Combination Ibrutinib and Rituximab for Treatment of Chronic Graft-Versus-Host Disease Following Allogeneic Stem Cell Transplant

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List of Abbreviations

*AE: Adverse event
*aGVHD: Acute Graft Versus Host Disease
*Allo-SCT: Allogeneic stem cell transplant
*BTK: Bruton's tyrosine kinase
*cGVHD: Chronic Graft versus Host Disease
*CLL: Chronic lymphocytic leukemia
*CTCAE: Common terminology criteria for adverse events
* DSMAC: Data Safety Monitoring and Accrual Committee
*EMR: Electronic medical record
*GVHD: Graft Versus Host Disease
*ITK: IL-2 inducible T cell kinase
*NHL: Non-Hodgkin's lymphoma
*SAE: Serious adverse event

Study Summary

Title	Combination Ibrutinib and Rituximab for Treatment of Chronic Graft-Versus-Host Disease Following Allogeneic Stem Cell Transplant
Short Title	Ibrutinib and Rituximab for Steroid-Refractory or Dependent Chronic GVHD
Protocol Number	D17120
Phase	Phase 1/2
Methodology	Open label, Within-Subject Dose-Escalation Study
Study Duration	2 years (patients will be followed after 6 months for survival only)
Study Center(s)	Single center
Objectives	To determine the safety and efficacy of Ibrutinib and Rituximab combination therapy for steroid-refractory or -dependent chronic GVHD following allogeneic stem cell transplant.
Number of Subjects	15
Diagnosis and Main Inclusion Criteria	Steroid refractory or dependent chronic graft-versus-host disease (diagnosis to be based on histologic sampling and/or via clinical criteria; see Attachments) > 18 years old Karnofsky Performance Status 60 or greater

Study Product, Dose, Route, Regimen	Within-Subject Dose-Escalation Format: -The first 5 subjects will receive treatment as follows: -Ibrutinib 140 mg po once daily -Rituximab 375 mg/m^2 IV weekly x4 -Adverse events will be defined as per the NCI Common Terminology Criteria for Adverse Events (CTCAE) -if no adverse events >/= non-hematologic grade 3 or >/= hematologic grade 4 are noted after 1 week at 140 mg daily, the Ibrutinib dose schedule will be increased to 280 mg daily -if no adverse events >/= non-hematologic grade 3 or >/= to hematologic grade 4 are noted after 1 week at 280 mg daily, the Ibrutinib dose schedule will be increased to 420 mg daily - the potential exists for a 2nd weekly x4 Rituximab course 8 weeks after initial Rituximab therapy, if no response or an incomplete response is noted Expansion cohort: - following accrual of the 5 initial subjects, an additional 10 subjects will be accrued, with dosing to be informed by the results of the within-subject dose escalation cohort
Duration of administration	Ibrutinib: ongoing (indefinite), with re-assessment of patient tolerance and response at 6 weeks, 3 months and 6 months Rituximab: weekly x4, with or without a repeat 8 weeks after the initial therapy, depending on the patient's initial clinical response
Reference therapy	Patients may have received steroids or other alternative GVHD regimens (with no new therapy for at least two weeks prior to the start of this protocol), without benefit, OR Patients may have shown an initial steroid benefit, but demonstrate an inability to undergo steroid taper due to persistent GVHD upon attempted steroid dose reduction.

Statistical Methodology	GVHD response rates at 6 weeks, 3 months and 6 months will be assessed using exact binomial methods combining the initial dose escalation and expansion cohorts. Univariate and multivariate analyses will be used to identify independent correlates of both safety and efficacy.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Allogeneic stem cell transplant (allo-SCT) remains a potentially curative treatment modality for a variety of hematologic malignancies. Development of graft-versus-host disease (GVHD) following transplant poses clinical challenges and contributes significantly to post-transplant morbidity and mortality (1,2,3). GVHD is an immunologic condition caused by a reaction of donor T lymphocytes against host tissues after allogeneic transplant. The pathophysiology of GVHD is dependent on the presence of T-cells in the donor graft, allo-antigenicity between donor and recipient and an immunologically incompetent host. GVHD can manifest as either acute disease, generally affecting the skin, GI tract and liver, or chronic, with the latter being the primary cause of late morbidity and mortality following allo-SCT (1,2). Traditional distinctions between acute and chronic GVHD, based on time of onset following transplant, have largely given way to qualitative clinical differences, as the temporal onset has varied in the era of non-ablative allo-SCT and the National Institutes of Health (NIH) consensus development project has better defined diagnostic and staging criteria for chronic GVHD (2).

Acute GVHD (aGVHD) is known to be mediated almost exclusively by donor T cells, whereas the pathophysiology of chronic GVHD (cGVHD) is less well defined, though both CD4+ T-cells and B cells have been implicated. Thus, treatment of cGVHD remains challenging, with only 30-50% of patients responding to first-line (steroid) therapy. Those patients who develop steroid-refractory disease carry a poor prognosis, owing to the lack of any clear consensus on second-line therapy. Even those who initially respond to steroid therapy warrant second-line intervention to minimize the significant morbidity and mortality risks of longstanding steroid use (1,2,3). Since donor B cells have been shown to play an increasing role in the pathophysiology of cGVHD, the prospect of B-cell depletion has been raised as an effective modality for chronic GVHD management (4). Cutler et al. demonstrated the benefit of rituximab in the treatment of steroid-refractory cGVHD (5), and follow-up studies have confirmed the prophylactic efficacy of this agent in minimizing development of steroid-requiring cGVHD (6,7). Notably, although the overall clinical response rate of established cGVHD to rituximab was high (70%), complete responses were rare, emphasizing the need for additional agents in this area (5).

In light of data indicating a role of Th2 cells in the development of cGVHD (8), studies have suggested the potential utility of ibrutinib in cGVHD treatment (9). Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK) and IL-2 inducible T cell kinase (ITK) that targets Th2 cells and B cells (9). It has been used as mono- or combination therapy in various hematologic malignancies (10,11), including mantle cell lymphoma (MCL;12) and chronic lymphocytic leukemia (CLL;13). Various murine studies have supported ibrutinib as a potential agent to treat GVHD, including demonstration of efficacy in two complementary murine models (14). One involved T-cell driven sclerodermatous cGVHD and another demonstrated allo-antibody driven multi-organ system cGVHD, with manifestation of bronchiolitis obliterans chronic pulmonary GVHD. These data suggest a promising therapeutic role for ibrutinib in the management of (B-/T-cell driven) cGVHD, and this has been borne out by human studies, including a multi-center, open-label, phase II trial showing efficacy in steroid-refractory GVHD (15). This study, consisting of 42 patients with cGVHD who had failed 1-3 prior therapies, demonstrated an overall response rate (ORR) of 67%, with over 70% sustained responses (at least 20 weeks), leading to ibrutinib having recently been granted FDA approval for the treatment of cGVHD after failure of at least one line of systemic therapy.

While identification of uniquely correlative plasma biomarkers in the cGVHD setting remains incomplete, two potential biomarkers of interest include suppression of tumorigenicity 2 (ST2) (16) and CD4CD25FOXp3 Tregs (17), with potential relevance of these to both cGVHD development and therapeutic response. In addition, an activated Th17-prone T-cell subset expressing both CD146 and CCR5 has been shown to play a role in cGVHD, with potential sensitivity to pharmacologic inhibition (18, 19). Further, in a subset of 42 patients with cGVHD receiving ibrutinib following resistance to prior intervention, those responding were found to manifest decreased levels of sIL-2Ra, CX3CL1, CXCL9, CXCL10, CCL22 and CCL4 (18, 20).

Another development on the clinical front has been the use of combination ibrutinib/rituximab therapy for patients with CLL, shown to be a well-tolerated, effective regimen, with minimal toxicity (21). To that end, we recently

managed a patient with high-risk CLL at our center with post-transplant relapse and concurrent cGVHD, treating successfully with combination ibrutinib/rituximab therapy. Given existing data supporting the efficacy of both ibrutinib and rituximab in human cGVHD, as well as the demonstrated tolerability of combination ibrutinib/rituximab in CLL, we propose a study to evaluate the tolerability and efficacy of combination ibrutinib/rituximab in patients with steroid-resistant or -dependent cGVHD.

1.2 Pharmaceutical agent data from clinical pharmacology

Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody, directed against the CD20 antigen expressed on B-lymphocytes. It has IgG-1 kappa immunoglobulin containing murine light- and heavy-chain variable regions and human constant regions. Rituximab is routinely used for B-cell non-Hodgkin's lymphoma (NHL) and other CD20 expressing B-cell hematologic malignancies and is FDA approved for diffuse large B-cell, CD20 positive NHL in combination with CHOP or other lymphoma-specific cytotoxic chemotherapy regimens. It is also FDA approved in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy as first-line treatment for untreated CD20 positive follicular non-Hodgkin's lymphoma, as well as in combination with fludarabine and cyclophosphamide for CD20 positive chronic lymphocytic leukemia (CLL). Ritxumab is FDA approved as single-agent maintenance therapy for patients with CD20 positive follicular NHL.

Ibrutinib

Ibrutinib is a potent and irreversible Bruton's tyrosine kinase (BTK) inhibitor (9). BTK is responsible for the proliferation, differentiation, apoptosis, and cell migration of B cells (9). A Phase II study showed benefit for relapsed or refractory mantle cell lymphoma (MCL) in median progression-free survival (PFS) and median overall survival (OS). (12) A Phase III trial (MCL3001) demonstrated benefit in PFS with single-agent ibrutinib as compared with single-agent temsirolimus for patients who had received at least one prior rituximab-containing regimen for relapsed or refractory MCL (22) Another Phase III trial, RESONATE, showed significantly improved response rate (RR), PFS and OS with ibrutinib versus ofatumumab for patients with CLL or small lymphocytic lymphoma (SLL). (23) In addition, results of the Phase III RESONATE-2 trial showed that ibrutinib was superior to chlorambucil as assessed by RR, PFS, OS and improved hematologic variables for patients with previously untreated CLL or SLL (24).

1.3 Preclinical Data

Available data on ibrutinib as an irreversible inhibitor of BTK and IL-2 inducible kinase targeting Th2 cells and B cells (30).

Murine study data support prophylactic benefit of ibrutinib in chronic GVHD (25).

1.4 Clinical Data, to Date

Phase 2 data for ibrutinib in human cGVHD, specifically, a multi-center, open-label trial showing efficacy in steroid-refractory GVHD. This study, consisting of 42 patients with cGVHD who had failed 1-3 prior therapies, demonstrated an overall response rate (ORR) of 67%, with over 70% sustained responses, leading to ibrutinib being granted FDA approval for the treatment of cGVHD after failure of at least one line of systemic therapy (15).

* Single arm phase 2 study showing well-tolerated ibrutinib and rituximab combination regimen for patients with CLL. This study assessed the safety and efficacy of the ibrutinib/rituximab combination in 40 high-risk CLL patients, with the 18-month PFS being 78% and toxicity mainly mild-to-moderate, including gastro-intestinal, bleeding, infection and fatigue (21).

* Recent DHMC case demonstrating successful treatment of a patient with relapsed CLL and concurrent cGVHD.

* No study has thus far assessed the efficacy of ibrutinib and rituximab combination therapy for cGVHD.

1.5 Dose Rationale and Risk/Benefits

There are multiple studies supporting the tolerability and efficacy of rituximab in patients with cGVHD after allogeneic stem cell transplant, primarily patients with sclerodermatous and/or lichenoid cutaneous disease (3). Several prospective studies have used rituximab 375 mg/m2 weekly x4, with the option for a second course at 8 weeks following initial therapy, based on the adequacy of response. There are also phase 1b/2 data supporting 420 mg daily as a safe and effective dose schedule for ibrutinib in post-transplant human cGVHD (15).

A single-arm phase II study assessing the safety and activity of ibrutinib and rituximab for patients with high risk CLL supports the tolerability of this combination at respective dose schedules of 420 mg daily (indefinite) and 375 mg/m2 weekly x4, then monthly x5, with the total duration of rituximab being 6 months. However, since those patients were not allogeneic stem cell transplant recipients, a within-subject dose-escalation format will be utilized in this current study to optimize risk assessment in the post-transplant setting (see Study Summary, pages 1-2).

2 Study Objectives

Primary objective: to assess the safety and tolerability of ibrutinib/rituximab combined therapy in patients with steroid dependent or refractory GVHD.

Secondary Objectives: 1) to assess the clinical efficacy of ibrutinib/rituximab combined therapy in patients with steroid dependent or refractory GVHD.

2) To determine relevant laboratory correlates underlying clinical response, or lack thereof.

3 Study Design

3.1 General Design

This is a non-randomized, open label, within-subject study to assess safety and preliminary efficacy for combination ibrutinib and rituximab in an allogeneic stem cell transplant recipient population, using a within-subject dose-escalation format.

Duration: 6 months, depending on response to therapy and ongoing clinical status.

3.2 Primary Study Endpoints

1. Safety of combination Ibrutinib and Rituximab therapy for steroid refractory or dependent chronic GVHD, based on review of dose-limiting toxicities and results of the within-subject dose-escalation format.

3.3 Secondary Study Endpoints

1. Response rate of clinically significant GVHD based on NIH criteria (from 2014 NIH Consensus Development Project, see Attachment 1) at the following time points: six weeks, three months, and six months after initiation of therapy.

2. Laboratory correlates: The following serum biomarkers will be checked at the specified time points: pre-treatment; six weeks; three months; six months.

Elisa/Luminex	Flow Cytometry
sIL2Ra	CD146
CX3CLI	CCR5
CXCL9	
CXCL10	
CCL22	
CCL4	
ST2	FOXp3

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Patients fulfilling the following criteria will be eligible for registration onto this study:

1. Men and women ≥18 years old who are recipients of an allogeneic bone marrow, cord blood or peripheral blood stem cell transplant.
   (There will be no restrictions based upon underlying disease, donor source, degree of HLA match, intensity of pre-transplant conditioning regimen or use of prior donor lymphocyte infusion(s).)

2. Chronic GVHD that is confirmed by clinical assessment and/or biopsy.

3 . Either steroid-refractory or steroid-dependent cGVHD.

4. Karnofsky performance status ≥ 60.

4.2 Exclusion Criteria

Patients with the following will be ineligible for registration onto this study:

1. History of treatment with a tyrosine kinase inhibitor (eg, imatinib) or other moderate-to-significant CYPA4 inhibitor within 2 weeks of enrollment.

2. Renal insufficiency as follows: creatinine > 2.5 mg/dL or CrCl < 30 ml/min.

3. Hepatic insufficiency as follows: serum bilirubin >3 mg/dL or grade 3 or greater transaminitis at baseline (even if deemed due to GVHD) or cirrhosis (any Childs Pugh class).

4. History of cardiac dysrhythmias or known cardiovascular disease without formal Cardiology clearance.

5 . History of cerebro-vascular accident or intracranial hemorrhage within 6 months prior to enrollment.

6. History of non-intracranial hemorrhage and/or coagulopathy without formal Coagulation clearance.

7. Uncontrolled infections not responsive to antibiotics, anti-viral medicines, or anti-fungal medicines; or infection requiring systemic treatment that was completed ≤14 days before enrollment.

8. History of other hematologic malignancy.

9. History of human immunodeficiency virus (HIV).

10. History of active hepatitis B virus (HBV) or hepatitis C virus (HCV) without formal Infectious Disease clearance.

1 1 Patients incapable of complying with routine follow up schedule or unable to be compliant with study therapy.

12. Active or within 3 months use of prohibited medications or substances (e.g., illicit drugs).

4.3 Subject Recruitment and Screening

- Patients will be recruited from the Norris Cotton Cancer Center. Subjects will have demonstrated active cGVHD and either primary refractoriness to a trial of steroids (Methyl-prednisolone or prednisone at a dose range of 0.5-2 mg/kg/day) or intolerance to a steroid taper ***prior to*** being enrolled in this study and beginning ibrutinib and rituximab therapy.

The study will be introduced to patients during clinical appointments if they meet eligibility criteria. Informed consent, including purpose of the study, risks and benefits of participation, and rights of participants, will be discussed either at that time or separately by available study staff in an individual session.

In order to confirm and assess the extent of GVHD and meet inclusion criteria, this study may require evaluation of participants by utilizing various diagnostic measures (within one week of enrollment):

Medical history

Physical examination, including height and weight
Blood studies (baseline CBC/diff, CMP, PT/PTT)
Urinalysis, culture, urine for CrCl, as indicated
Additional studies, as clinically indicated

Studies pertinent to the organ system under consideration for the diagnosis of chronic GVHD

-biopsy proven or strong clinical suspicion of a chronic GVHD diagnosis will be required

New pregnancy test
New comprehensive infectious work-up with negative findings in the appropriate clinical setting (eg, Pulmonary cGVHD) will be required

The decision to obtain tests and procedures noted above will depend on the individual clinical scenario. The guidelines for standard cGVHD intervention will be followed.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

A subject may choose to not be in this study at any time. Leaving the study will not affect regular medical care in any way. Participants will be asked to contact study staff if they are thinking about leaving the study. In addition, a follow-up visit will be utilized to ensure the safety of any participant who chooses to discontinue enrollment on this study. Any subject withdrawing from the study prematurely due to toxicity will be evaluable for toxicity and will not be replaced. Subjects withdrawing from the study for reasons other than toxicity (eg, due to relapse of malignancy) will be replaced. All subjects remaining on the study for at least 6 weeks will be evaluable for efficacy.

Any protocol physician may stop the study at any time. In addition, participants may be asked to leave the study. Possible reasons to terminate participation may include:

1. Serious side effect (>/= grade 4 adverse event)
2. Inability to tolerate dose of medication.
3. No longer meeting criteria for this study.
4. Development of new conditions needing other treatments.
5. Emergence of new therapy or studies.
6. Progression of disease.
7. Personal choice of the subject to stop study participation.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record data (including survival data) up to the protocol-described end of the subject's follow-up period. In such an instance, the patient will be contacted by phone.

5 Study Drug

5.1 Treatment Regimen

Rituximab
*375 mg/m2 IV infusion weekly for 4 (may repeat 8 weeks after initial therapy, if suboptimal response)

Ibrutinib
*420 mg (140 mg capsule x3) by mouth daily

* May be given beyond 3-6 months (for maintenance).

5.1.1 Details of the Treatment Regimen

Initial cohort (first 5 patients accrued) will be treated as follows:
Ibrutinib 140 mg po once daily with
Rituximab 375 mg/m2 IV weekly x4 (with pre-medications and infusion procedure as per standard protocol)
Rituximab Pre-medications: Acetaminophen 650 mg po; Diphenhydramine 25 mg po/IV; Dexamethasone 20 mg IV

If no adverse events >/= nonhematologic grade 3 or >/= hematologic grade 4 are noted after 1 week at 140 mg daily, the Ibrutinib dose schedule will be increased to 280 mg daily

If no adverse events >/= nonhematologic grade 3 or >/= hematologic grade 4 are noted after 1 week at 280 mg daily, the Ibrutinib dose schedule will be increased to 420 mg daily.

If grade >/= 3 non-hematologic toxicity and/or grade 4 hematologic toxicity are noted, a dose de-escalation to the prior dose level will be made. Resumption of treatment at this dose level may begin once Ibrutinib toxicity has improved to the grade 1 (or baseline) level.

If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in any one of the 5 subjects at the 140 mg dose level, a thorough review of this AE will be undertaken, and if deemed causative, treatment for that subject will be discontinued.
If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in >2 of the 5 subjects at the 140 mg dose level, the study will be discontinued.

If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in a subject at the 280 mg dose level, the subject will then be dropped back to the prior dose level or treatment for that subject will be discontinued.
If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in a subject at the 420 mg dose level, the subject will then be dropped back to the prior dose level or treatment for that subject will be discontinued.

If therapy for 2 or more subjects at either the 280 mg or 420 mg dose level requires discontinuation, per the above parameters, no further escalation to those dose levels will be attempted for future patients.

Expansion cohort (additional 10 patients accrued) will be treated as follows:

Ibrutinib 420 mg po once daily with
Rituximab 375 mg/m2 IV weekly x4

If, based on above toxicity criteria, the Ibrutinib 420 mg daily dose schedule has been discontinued, then 280 mg po once daily will be the expansion cohort dose schedule
If, based on above toxicity criteria, the Ibrutinib 280 mg daily dose schedule has been discontinued, then 140 mg po once daily will be the expansion cohort dose schedule

Duration of therapy:
Ibrutinib -> 420 mg daily (or adjusted dose) will continue until progression of cGVHD or development of significant side effects.
Rituximab -> there is the potential for a 2nd weekly x4 Rituximab course 8 weeks after initial therapy, if no response or an incomplete response is noted.

5.1.2 Baseline Assessment and Follow-Up Determination of Therapeutic Response

The baseline and follow-up assessments of protocol participants will be done utilizing NIH criteria, as outlined in the 2014 NIH Consensus Development Project Report on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease (26) and Measuring Therapeutic Response in Chronic Graft-versus-Host Disease (27).

See Attachments:

Attachment 1: Chronic GVHD Scoring Assessment – Clinician (26)

Attachment 2: Response Determination Table for Chronic GVHD Clinical Trials (27)

The timeframe for assessments will be as follows: baseline (pre-treatment); 6 weeks, 3 months and 6 months after initiation of therapy.

The mode of assessment will include the following (to be undertaken by a limited number of team members who will do these assessments, so as to ensure consistency and minimize subjectivity).

5.2 Supportive Care Recommendations

5.2.1 Infectious prophylaxis will include fluconazole, acyclovir and both PJP and encapsulated organism prophylaxis (recommendations from DHMC SOP addressing antimicrobial prophylaxis following hematopoietic transplantation, and adapted from BBMT 2009; 15: 1143). The following are recommended:

Fluconazole 400 mg po daily
Acyclovir 800 mg po bid
TMP-SMX or alternative PJP prophylaxis
TMP-SMX or alternative encapsulated organism prophylaxis (during steroid and other GVHD therapy).

5.2.2 CMV PCR monitoring - using standard guidelines and the DHMC SOP addressing monitoring of post-transplant CMV status, it is recommended that CMV PCR be tested during active cGVHD therapy, weekly if prior to post-transplant day +100 and prior to 1 year post-transplant timeframe if previous CMV activation was documented. If after day +100 in the absence of previous CMV reactivation, then CMV PCR monitoring should be done at two-week intervals. Monitoring will continue while the patient remains on immune suppression, as clinically indicated. Treatment for a positive result will be done according to standard guidelines, as outlined in the DHMC SOP regarding pre- emptive CMV therapy.

5.2.3 EBV monitoring - using standard guidelines and the DHMC SOP addressing monitoring of post-transplant EBV status, it is recommended that EBV PCR testing after transplant be considered between days +30 to 100, as clinically indicated, based on the presence of fever, adenopathy or other signs or symptoms of infection or post-transplant lymphoproliferative disorder (PTLD). PCR monitoring should be done periodically after this timeframe, following evidence of reactivation, including during active cGVHD treatment with steroids and/or other immunosuppressive agents. Treatment for a positive result will be done according to standard guidelines as outlined in the DHMC SOP for Management of Viral Infections after Hematopoietic Stem Cell Transplant.

5.3 Method for Assigning Subjects to Treatment Groups

Open label single arm study.

5.4 Preparation and Administration of Study Drug

Ibrutinib will be mailed to a participant's address.
Rituximab will be administered weekly in the infusion suite at the Hematology Outpatient Clinic, Norris Cotton Cancer Center (NCCC), Dartmouth-Hitchcock Medical Center (DHMC).
Rituximab will be prepared and dispensed through the Investigational Pharmacy, DHMC.

For more information:
Investigational Pharmacy, NCCC, DHMC
Contact phone number: 603-650-7890

5.5 Subject Compliance Monitoring

Each study subject will be assessed weekly from initiation of the study. A drug administration log for Ibrutinib will be utilized (including date, time and dose taken) and maintained, and patients will be queried about regular administration of Ibrunitib, as recorded in this log. Rituximab administration will be monitored through the electronic medical record (EMR) system.

5.6 Prior and Concomitant Therapy

5.6.1 Restricted and Allowable Concomitant Medications

1. History of treatment with a tyrosine kinase inhibitor (eg, imatinib) or other significant CYPA4 inhibitor within 2 weeks of enrollment is NOT allowed.
2. History of standard-dose Rituximab therapy within 6 months of study enrollment is NOT allowed.
3. Pre-transplant use of Ibrutinib for indications other than cGVHD (eg, lymphoma therapy) IS permitted.
4. Concomitant use of corticosteroids for cGVHD after transplant, prior to and during this study, IS permitted and anticipated (with no dose change allowed for a period of at least 14 days prior to enrollment).
5. Concomitant use of other immunosuppressive therapies prior to and during this study IS also permitted (with no dose change allowed for a period of at least 14 days prior to enrollment).
6. Doses of concomitant steroids and other immunosuppressants may be tapered during the study, as clinically feasible.
7. Study subjects may receive prophylactic antimicrobials, based on post-transplant status.

5.7 Treatment Discontinuation and Subsequent Therapy

If there is progression of disease on evaluation at 6 weeks, 3 months or 6 months, the patient will be considered for other secondary therapies, depending on the severity of the cGVHD and his/her overall clinical status. Other commonly used secondary therapies include Tacrolimus/sirolimus, Mycophenolate mofetil, extracorporeal photophoresis (ECP), JAK1/2 inhibitors and other monoclonal antibodies. Pulsed steroid therapy may also need to be considered in an effort to control the degree of GVHD as a purely temporary measure (ie, "bridge" to secondary therapy).

5.8 Packaging

Ibrutinib will be prescribed via patient's preferred pharmacy, as per the appropriate dose schedule.

5.9 Blinding of Study Drug

N/A

5.10 Receiving, Storage, Dispensing and Return

5.10.1 Receipt of Drug Supplies

Rituximab will be prescribed and dispensed at the infusion clinic at Dartmouth-Hitchcock Norris Cancer Center.
Ibrutinib will be prescribed and filled at patient's preferred pharmacy.

5.10.2 Return or Destruction of Ibrutinib

At the completion of the study, there will be a final reconciliation of drug received, consumed, and remaining, since our pharmacy may not be shipping drug. Each subject will be asked to bring remaining medications back to our clinic or to dispose of them.

6 Study Procedures

Visit 1 (prior to or at the start of therapy)

Initial visit

1. Initiation of therapy as described above
   A subject will be reviewed for:
   In order to confirm and assess the extent of GVHD and meet inclusion criteria, this study may require evaluation of participants by utilizing various diagnostic measures (within one week of enrollment):
   Medical history
   Physical examination, including ht and weight

2. The subject will sign an informed consent
3. Blood Studies
   -baseline CBC/diff, CMP, PT/PTT

   -biomarker assays will be drawn

Elisa/Luminex	Flow Cytometry
sIL2Ra	CD146
CX3CLI	CCR5
CXCL9	
CXCL10	
CCL22	
CCL4	
ST2	FOXp3

4. Urine studies
   -urinalysis, culture
   -urine for CrCl, as indicated
5. Additional studies, as clinically indicated
6. Studies pertinent to the organ system under consideration for the diagnosis of cGVHD

   -biopsy proven or strong clinical suspicion of a cGVHD diagnosis will be required

7. New pregnancy test
8. New comprehensive infectious work-up with negative findings in the appropriate clinical setting (eg, Pulmonary cGVHD) will be required

The decision to obtain tests and procedures noted above will depend on the individual clinical scenario.

The guidelines for standard cGVHD intervention will be followed

1. Establishment of baseline
   The degree of cGVHD will be assessed (baseline) prior to initiation of protocol treatment by using chronic graft-versus-host disease assessment and scoring criteria, as referenced in the NIH Consensus Development Project (see Attachments).

2. Treatment initiation
   Treatment will start once the subject has the ibrutinib pills, on the first day of Rituximab.

Visit 2 at 1-2 weeks from initiation of the combination therapy (sooner as clinically indicated)

i. A subject will be assessed for:
   a. Medical history
   b. Physical examination, including height and weight
   c. Blood and urine tests, as clinically indicated
   d. Additional organ function, as clinically indicated

ii. Patients will be followed at no longer than two-week intervals over the first six weeks on trial, more frequently as clinically indicated. Note: participants in the dose escalation portion of the protocol will be followed via weekly visits, more frequently as indicated.

Visit 3 at 2-4 weeks from initiation of the combination therapy (sooner as clinically indicated)

i. A subject will be assessed for:
   a. Medical history
   b. Physical examination, including height and weight
   c. Blood and urine tests, as clinically indicated
   d. Additional organ function, as clinically indicated

ii. Patients will be followed at no longer than two-week intervals over the first six weeks on trial, more frequently as clinically indicated. Note: participants in the dose escalation portion of the protocol will be followed via weekly visits, more frequently as indicated.

Visit 4 at 4-6 weeks from initiation of the combination therapy (sooner as clinically indicated)

i. A subject will be assessed for:
   a. Medical history
   b. Physical examination, including height and weight
   c. Blood and urine tests, as clinically indicated
   d. Additional organ function, as clinically indicated

ii. Patients will be followed at no longer than two-week intervals over the first six weeks on trial, more frequently as clinically indicated. Note: participants in the dose escalation portion of the protocol will be followed via weekly visits, more frequently as indicated.

2. Assessment
   a. **At the 6 week (+/- 3 days) follow up visit, the degree of cGvHD will be formally re-assessed**, again using NIH assessment and scoring forms (Attachment 1)
   b. After the 6 week follow up visit, patients may be followed at 2-4 week intervals, if clinically appropriate
   c. Subjects may undergo repeat Rituximab weekly x4 therapy at 8 weeks after the initial therapy, depending on their prior clinical response
   d. Formal re-assessment of cGvHD response via NIH criteria (Attachment 1 forms) will again be undertaken at the 3 month (+/- 7 days) and 6 month (+/- 7 days) follow up visits, to determine updated cGvHD status
   e. If the subject shows progression of cGvHD, alternative treatment options will be discussed, including the appropriateness for removal from the study
   f. If the subject shows improvement (at least a partial response, by NIH response criteria), he/she will be continued on Ibrutinib for maintenance
   g. After 6 months, subjects will be followed for survival only.

Subsequent visits between the 6 week post-initiation period and 6 month follow-up timeframe will be at 2-4 week intervals, more frequently if clinically indicated (as outlined above). Serum biomarkers will be drawn at the 6 week, 3 month and 6 month post-initiation visits.

7 Statistical Plan

7.1 Statistical Methods

GVHD response rates based on the GVHD Global Severity Score and Clinical Assessment (Attachment 1) at 6 weeks, 3 months and 6 months will be assessed using exact binomial methods combining the initial dose escalation and expansion cohorts. With the expansion cohort after the safety dose escalation phase, a total of 15 patients will be available for evaluation. An exact test for proportions with a null hypothesis of a 15% response rate, an alternative hypothesis of a 50% response rate, and a one-sided significance level of 0.10, would have a power of 85% using 15 subjects, including a Bonferroni correction for looking at the 6 week, 3 month and 6 month response rates. This test rejects the null hypothesis if 6 out of 15 subjects respond. If only the 10 subjects from the expansion cohort are used, the null is rejected if 4 out of 10 respond, and the power is reduced to 0.83. Calculations were done in the PASS 2008 package.

Two-sample t-tests for continuous data and Fisher's exact test for binary data will be used to compare responders and non-responders for the purpose of identifying independent *biomarker* correlates of treatment response. The power and precision of these comparisons will depend on the number of responders and non-responders compared.

7.2 Subject Population(s) for Analysis

Any subject withdrawing from the study prematurely due to toxicity will be evaluable for toxicity and will not be replaced. Subjects withdrawing from the study for reasons other than toxicity (eg, due to relapse of malignancy) will be replaced. All subjects remaining on the study for at least 6 weeks will be evaluable for efficacy.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a dgree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly

related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. At a minimum, serious adverse events (SAEs) that must be reported to the principal investigator (PI), or the covering BMT Attending on the Transplant Service, are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
  (if multi-center study)
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the PI

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the PI by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

John M. Hill, Jr, MD
Section of Hematology/Oncology
Norris Cotton Cancer Center
Dartmouth-Hitchcock Medical Center
1 Medical Center Drive
Lebanon, NH, 03756
603-650-4628

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the Dartmouth IRB

This section describes the requirements for safety reporting by investigators who are Dartmouth faculty, affiliated with a Dartmouth research site, or otherwise responsible for safety reporting to the Dartmouth IRB. The Dartmouth College IRB (CPHS) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Dartmouth IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Dartmouth IRB requires researchers to submit reports of the following problems, once the investigator becomes aware of the event:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.

2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Unanticipated Problem Involving Risks to Subjects or Others (UPRs) Any incident, experience or outcome that meets ALL 3 of the following criteria:

1.Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

2. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPRs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects (see below). Please note that adverse events (as defined below) are reportable to the IRB as UPRs only if they meet all 3 criteria listed above.

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Dartmouth IRB via the RAPPORT format. using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with

information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Dartmouth IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the PI to modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Investigator reporting: Notifying a another IRB

N/A

8.3.4 Sponsor reporting: Notifying the FDA

- **Within 7 calendar days**
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening, and

- **Within 15 calendar days**
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Reporting Process
Adverse events may be submitted on FDA Form 3500A or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3.

8.4 Unblinding Procedures

N/A

8.5 Stopping Rules

Within-Subject Dose-Escalation Study stopping rules-

Initial cohort (first 5 patients accrued) will be treated as follows:
Ibrutinib 140 mg po once daily with
Rituximab 375 mg/m2 IV weekly x4 (with pre-medications and infusion procedure as per standard protocol)
Rituximab Pre-medications: Acetaminophen 650 mg po; Diphenhydramine 25 mg po/IV; Dexamethasone 20 mg IV

If no adverse events >/= nonhematologic grade 3 or >/= hematologic grade 4 are noted after 1 week at 140 mg daily, the Ibrutinib dose schedule will be increased to 280 mg daily

If no adverse events >/= nonhematologic grade 3 or >/= hematologic grade 4 are noted after 1 week at 280 mg daily, the Ibrutinib dose schedule will be increased to 420 mg daily.

If grade >/= 3 non-hematologic toxicity and/or grade 4 hematologic toxicity are noted, a dose de-escalation to the prior dose level will be made. Resumption of treatment at this dose level may begin once Ibrutinib toxicity has improved to the grade 1 (or baseline) level.

If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in any one of the 5 subjects at the 140 mg dose level, a thorough review of this AE will be undertaken, and if deemed causative, treatment for that subject will be discontinued.
If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in >2 of the 5 subjects at the 140 mg dose level, the study will be discontinued.

If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in a subject at the 280 mg dose level, the subject will then be dropped back to the prior dose level or treatment for that subject will be discontinued.
If a >/= nonhematologic grade 3 or >=hematologic grade 4 adverse event is noted in a subject at the 420 mg dose level, the subject will then be dropped back to the prior dose level or treatment for that subject will be discontinued.

If therapy for 2 or more subjects at either the 280 mg or 420 mg dose level requires discontinuation, per the above parameters, no further escalation to those dose levels will be attempted for future patients.

Expansion cohort (additional 10 patients accrued) will be treated as follows:

Ibrutinib 420 mg po once daily with
Rituximab 375 mg/m2 IV weekly x4

If, based on above toxicity criteria, the Ibrutinib 420 mg daily dose schedule has been discontinued, then 280 mg po once daily will be the expansion cohort dose schedule
If, based on above toxicity criteria, the Ibrutinib 280 mg daily dose schedule has been discontinued, then 140 mg po once daily will be the expansion cohort dose schedule

Duration of therapy:
Ibrutinib -> 420 mg daily (or adjusted dose) will continue until progression of cGVHD or development of significant side effects.
Rituximab -> there is the potential for a 2nd weekly x4 Rituximab course 8 weeks after initial therapy, if no response or an incomplete response is noted.
If, based on above toxicity criteria, the Ibrutinib 280 mg daily dose schedule has been discontinued, then 140 mg po once daily will be the expansion cohort dose schedule

Duration of therapy:

Ibrutinib -> 420 mg daily (or adjusted dose) will continue until progression of cGVHD or development of significant side effects.
Rituximab -> there is the potential for a 2nd weekly x4 Rituximab course 8 weeks after initial therapy, if no response or an incomplete response is noted.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

10 Study Monitoring, Auditing, and Inspecting

10.1 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10.2). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10.2 Safety and Data Monitoring

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the CPHS (Dartmouth IRB) office.

10.3 On-Site Monitoring

Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC Data and Safety Monitoring Plan. Internal monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center Clinical Trials Office who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. Study records will be reviewed and directly compared to source documents, and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

10.4 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and Dartmouth compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB- approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This research protocol is not currently sponsored, though funding is being requested in the form of a 2018 NCCC Pilot (PROUTY) Grant.

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14 Attachments

Attachment 1: Chronic GVHD Assessment (26)
Attachment 2: Response Determination Table for Chronic GVHD Clinical Trials (27)

CHRONIC GVHD ASSESSMENT

Patient:_____ Date of Visit:_____

MRN:_____ Completed by:_____

Form adapted from Jagasia, MH, BBMT 21 (2015) 389-401.

Karnofsky Performance Score	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
	☐ Asymptomatic and fully active (KPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (KPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (KPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (KPS <60%)

Skin†	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
Score by % BSA **Check all that apply:** ☐ Maculopapular rash/Erythema ☐ Lichen-planus features ☐ Sclerotic features ☐ Papulosquamous lesions or icthyosis ☐ Keratosis pilaris-like GVHD	☐	☐ No BSA Involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
Cutaneous features score†	☐	☐ No Sclerotic Features		☐ Superficial sclerotic features, "not hidebound"	**Check all that apply** ☐ Deep sclerotic features ☐ "Hidebound", impaired mobility ☐ Ulceration
Other skin features not scored by BSA **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair or nail involvement		†Skin scoring should use both percentage of BSA involved by disease signs and cutaneous features score. When a discrepancy exists between the percentage o total body surface area score and the skin features score, OR if superficial sclerotic features are present (score 2), but there is impaired mobility or ulceration (score 3), the higher level should be used for final skin scoring.			
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):*_____					

Mouth	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
Lichen planus-like features present? ☐ Yes ☐ No	☐	☐ 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
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):*_____					

Eyes	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
Keratoconjuntivitis sicca (KCS) confirmed by Ophthalmologist? ☐ Yes ☐ No ☐ Not examined	☐	☐ No Symptoms	☐ Mild dry eye not affecting ADL; requiring lubricant drops ≤3 x per day	☐ Moderate dry eye sxs partially affecting ADL (requiring lubricant eye drops >3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (eyeware to relieve pain) **OR** unable to work because of ocular sxs **OR** loss of vision due to KCS
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):*_____					

Liver	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
	☐	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 x ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):*_____					

Lungs	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
Symptom score*	☐	☐ No Symptoms	☐ Mild symptoms (SOB after one flight of steps)	☐ Moderate symptoms (SOB after walking on flat ground)	☐ Severe symptoms (SOB at rest; requiring oxygen)
FEV1 score* ☐ PFT not Done	☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
** Lung scoring should be performed using both the symptom and FEV1 scores when possible. FEV1 should be used in the final lung scoring where there is a discrepancy between symptoms and FEV1 scores.*					
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):*_____					

CHRONIC GVHD ASSESSMENT

Patient:_____ Date of Visit:_____

MRN:_____ Completed by:_____

Form adapted from Jagasia, MH, BBMT 21 (2015) 389-401.

GI Tract	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
Check all that apply: ☐ Esophageal web/proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss >5% within 3 months ☐ Failure to thrive	☐	☐ No Symptoms	☐ Symptoms without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss within 3 months (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with >15% weight loss within 3 months, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):* _____					

Genital Tract [$]	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐	☐ No signs	☐ Mild signs[‡] and females with or without discomfort on exam	☐ Moderate signs[‡] and may have symptoms with discomfort on exam	☐ Severe signs[‡] with or without symptoms
[$] *To be completed by a specialist or trained medical providers.*					
☐ *Abnormality present, but explained entirely by documented non-GVHD cause (specify):* _____					

JOINTS AND FACIA NEXT PAGE

Other GVHD Manifestations

☐ **Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)**

☐ Ascites (serositis)_____	☐ Myasthenia Gravis_____	☐ Eosinophilia > 500/µl_____
☐ Pericardial Effusion_____	☐ Peripheral Neuropathy_____	☐ Platelets <100,000/µl _____
☐ Pleural Effusion(s)_____	☐ Polymyositis_____	☐
☐ Nephrotic syndrome_____	☐ Weight loss >5% without GI symptoms _____	☐

Global Severity Score – Please check one.

	Mild	1 or 2 organs involved with no more than score 1 **PLUS** lung score 0
	Moderate	3 or more organs involved with no more than score 1 **OR** At least 1 organ with a score of 2 (not lung) **OR** Lung score 1
	Severe	At least one organ with a score of 3 **OR** Lung score 2 or 3

- In Skin: higher of the 2 scores is used for global severity.
- In Lung: FEV1 is used instead of clinical score for global severity.
- If the entire abnormality in an organ is noted to be unequivocally explain by a non-GVHD cause, that organ is not included in the global severity score.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), the scored organ will be used for calculation of the global severity score, regardless of the contributing causes. (No downgrading of the organ severity score.)

CLINICIAN ASSESSMENT - Since the last evaluation, this patient's cGVHD is:

CHRONIC GVHD ASSESSMENT

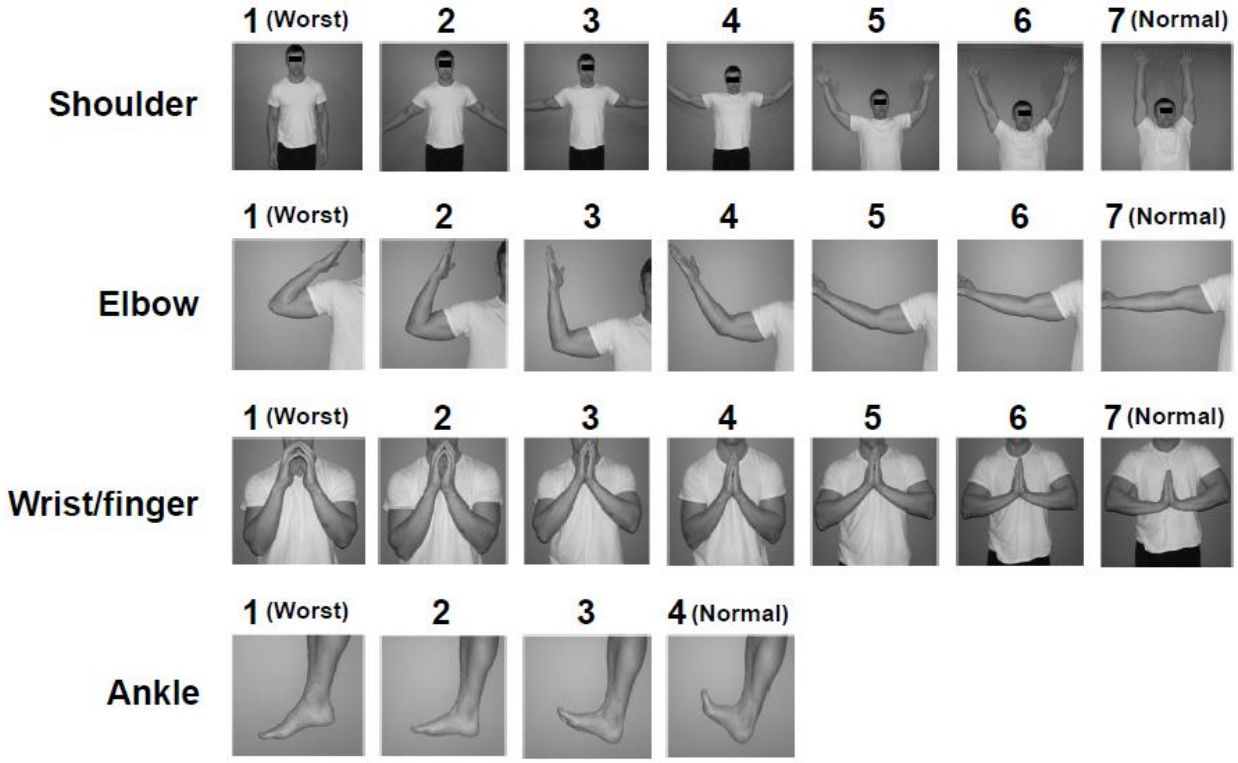
Patient:_____ Date of Visit:_____

MRN:_____ Completed by:_____

Form adapted from Jagasia, MH, BBMT 21 (2015) 389-401.

+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
Since the last evaluation, have immunosuppression and/or steroid therapy dosages been changed?						
Comments:						

JOINTS AND FASCIA ☐	**None**	**SCORE 0**	**SCORE 1**	**SCORE 2**	**SCORE 3**
P-ROM score *(see below)* Shoulder (1-7):_____ Elbow (1-7): _____ Wrist/finger (1-7):_____ Ankle (1-4):_____	☐	☐ 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 thought 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.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____					



Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale