decrease	6 – 9
IV	Severe decrease	10 – 12

It is important to emphasize that LFS has never been used in chronic GVHD response assessments and its exact role in this setting needs to be determined. To allow validation in trials absolute values of both FEV_1 and DLCO are recorded on the data collection forms.

31 Appendix P: Scoring of non-ScGVHD cGVHD manifestations

1. Skin GVHD (Dermatology): Total skin score (Appendix E)
2. Oral GVHD (Dental): Total mouth score (Appendix E)
3. Ophthalmologic GVHD (Ophthalmology): Response based on determination of bilateral Schirmer's Test (without topical anesthesia >9 y/o, with topical anesthesia <9 years old.)
4. Bronchiolitis obliterans (PFTs): Measure of absolute FEV1 and lung function score (Appendix O). BO response will be measured by standard pulmonary function tests. Patients will be evaluated by complete PFT's (with and without bronchodilators) and baseline will be the best measured FEV1. Percent change is based on the relative change as compared to baseline. PFT testing variability is typically <10% and a 20% change is thought to be significant.
5. Liver GVHD: Laboratory values: ALT, AST, total bilirubin, alkaline phosphatase.
6. Gastrointestinal GVHD: Gastrointestinal symptom score (Appendix E).

Progression (PD): defined as at least one of the following:

Organ and Starting Score or Value	Progression Criterion
Skin (% of BSA)	e – s ≥ 25
Eye (mm Schirmer's test)	s – e ≥ 5 mm
Mouth (Schubert Scale 0-15)	e – s ≥ 3
Hematology 3 Platelet count 4 Eosinophil count 5 ≥ 3 X ULN • < 3 X ULN	 s – e ≥ 50,000/μL and e < LLN e - s ≥ 3 X ULN e - s ≥ 2 X ULN
Gastrointestinal (0 -3 scales)	e – s ≥ 1
Liver function (ALT, alkaline phosphatase and bilirubin) 6 s ≥ 3 X ULN 7 s < 3 X ULN	 e - s ≥ 3 X ULN e - s ≥ 2 X ULN
Lungs (Lung function scale 12 points)[2]	e - s ≥ 3
Other	> 1 steroid pulse per 3 month period

Abbreviation: s: starting score or value; e: ending score or value; ULN: upper limit of normal; LLN: lower limit of normal. If the starting lung function score is ≥ 10, progression is defined as ≥ 5% decrease of FEV_1 in two tests measured at least 2 weeks apart.

Partial Response (PR): defined as at least one of the following:

Organ and Starting Score or Value at Baseline	Partial Response Criterion[1]
Skin (% of BSA)	
8 > 50	e/s ≤ 0.5 and e > 0
9 25-50	s – e ≥ 25 and e > 0
10 < 25	Only CR; no PR possible
Eye (mm Schirmer's test)	
11 < 5 mm	e – s ≥ 5 mm and e < LLN
12 5-10 mm	Only CR; no PR possible
Mouth (Schubert Scale 0-15)	
13 > 8	e/s ≤ 0.5 and e > 0
14 4 – 7	s – e ≥ 4 and e > 0
15 < 4	Only CR; no PR possible
Hematology	
16 Platelet count	e – s ≥ 100,000/μL and e < LLN
17 Eosinophil count	
18 ≥ 3 X ULN	e/s ≤ 0.5 and e > ULN
19 < 3 X ULN	Only CR; no PR possible
Gastrointestinal (0 -3 scales)	
20 3	e = 1 or 2
21 2	e = 1
22 1	Only CR; no PR possible
Liver function (ALT, alkaline phosphatase and bilirubin)	
23 ≥ 3 X ULN	e/s ≤ 0.5 and e > ULN
24 < 3 X ULN	Only CR; no PR possible
Other	Stable disease in the face of weaning steroid.

Abbreviations. s: starting score or value; e: ending score or value; ULN: upper limit of normal; LLN: lower limit of normal

Complete Response (CR): defined as at least one of the following

1. Skin: >90% reduction of baseline involvement.
2. Ophthalmologic: Return to normal Schirmer's score in both eyes.
3. Oral: Resolution of oral mucosal involvement.
4. BO: PFT: improvement in FEV1 > 0.70.
5. Liver: Normalization of laboratory values of transaminases and bilirubin.
6. GI: (Upper GI) Absence of symptoms of nausea, dysphagia, vomiting, and odynophagia and stable weight. (Lower GI) Absence of diarrhea and stable weight.

32 Appendix Q: Patient Instructions

You should not receive this medicine if you have had an allergic reaction to imatinib, or if you are pregnant. Do not handle broken tablets with unprotected hands.

How to Use This Medicine:

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to**. Your daily dose of imatinib mesylate is: _____.**

It is best to take this medicine with food and a large glass of water.

If you are not able to swallow the tablet, you may dissolve the tablet in a glass of water or apple juice. If you are taking ½ tablet (50 mg), dissolve it in 1 ounce (1/8 cup) of water or juice. If you are taking the 100 mg tablet, dissolve it in 2 ounces (1/4 cup) of water or juice. If you are taking 200 mg (2 tablets), dissolve it in 4 ounces (about 1/2 cup) of water or juice. If you are taking 300 mg (3 tablets), dissolve it in 6 ounces (about 3/4 cup) of water or juice. Stir with a spoon and drink immediately after the tablet has dissolved.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Handle, Store and Dispose of This Medicine:

Patients who require a ½ tablet (50mg) dose will be required to split the scored tablets. Parents will be taught the proper technique for breaking tablets according to standard procedure. Do not handle broken tablets with unprotected hands. Wear gloves when handling broken or cut tablets.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed. Under no circumstance should medication be flushed down the toilet.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Grapefruit juice.

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, iron supplements, and herbal products.

Make sure your doctor knows if you are also using ketoconazole (Nizoral®), itraconazole (Sporanox®), erythromycin (such as E-mycin®, Eryc®, Ery-Tab®, P.C.E.®), clarithromycin (Biaxin®), dexamethasone (such as Decadron®, Hexadrol®), phenytoin (Dilantin®), carbamazepine (such as Carbatrol®, Tegretol®), rifampin (such as Rifadin®, Rimactane®), phenobarbital (Solfoton®), cyclosporine (such as Gengraf®, Neoral®, Sandimmune®), pimozide (Orap®), estazolam (Prosom®), triazolam (Halcion®),

alprazolam (Xanax®) sirolimus (Rapamune®rapamycin), tacrolimus (Prograf®, KF506), alfuzosin, (Uroxatral®) aprepitant, (Emend®), or eletriptan, (Relpax®).Tell your doctor if you are also using medicines to lower cholesterol or triglycerides (such as lovastatin, Lescol®, Lipitor®, Pravachol®, or Zocor®), certain blood pressure medicines (such as diltiazem, nifedipine, verapamil, Cartia®, Lotrel®, Norvasc®, Plendil®, or Tiazac®), St. John's Wort, or a blood thinner such as warfarin (Coumadin®).

You Should Contact Your Research Team If You Are Experiencing Any Side Effect(s) From Your Medication

Research Nurse, Susan Booher, telephone: 301-402-1474. Pager #15219.
Principal Investigator, Dr. Edward W. Cowen, telephone: 301-496-4299. Pager # 13483.
Lead Associate Investigator: Dr. Kristin Baird, telephone: 301-451-0391. Pager #13523

To call an NIH pager, dial 1-800-NIH-BEEP, and follow the instructions to enter the pager number.

33 Appendix R: Patient Calendar for Imatinib Mesylate

Patient ID number:_____ **Cycle Number:**_____ **Cycle Start Date:**_____

(Week) Date ☐								
# of days with symptoms ☐								
SIDE EFFECTS								
Nausea (see scale below)† ☐								
Vomiting (# of times in 24 hr) ☐								
Diarrhea (# of times in 24 hr) ☐								
Fatigue (# of times in 24 hr) ☐								
Rash (# of times in 24 hr)								
OTHER SIDE EFFECTS (list below)								
☐								
☐								

OTHER MEDICATIONS (Name)	Dose	Frequency	Start Date	Stop Date	Reason for Use of Medication

Missed study medication on _____ **because** _____

on _____ **because** _____

on _____ **because** _____

Additional information about my side effects is:

*If you miss a treatment write "M" in the box.

†Rate nausea **mild** if you are able to eat and drink a reasonable amount, **moderate** if you can eat and drink but the amount is substantially decreased, or **severe** if you are unable to eat and drink.

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Physicians should fax completed form to (Susan Booher, RN) call with questions: F 301-402-2943-, O:301-402-1474.

Parent/patient initials:_____

34 Appendix S: Occupational Therapy Assessment

Four Assessments of Manual Ability:

1. 36 item Manual Ability Measure (MAM-36)-self report which elicits the patient responses about the ease or difficulty in performing 36 common, everyday activities. Its items consist of common one-and two handed tasks that cover a wide range of difficulty and that distinguish different patient ability levels. The ratings are Rasch transformed into measures, with higher scores indicating more ability. [39-41]

2. Jebsen-Taylor Hand Function Test: Patient-completed, staff-timed measure involving 7 major hand activities designed to simulate or sample functional hand tasks: (feeding; writing; turning pages; stacking checkers; picking up: small objects; large light objects; large heavy objects). Both hands are tested with the non-dominant hand tested before the dominant hand. Normative data is presented for males and females in 20-60 year age range for both the dominant and non-dominant hand. Item scores (and total scores for children) are compared with normative tables according to age and sex. Reassessments allow the subject to be compared with his or her own scores as well as with norms to measure effectiveness of a given intervention. [42-44] www.sammonspreston.com

3. Disabilities of the Arm, Shoulder and Hand (DASH) The Disabilities of the Arm, Shoulder and Hand (DASH) Outcome Measure is a 30-item, self-report questionnaire designed to measure physical function, limitations and symptoms in subjects with any or several musculoskeletal disorders of the upper limb. The optional high-performance Work Module and Sport/Performing Arts Module each contain an additional four questions. DASH is scored in two components: upper–extremity disability and symptom scale and optional Work and Sport/Performing Art Modules. [45-47] www.dahs.iwh.on.ca

4. Grooved Pegboard: The Grooved Pegboard is a manipulative dexterity test consisting of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be inserted. This test requires more complex visual-motor coordination than most pegboard tests. The tool has been found to be a reliable measure of manual dexterity. [48,49] www.lafayetteinstrument.com

Observation Based Functional Assessment:

1. Assessment of Motor and Process Skills: is an observational tool that is used to measure the quality of a person's activities of daily living (ADL). The quality of the person's ADL performance is assessed by rating the effort, efficiency, safety, and independence of 16 ADL motor(e.g walk, reach, lift, transport) and 20 ADL process (e.g. choose, use, sequence, accommodate) skill items. ADL motor skills are observable actions of task performance used to move oneself and task objects. ADL process skills are observable actions used to organize and adapt actions to complete a task. During administration of the AMPS, an occupational therapist observes the person performing two culturally relevant and familiar ADL tasks, then rates the person's performance on a four-point scale ranging from deficit=1 to competent =4. AMPS ADL motor and ADL process skills scores are converted to interval level ability motor and process measures using a multi-faceted Rasch Analysis. This analysis allows the difficulty level of ADL motor skills, ADL process skills and ADL tasks and the severity of the calibrated rater to be accounted for in computing the ability measures and for comparisons between different tasks, raters, subjects and over time within subjects. The AMPS has been standardized on over 125,000 persons worldwide and has been used for clinical and research purposes with clients age 4 and up with various physical and mental disabilities. High ADL motor or process ability scores indicate that the participant is "more able" on a continuum of AMPS motor and process scales. [50] www.ampsintl.com

Assessments of Social Participation and Quality of Life

1. Short Form -36 Health Survey (SF-36): The SF-36 is generally considered the gold standard for measuring health related quality of life. The SF-36v2 Health Survey can be self-administered to persons ages 14 and older and can usually be completed in 5 to 10 minutes. 36 questions measure eight domains of physical and mental health. Respondents select ratings on various topics such as activities they might do on a typical day or whether they experienced limitations due to physical or emotional health problems. Eight scale scores are reported as well as summary scores for physical health and mental health. The eight scale scores relate to physical functioning, role limitations due to physical health problems, bodily pain, social functioning, and general mental health, role limitations, due to emotional problems, vitality, and general health perceptions. Scoring the instrument requires detailed guidance to calculate raw scores and t scores. [51] www.qualitymetric.com/products.

2. Human Activity Profile (HAP), a self-report measure of energy expenditure or physical fitness. The questionnaire has been used as a measure of physical activity in both healthy and impaired populations. The HAP consists of 94 common daily activities listed in ascending order according to the energy required to perform them. A wide variety of activities is represented, including self-care tasks, personal/household work, entertainment/social activities, and independent exercise pursuits. With regard to each of the listed activities, respondents are requested to indicate if (1) they are currently able to perform the activity (unassisted), (2) they have stopped performing the activity, or (3) they have never performed the activity. [52]

Time Frame:

- Baseline testing battery: all instruments (HAP, SF-36, AMPS, grooved pegboard, Jebsen-Taylor hand function test, DASH and MAM-36)
- 3 month: (grooved pegboard, Jebsen –Taylor Hand Function test, DASH and MAM-36)
- 6 month: all instruments (HAP, SF-36, AMPS, grooved pegboard, Jebsen-Taylor hand function test, DASH and MAM-36)
- One year: all instruments (HAP, SF-36, AMPS, grooved pegboard, Jebsen-Taylor hand function test, DASH and MAM-36)
- Two year: all instruments (HAP, SF-36, AMPS, grooved pegboard, Jebsen-Taylor hand function test, DASH and MAM-36)

35 Appendix T: Imatinib Mesylate Pharmacokinetic Case Report Form

Appendix T: Imatinib Mesylate Pharmacokinetic Case Report Form

Imatinib Mesylate Pharmacokinetic Case Report Form

Protocol # 08-C-0148 Drug: Imatinib Dose: mg

All PK's to Doug Figg's Lab: 5A01
Page 102-11964 for PK Pickup.
Lab phone: 402-3622

Ht _____
Wt _____
BSA _____

Cycle _____
Week _____

Clock Used _____

Research Nurse:	**Susan Booher**
Phone:	402-1474
Pager:	102-15219
PI:	Edward Cowen, MD
Phone:	496-4299
Pager:	102-13483
Lead AI:	Kristin Baird, MD: 451-0391

You may draw PK's through a CVC if patient has one; or, through a peripheral line (please note the location of the blood draw under "Comments")

Date	Time Interval	Amount/Type/Tube/ Handling	Send To:	Special Instructions	Ideal Time (Military)	Actual Time (Military)	Comments	Signature	If missed Reason
Baseline	pre	4 ml Na Hep Green top	5A01	refrigerate/ page Dr. Figg's Lab at 102-11964					
DATE: _____ Imatinib Mesylate dose at: date:_____ time: _____ Deviations from Protocol/Problems during administration:									
Month 1		4 ml Na Hep Green top	5A01	refrigerate/ page Dr. Figg's lab at 102-11964					
Month 3		4 ml Na Hep Green top	5A01	refrigerate/ page Dr. Figg's lab at 102-11964					

Please SIGN each time you draw a PK. Please Send a Copy of the PK sheet with the Last Specimen to the Figg lab - 5A09.