PROTOCOL

TITLE:	Phase II Trial Evaluating the Safety and Efficacy of Combined CD20- and BTK-Targeted B cell Depleting Therapy with Rituximab and Ibrutinib in the Primary Treatment of Chronic Graft-Versus-Host Disease
PROTOCOL NUMBER:	**NSH 1219**
STUDY DRUG:	Ibrutinib (PCI-32765)
INVESTIGATOR:	Scott R. Solomon, MD, Principal Investigator Melhem Solh, MD, Associate Investigator Asad Bashey, MD, Associate Investigator Lawrence E. Morris, MD, Associate Investigator H. Kent Holland, MD, Associate Investigator Lizamarie Bachier-Rodriguez, MD, Associate Investigator
SPONSOR:	Pharmacyclics
DATE FINAL:	8/12/2022 version 4.0

Confidentiality Statement

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF IN-TEXT TABLES AND FIGURES

Tables

SYNOPSIS

Study Title:	Phase II Trial Evaluating the Safety and Efficacy of Combined CD20- and BTK-Targeted B cell Depleting Therapy with Rituximab and Ibrutinib in the Primary Treatment of Chronic Graft-Versus-Host Disease
Protocol Number:	NSH 1219
Study Phase:	II
Study Duration:	Estimated to be 3 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. 70mg hard gelatin capsules will also be provided for patients requiring dose reduction. Rituximab will be utilized at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials.
Objectives:	**Primary Objective:** Efficacy The primary endpoint is to estimate the proportion of patients that are alive and off systemic immunosuppression therapies (IST) at 12 months following initiation of treatment. To meet this endpoint, patients need to remain off IST (e.g. sirolimus, tacrolimus, steroids, etc). for at least 8 weeks. The use of rituximab and ibrutinib are not considered IST for this endpoint. **Secondary Objectives**: *Efficacy* To estimate: 1. Chronic GVHD response (CR + PR, both individual organ response and overall response, according to 2014 NIH Response Criteria Working Group Report) – See Appendix G. 2. Cumulative steroid exposure (total mg methylprednisolone or equivalent). 3. Time to discontinuation of systemic immunosuppression, defined as the date that all systemic IST such as sirolimus, tacrolimus, steroids, etc. have been discontinued after resolution of all reversible manifestations of cGVHD. The use of rituximab and ibrutinib are not considered IST for this endpoint. Discontinuation of immunosuppressive medications for the purpose of inducing an anti-tumor response after the development of recurrent or secondary malignancy will not be counted as successful discontinuation of IST.

	4. Failure-free survival (defined as being alive without the requirement for second-line cGVHD therapy). See section 6.3 for definition of second-line cGVHD therapy. 5. Non-relapse and overall mortality *Safety* To estimate: 1. Incidence of grade ≥3 adverse events, possibly or probably related to either ibrutinib and/or rituximab.
Study Design:	This is an open-label, Phase 2 study designed to evaluate the safety and efficacy of ibrutinib and rituximab as primary treatment of cGVHD.
Population:	35 patients
Centers:	One
Inclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.*	1. First episode of systemic immunosuppression-requiring cGVHD, defined as classic or overlap cGVHD by the NIH consensus criteria. 2. Previously untreated cGVHD, defined by having received <10 days of corticosteroids or alternative systemic immunosuppressive agent started specifically for a new diagnosis of cGVHD. 3. Age ≥18 years 4. Karnofsky performance status ≥70% 5. Patient willing and able to provide informed consent 6. Adequate hematologic function defined as: • Absolute neutrophil count (ANC) ≥1.0 x 109/L and off growth factor support for 7 days. • Platelet count ≥30 x 109/L and no platelet transfusions for 7 days. 7. Adequate hepatic function as defined by: • Total bilirubin of ≤ 1.5 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome) or • Total bilirubin of > 1.5 x ULN to 3.0 x ULN if due to cGVHD. 8. Women of childbearing potential and men who are sexually active with a woman of childbearing potential must be practicing a

	highly effective, preferably user-independent method of birth control (failure rate of <1% per year when used consistently and correctly) during treatment and for up to 90 days after the last dose of ibrutinib, consistent with local regulations regarding the use of birth control methods for subject participating in clinical studies.
Exclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.*	Active uncontrolled infection History of HIV infection Active HBV or HCV infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded Inability to tolerate oral medications. Progressive or recurrent malignancy following allogeneic transplant 1. Known severe or life-threatening hypersensitivity to ibrutinib or rituximab Uncontrolled hypertension Known bleeding disorder Major surgery within 4 weeks of first dose of study drug History of stroke or intracranial hemorrhage within 6 months prior to enrollment Unable to swallow capsules Subjects with chronic liver disease and hepatic impairment meeting Child-Pugh Class C (Appendix D). Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug. Unwilling or unable to participate in all required study evaluations and procedures Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) Exposure to BTK inhibitor following transplant. Prior exposure to BTK inhibitor pre-transplant is allowed. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v5.0), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia

	Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to study entry Subject who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP3A inhibitor (Appendix C), with the exception of voriconazole or posaconazole which are permitted on study with appropriate dose modification. Subjects who have received prior treatment with extracorporeal photopheresis (ECP) for cGVHD.
Study Treatment:	1. Ibrutinib 420mg PO QDAY (28-day cycles) for a total of 12 cycles (dose adjustment required in patient with hepatic impairment or those receiving concomitant voriconazole or posaconazole or other strong CyP 3A4 inhibitor). 2. Rituximab 375mg/m2 IV weekly x 4 weeks (to be started on study day 7 ± 3 days) , then 375mg/m2 IV q3months x 4 doses (months 4, 7, 10, 13).
Concomitant Therapy:	1. **Sirolimus** (target level 4-10 ng/mL) – patients currently receiving a calcineurin inhibitor (tacrolimus or cyclosporine) and/or mycophenolate mofetil for GVHD prophylaxis will be converted to sirolimus per institutional guidelines. In the case of contraindication or intolerance to sirolimus, another systemic immunosuppressive (IS) drug (i.e. tacrolimus or cyclosporine) may be substituted at the discretion of the treating investigator. 2. Short-course corticosteroids may be used, if necessary, for more rapid symptom control (≤1mg/kg Medrol, with planned taper to be completed no longer than 4 weeks).
Statistical Methods/ Data Analysis: *Refer to Section 10 for additional details.*	This is a phase II trial evaluating the safety and efficacy of ibrutinib and rituximab as primary treatment of cGVHD. We plan to enroll 35 patients on this study. Patients will be formally monitored for 12 months to evaluate for outcome and safety endpoints. All patients, responders and treatment failures, will be followed for a period of one year. The primary outcome measure will be the proportion of patients that are alive and off systemic immunosuppression therapies (IST) at 12 months following initiation of treatment.. Secondary outcome measures will be cGVHD response, cumulative steroid exposure, time to discontinuation of systemic immunosuppression, requirement for second-line GVHD therapy, non-relapse and overall mortality, and safety.

Sample Size Determination	The study will be powered to detect a clinically meaningful improvement in treatment success at 12 months post-treatment, defined as being alive and off all systemic immunosuppression. Experience from our phase II study of rituximab in the upfront treatment of cGVHD found that 56% of patients were alive and free of systemic immunosuppression at 12 months post treatment. It is hoped that under this protocol, this rate will be at least 75%. Thus we statistically formalize this study by testing the null hypothesis that p, the treatment success rate is 0.55 or less versus the alternative hypothesis that p is at least 0.75 A sample size of 35 patients gives 80% power with an alpha=0.05, using the formula for a one sample binomial (one-sided) test of a proportion.

ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CrCl	creatinine clearance
CRF	case report form (paper or electronic as appropriate for this study)
CT	computed tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IAC	Interim Analysis Committee
IB	Investigator's Brochure
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
IEC	Independent Ethics Committee
INR	International normal ratio
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization

MTD	maximum tolerated dose
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
P-gp	P-glycoprotein
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome(s)
aPTT	activated partial thromboplastin time
PT	prothrombin time
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SCARs	severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal

1. BACKGROUND

1.1. Chronic GVHD

1.1.1. Chronic GVHD Background

Chronic GVHD (cGVHD) is the most important cause of late morbidity and mortality after allogeneic stem cell transplantation, occurring in up to 60% of long-term survivors(Higman and Vogelsang 2004; Schmitz, Eapen et al. 2006; Bhatia, Francisco et al. 2007; Abou-Mourad, Lau et al. 2010) With the increasing number of allogeneic transplants using peripheral blood stem cells (PBSCs), mismatched and unrelated donors and the increasing age of transplant recipients, cGVHD will continue to be a serious challenge following allogeneic transplantation. Chronic GVHD requires therapy for many months and often years(Vogelsang 2001; Koc, Leisenring et al. 2002) and is the cause of death in up to one third of all long-term survivors after transplantation for leukemia(Ratanatharathorn, Ayash et al. 2001). In addition to the effects on mortality, moderate-to-severe cGVHD markedly reduces quality of life (Sutherland, Fyles et al. 1997; Chiodi, Spinelli et al. 2000; Kiss, Abdolell et al. 2002; Fraser, Bhatia et al. 2006). Despite its prevalence and importance, an effective treatment strategy for cGVHD has been difficult to achieve due to the heterogeneous nature of the problem and the lack of clear evidence for the majority of treatment options.

Standard immunosuppressive therapy (IST) for cGVHD using glucocorticoids with a calcineurin inhibitor has not changed in several decades even though most patients respond inadequately. If the total time to discontinue all systemic IST is measured as a surrogate for allograft tolerance, it takes a median of 2-3 years from the onset of cGVHD therapy depending on stem cell source and other factors(Stewart, Storer et al. 2004). Unfortunately, despite the relationship between cGVHD and reduced relapse risk, the prolonged duration of cGVHD makes it the leading cause of infection, morbidity, and late treatment-related deaths (Sullivan, Witherspoon et al. 1988; Wingard, Piantadosi et al. 1989; Syrjala, Chapko et al. 1993; Duell, van Lint et al. 1997; Sutherland, Fyles et al. 1997; Socie, Stone et al. 1999). Furthermore, the widespread and sometimes irreversible manifestations of cGVHD may negatively impact quality of life even after tolerance is achieved. New approaches to the treatment of cGVHD are needed to achieve early control of cGVHD manifestations and facilitate tolerance.

The morbidity and mortality associated with chronic GVHD is caused not only by cGVHD-associated immunodeficiency and organ dysfunction, but also by the immunosuppressive medications used treat it. Long-term glucocorticoid treatment impairs immune function and can therefore increase the risk of opportunistic infections. Other glucocorticoid therapy-related complications include avascular necrosis, glucose intolerance, hypertension, weight gain, changes in body habitus, cataracts, osteoporosis, myopathy, and disturbances of mood and sleep. Attempts to improve upon corticosteroids and a calcineurin inhibitor as initial therapy for cGVHD have been unsuccessful.

1.1.2. B cell depleting therapy for the treatment of cGVHD utilizing Rituximab, an anti-CD20 monoclonal antibody.

Failure to improve cGVHD therapy may be partly attributed to an incomplete understanding of the pathophysiology of cGVHD. Chronic GVHD was traditionally thought to be mediated by donor-derived, alloreactive T cells, although studies have not consistently shown a favorable impact of T-cell depletion on cGVHD (Champlin, Passweg et al. 2000; Pavletic, Carter et al. 2005). There is now mounting evidence implicating B cells in the pathophysiology of chronic GVHD. Antibodies to Y chromosome–encoded minor histocompatibility antigens are generated after sex-mismatched allogeneic transplantation (Miklos, Kim et al. 2004) and the presence of these antibodies has been correlated with the occurrence of cGVHD (Miklos, Kim et al. 2005). The findings led to the hypothesis that an anti-B-cell monoclonal antibody may be an effective therapy for cGVHD. Clinical studies have subsequently confirmed the efficacy of rituximab in steroid-refractory cGVHD with objective responses noted in 50-70% of patients, allowing tapering, and in some cases withdrawal of immunosuppressant therapy (Ratanatharathorn, Ayash et al. 2003; Canninga-van Dijk, van der Straaten et al. 2004; Cutler, Miklos et al. 2006; Okamoto, Okano et al. 2006; Zaja, Bacigalupo et al. 2007). Early evidence also suggests a role for rituximab during the early post-transplant period for prevention of cGVHD (Cutler, Kim et al. 2013; Sauter, Barker et al. 2014).

In a completed phase II trial, our group tested rituximab in the upfront treatment of patients with cGVHD, and the results of this study were recently published in Biology of Blood and Marrow Transplantation: *Corticosteroid-Free Primary Treatment of Chronic Extensive Graft-versus-Host Disease Incorporating Rituximab* (Solomon, Sizemore et al. 2015). We hypothesized that the early use of rituximab would allow for more rapid discontinuation of immunosuppression while obviating the need for long courses of systemic corticosteroids, which would translate into reduced treatment-related morbidity and mortality associated with cGVHD.

Twenty-five patients (median age 56 years [range 29 – 77]) with extensive cGVHD were enrolled on a prospective phase II trial at our institution. Enrollment was limited to patients with first onset extensive cGVHD requiring systemic immunosuppression and without residual or concurrent acute GVHD. All patients received Rituximab 375mg/m2 x 4 weekly doses, then one dose q3months x 4 doses. Twenty-two of 25 patients (88%) responded to treatment. Of the 22 responding patients, median time to maximum response was 161 days (range 35 – 300 days) with maximum response being complete in 21/22 patients and partial in 1 patient. Corticosteroids were used sparingly or not at all in the majority of patients. Immunosuppression was discontinued in 17 of 22 evaluable patients (77%) with median time to discontinuation of 300 days (range 138 – 488 days). With a median f/u of 27 months, estimated 2-year overall survival is 82%. Following immunosuppression discontinuation, cGVHD did recur in 7 patients after a median of 166 days (range 21-393 days), requiring reinstitution of systemic immunosuppression. When patients were analyzed 12 months following treatment initiation, 56% were alive, free of active GVHD, and off all systemic immunosuppression.

1.1.3. Targeting the Bruton's tyrosine kinase (BTK) and IL-2 inducible T-cell kinase (ITK) pathways with Ibrutinib for the treatment of cGVHD

BTK and ITK are enzymes responsible for the phosphorylation and activation of downstream effectors in the B-cell receptor (BCR) signaling and T cell receptor (TCR) signaling pathways, respectively. Murine studies suggest that both BTK and ITK are required for the development of cGVHD and that ibrutinib treatment can ameliorate cGVHD severity (Dubovsky, Flynn et al. 2014). Similar to murine studies, CD4 T cells and B cells appear essential in humans for the induction of cGVHD (Cooke, Luznik et al. 2017). Ibrutinib is a potent inhibitor of both BTK and ITK that impairs both B-cell and T-cell function. In response to these preclinical findings, ibrutinib was studied in a phase II trial in 42 steroid-refractory cGVHD patients (Miklos, Cutler et al. 2017). This study demonstrated an overall response rate of 67%, with a durable response at ≥20 weeks and ≥32 weeks of 71% and 48% respectively. Five of the 28 responders discontinued corticosteroids entirely. Based on the results of this trial, ibrutinib received FDA approval in August 2017 for the treatment of adult patients with cGVHD following the failure of 1 or more lines of systemic therapy.

1.1.4. Rationale for combining Rituximab with Ibrutinib for the treatment of cGVHD

The clinical efficacy of rituximab has provided compelling evidence that B cells play an important role in human cGVHD, but the mechanisms that promote and sustain B-cell involvement remain poorly studied. The durability of clinical responses to rituximab in patients with cGVHD remains unclear (Cutler, Miklos et al. 2006; Zaja, Bacigalupo et al. 2007). In patients with autoimmune diseases, initial clinical responses to rituximab are inevitably followed by clinical relapse in the majority of patients. Thus, although clinical responses to rituximab are compelling, incomplete elimination of potentially autoreactive B cells may lead to cGVHD recurrence. Therefore, there is a rationale for combining CD20-targenting antibodies with B cell signaling inhibitors in the hopes of improving the efficacy and durability of the response.

The combination of Rituximab and Ibrutinib has been used successfully to treat patients with chronic lymphocytic leukemia (Burger, Keating et al. 2014) and mantle cell lymphoma (Wang, Lee et al. 2016), demonstrating safety for this combination.

1.2. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in over 80 countries, including the United States (US) and European Union (EU), for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia (WM), patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and adult patients with cGVHD after failure of 1 or more

lines of systemic therapy. For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, in vitro and in vivo preclinical activity, pharmacokinetics, and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1. Risks

1.2.1.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 6.2.3. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. See Section 6.2.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures. Patients with congenital bleeding diathesis have not been studied.

1.2.1.2. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.2.1.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

1.2.1.4. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed (see Section 5.1.1.4).

1.2.1.5. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.1.1.4).

1.2.1.6. Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.2.1.7. Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

1.2.1.8. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.1.1.4).

1.2.1.9. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases

of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.2.1.10. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3. Study Rationale

Despite the importance of cGVHD as a major cause of morbidity and mortality following allogeneic transplant, therapies for this common post-transplant complication remain inadequate. Standard initial therapy of cGVHD is based on prolonged use of corticosteroids and a calcineurin inhibitor and has not changed for over 3 decades, despite limited efficacy and long-term toxicity. New treatments are clearly needed.

There is now considerable evidence from animal and human studies implicating B cells as an important player in the pathophysiology of cGVHD. This is best exemplified by the efficacy of both Rituximab (anti-CD20 B cell depleting antibody) and Ibrutinib (BTK inhibitor effecting B cell signaling) in the treatment of steroid-refractory cGVHD.

Given the effectiveness and favorable safety profile of both Rituximab and Ibrutinib in the steroid-refractory cGVHD patients, it is natural to study these agents in the upfront cGVHD setting. Rituximab has been studied in the upfront treatment of cGVHD in two recently published phase II studies, showing efficacy as a steroid-sparing agent with relatively low toxicity. We have previously shown that upfront Rituximab therapy can reduce the time to discontinuation of systemic immunosuppression, while limiting a patient's cumulative exposure to corticosteroids.

We hypothesize that combined CD20- and BTK-targeted B cell depleting therapy (BCDT) with Rituximab and Ibrutinib in the primary treatment of extensive cGVHD will produce quicker, better and more durable responses and improve outcomes in patients with cGVHD. The combination of Rituximab and Ibrutinib has been used successfully to treat patients with chronic lymphocytic leukemia (Burger, Keating et al. 2014) and mantle cell lymphoma (Wang, Lee et al. 2016), demonstrating safety for this combination.

2. STUDY OBJECTIVE

2.1. Primary Objective

The primary objective is to evaluate the efficacy of the combination of rituximab and ibrutinib versus the historical experience with rituximab alone in the upfront treatment of cGVHD. The primary efficacy endpoint is to estimate the proportion of patients that are alive and off IST at 12 months following initiation of treatment. To meet this endpoint, patients need to remain off IST (e.g. sirolimus, tacrolimus, steroids, etc). for at least 8 weeks. The use of rituximab and ibrutinib are not considered IST for this endpoint.

2.2. Secondary Objective(s)

Efficacy

To estimate:

- Chronic GVHD response (CR + PR, both individual organ response and overall response, according to 2014 NIH Response Criteria Working Group Report) – See Appendix G.
- Cumulative steroid exposure (total mg methylprednisolone or equivalent).
- Time to discontinuation of systemic immunosuppression (defined as the date that all systemic IST has been discontinued after resolution of all reversible manifestations of cGVHD. Discontinuation of immunosuppressive medications for the purpose of inducing an anti-tumor response after the development of recurrent or secondary malignancy will not be counted as successful discontinuation of IST).
- Failure-free survival (defined as being alive without the requirement for second-line cGVHD therapy). See section 6.3 for definition of second-line cGVHD therapy.
- Non-relapse and overall mortality

Safety

To estimate:

- Incidence of grade ≥3 adverse events, possibly or probably related to either ibrutinib and/or rituximab.

- To evaluate the safety and tolerability of combination of rituximab and ibrutinib versus the historical experience with rituximab alone in the upfront treatment of cGVHD.

2.3. Exploratory Objective

- To evaluate laboratory-based correlates associated with response to treatment.

3. STUDY DESIGN

3.1. Overview of Study Design

The rationale for the study concept is provided in Section 1.3.

This is a phase II trial evaluating the safety and efficacy of the combination of Ibrutinib and Rituximab as primary treatment of cGVHD. We plan to enroll 35 patients on this study. Patients will be formally monitored monthly for 12 months to evaluate for outcome and safety endpoints. All other assessments will be done at the physician's discretion or institutional standards. All patients, responders and treatment failures, will be followed for a period of one year from the time of initiation of therapy. The primary endpoint will be the proportion of patients that are alive and off all systemic IST at 12 months following initiation of treatment.

Eligible patients will be those with a first episode of symptomatic cGVHD, requiring systemic immunosuppression for control of symptoms. Following study entry, patients will be started on:

1. Ibrutinib 420mg PO QDAY (28-day cycles) for a total of 12 cycles unless discontinued early due to toxicity (see stopping rules in section 5.1.1.4). Dose adjustments are required for patients with hepatic impairment or those receiving concomitant voriconazole or posaconazole or other strong CyP 3A4 inhibitor according to sections 5.1.1.5 and 5.1.1.6.
2. Rituximab 375mg/m2 IV weekly x 4 weeks (to be started on study day 7 ± 3 days), then 375mg/m2 IV q3months x 4 doses (months 4, 7, 10, 13).

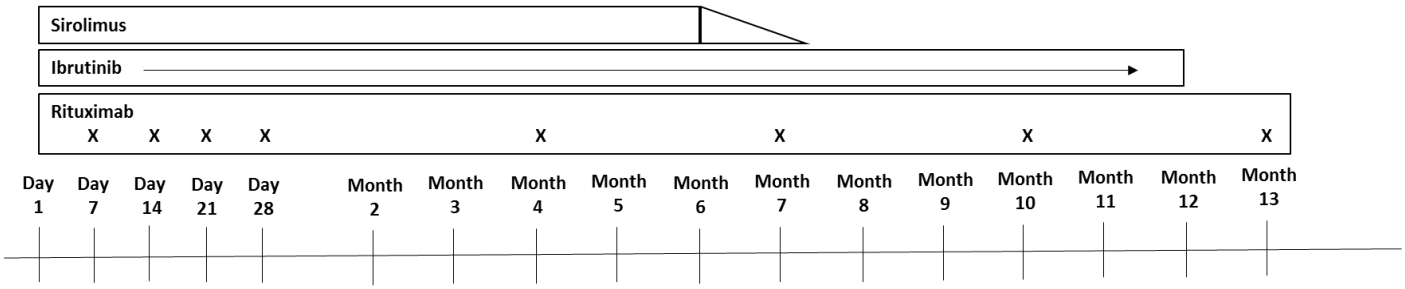
Additional cGVHD treatment will include:

- **Sirolimus** (target level 4-10 ng/mL) – patients currently receiving a calcineurin inhibitor (tacrolimus or cyclosporine) and/or mycophenolate mofetil for GVHD prophylaxis will be converted to sirolimus per institutional guidelines. In the case of contraindication or intolerance to sirolimus, another systemic immunosuppressive (IS) drug (i.e. tacrolimus or cyclosporine) may be substituted at the discretion of the treating investigator.

- Short-course corticosteroids may be used, if necessary, for more rapid symptom control (≤1mg/kg Medrol, with planned taper to be completed no longer than 4 weeks).

When cGVHD manifestations have been quiescent for at least 4 weeks, sirolimus (or other IS medication) should be tapered over 4 weeks or per investigator discretion.

3.2. Study schema



4. SUBJECT SELECTION

4.1. Inclusion Criteria

Prior to enrollment, each potential subject must satisfy all of the following inclusion criteria:

1. First episode of systemic immunosuppression-requiring cGVHD, defined as classic or overlap cGVHD by the NIH consensus criteria.

2. Previously untreated cGVHD, defined by having received <10 days of corticosteroids or alternative systemic immunosuppressive agent started specifically for a new diagnosis of cGVHD

3. Age ≥18 years

4. Karnofsky performance status ≥70%

5. Patient willing and able to provide informed consent

6. Adequate hematologic function defined as:

   - Absolute neutrophil count (ANC) ≥1.0 x 109/L and off growth factor support for 7 days.
   - Platelet count ≥30 x 109/L and no platelet transfusions for 7 days.

7. Adequate hepatic function as defined by:

   - Total bilirubin of ≤ 1.5 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome) or
   - Total bilirubin of > 1.5 x ULN to 3.0 x ULN if due to cGVHD.

8. Women of childbearing potential and men who are sexually active with a woman of childbearing potential must be practicing a highly effective, preferably user-independent method of birth control (failure rate of <1% per year when used consistently and correctly)

during treatment and for up to 90 days after the last dose of ibrutinib, consistent with local regulations regarding the use of birth control methods for subject participating in clinical studies.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

1. Patients with late persistent or recurrent acute GVHD
2. Active uncontrolled infection
3. History of HIV infection
4. Active HBV or HCV infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
5. Inability to tolerate oral medications.
6. Progressive or recurrent malignancy following allogeneic transplant
7. Known severe or life-threatening hypersensitivity to ibrutinib or rituximab
8. Creatinine > 2 mg/dl or calculated CrCl < 30ml/min
9. Requirement for anticoagulation therapy
10. Uncontrolled hypertension
11. Known bleeding disorder
12. Major surgery within 4 weeks of first dose of study drug
13. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
14. Unable to swallow capsules
15. Subjects with chronic liver disease and hepatic impairment meeting Child-Pugh Class C (Appendix D).
16. Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
17. Unwilling or unable to participate in all required study evaluations and procedures
18. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
19. Exposure to BTK inhibitor following transplant. Prior exposure to BTK inhibitor pre-transplant is allowed.
20. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug
21. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v5.0), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia

22. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk
23. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization

24. Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP3A inhibitor (Appendix C), with the exception of voriconazole or posaconazole which are permitted on study with appropriate dose modification.
25. Subjects who have received prior treatment with extracorporeal photopheresis (ECP) for cGVHD.

5. TREATMENT OF SUBJECTS

5.1. Study Medications

5.1.1. Ibrutinib

5.1.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 70 mg and 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients. 70 mg capsules will only be used for subjects who have dose reductions that require a dose of 70 mg and will not be used to constitute a dose larger than 70 mg (eg, 2 x 70 mg capsules to give 140 mg).

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.1.1.2. Dose and Administration

Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily. It is expected that many subjects commencing therapy for cGVHD will require anti-fungal prophylaxis. Please see Section 6.2.1 for dose modification guidelines with concomitant use of CYP3A inhibitors.

The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers (other

than those specifically permitted on study), and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix C).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Study drug may not be shipped to the subject without approval from PCYC and may not be dispensed to anyone other than the subject. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.5) updated at each visit. Returned capsules must not be redispensed to anyone.

5.1.1.3. Overdose

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1,400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.1.1.4. Dose Modification for Non-Cardiac Adverse Reactions

The dose of study drug must be modified according to the dose modification guidance in Table 1 and Table 2 if any of the following non-cardiac toxicities occur:

- Grade 4 neutropenia (ANC <500/µL) for more than 7 days. See Section 6.1 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets <50,000/µL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (platelets <25,000/µL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 non-cardiac toxicity

Adverse events that are considered related to concomitant high dose corticosteroids (e.g. hyperglycemia, insomnia) do not require dose modification or holding of ibrutinib.

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 4 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the CRF.

Table 1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (i.e., 280 mg/day for 420 mg/day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (i.e., 140 mg/day for 420 mg/day dose; 280 mg/day)
Fourth	Discontinue study drug

Table 2. Ibrutinib Dose Reduction Levels

Starting Dose Level	140 mg	280 mg	420 mg
Dose Reduction Level 1	70 mg	140 mg	280 mg
Dose Reduction Level 2	Discontinue	70 mg	140 mg
Dose Reduction Level 3	NA	Discontinue	Discontinue

For required dose modification for hepatic impairment refer to Section 5.1.1.5 and for concomitant treatment with CYP3A inhibitors refer to Section 5.1.1.6.

5.1.1.5. Dose Modification for Cardiac Toxicity

The dose of study drug must be modified for cardiac toxicity according to the guidance in Table 3:

Table 3: Dose Modification Guidance for Cardiac Toxicity

Adverse Reaction	Occurrence	Dose Modification After Recovery Starting Dose=420mg	Dose Modification After Recovery Starting Dose=280mg	Dose Modification After Recovery Starting Dose=140mg
Grade 2 cardiac failure[1]	First	Restart at 280 mg	Restart at 140 mg	Restart at 70 mg
	Second	Restart at 140 mg	Restart at 70 mg	Discontinue Drug
	Third	Discontinue Drug	Discontinue Drug	N/A
Grade 3 cardiac arrhythmias[1,2]	First	Restart at 280mg	Restart at 140 mg	Restart at 70 mg
	Second	Discontinue Drug	Discontinue Drug	Discontinue Drug
Grade 3 or 4 cardiac failure Grade 4 cardiac arrythmias	First	Discontinue Drug	Discontinue Drug	Discontinue Drug

[1]Evaluate the risk-benefit before resuming ibrutinib treatment
[2]If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for thromboprophylaxis of atrial fibrillation.

5.1.1.6. Dose Modification for Hepatic Impairment

Dose modifications for hepatic impairment will depend on total bilirubin level and subsequent changes in bilirubin levels per Table 3 below. If the elevation of bilirubin is due to a non-hepatic cause or Gilbert's Syndrome, then no dose modifications are necessary. Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class C) are excluded from study participation. Refer to Appendix D for Child-Pugh classification. Please refer to Table 3 for dose modifications due to hepatic impairment. Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines for unmanageable Grade 3 toxicity in Section 5.1.1.4.

Table 4. Dose Modification Guidance for Hepatic Impaired Subjects

Starting Dose Level by Bilirubin Levels	**Bili** ≤1.5 x ULN at baseline **420 mg**	**Bili** >1.5-3 x ULN at baseline **140 mg**
On-study **Bili** ≤1.5 x ULN	Continue 420 mg	Increase to 420 mg
On-study **Bili** >1.5-3 x ULN	Reduce to 140 mg	Continue 140 mg
On-study **Bili** >3 x ULN	Hold until **Bili** >1.5-3 x ULN, then restart 140 mg When bili level ≤1.5 x ULN restart at 420mg	Hold until **Bili** >1.5-3 x ULN, then restart 140 mg When bili level ≤1.5 x ULN restart at 420mg

In the event a patient has had a dose reduction due to a non-hepatic toxicity and then develops elevated bilirubin (or vice versa) that requires a dose reduction, the lower of the two dose reductions should be used.

5.1.1.7. Dose Modification for Concomitant Use of CYP3A Inhibitors

Dose adjustment of ibrutinib secondary to concomitant use of CYP 3A4 inhibitors should follow Table 4. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment.

Table 5. Dose Modification Guidance for CYP3A4 Inhibitors

Co-administered Drug	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use**
Mild CYP3A4 inhibitors	420 mg once daily. No dose adjustment required.
Moderate CYP3A4 inhibitors	420 mg once daily. No dose adjustment required.
Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID or delayed-release tablet 300mg QD	280 mg once daily.
Posaconazole at higher doses	140 mg once daily.
Other strong CYP3A4 inhibitors	Avoid concomitant use. If these inhibitors will be used short term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

After discontinuation of a CYP3A4 inhibitor, resume previous dose of ibrutinib.

If Bili >1.5 x ULN, avoid and/or discontinue voriconazole, posaconazole, or other strong CYP3A4 inhibitor.

5.1.2. Rituximab

5.1.2.1. Formulation/Packaging/Storage

Rituximab is a highly purified, 1328-amino acid antibody with an approximate molecular mass of 145 kD. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG_1 κ immunoglobulin containing murine light and heavy chain variable regions and human γ_1 heavy chain and κ light chain constant regions.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Rituximab vials are stable at 2° to 8°C (36° to 46°F). Rituximab vials should be protected from direct sunlight. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 24 hours. However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2° to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

5.1.2.2. Dose and Administration

The recommended dosage of rituximab is 375 mg/m^2 given as an IV infusion.

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have

completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy

5.1.2.3. Subsequent infusions: If the subject tolerated the first infusion well, subsequent Rituximab doses may be mixed in a total volume of 250 mL NS and administered at an initial rate of 100mL/hr for 30 minutes, then 200mL/hr for 60 minutes such that the entire dose is delivered over 90 minutes. If the first infusion was not well tolerated, the guidelines for the first infusion should be followed for the subsequent infusions. Overdose

There has been no experience with over-dosage of rituximab in human clinical trials. Single doses higher than 500 mg/m^2 have not been tested in controlled studies.

5.1.2.4. Dose Modification for Adverse Reactions

The dose of rituximab generally remains constant throughout the trial. Rituximab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions.

Subjects who meet the following criteria should be discontinued from the study:

- Active HBV infection or hepatitis
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

Usage of antimicrobial prophylaxis in accordance with standard practice is permitted and should be considered in subjects who are at increased risk for opportunistic infections.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) and transfusion is permitted in accordance with institutional policy.

Short courses (< 28 days) of steroid treatment are permitted at doses that do not exceed 1.0 mg/kg per day of methylprednisolone or equivalent.

Ancillary therapy and supportive care for cGVHD is permitted as outlined in the NIH Consensus Development Project 2014 Ancillary Therapy and Supportive Care Working Group Report (Carpenter 2015). In particular, the use of topical therapies (e.g. inhaled steroids, azithromycin, and monteleukast for bronchiolitis obliterans, budesonide for anorexia/nausea, steroid and/or tacrolimus rinses for oral symptoms, cyclosporine eye drops for xeropthalmia) will not be considered systemic therapy for cGVHD.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure. Dose adjustment of ibrutinib due to concomitant use of CYP3A4 inhibitors should follow Table 4 (Section 5.1.1.6)

Avoid concomitant use of systemic strong CYP3A4 inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A4 induction.

A list of common CYP3A4 inhibitors and inducers is provided in Appendix C. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin or methotrexate, should be taken at least 6 hours before or after ibrutinib.

6.2.3. Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the use of therapeutic anticoagulation therapy (e.g. Atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held while anticoagulation is being initiated and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Other Systemic Immunosuppression Therapy for cGVHD

Addition of any new systemic immunosuppressant therapy (including ECP) to treat worsening cGVHD is prohibited. This will be considered a treatment failure, patient will be removed from study and treated according to institutional standard-of-care.

Any increase in the dose of methylprednisolone (or equivalent) and any resumption of treatment with methylprednisolone, after previous discontinuation, is not considered as secondary systemic therapy.

Any increase in the dose of sirolimus or calcineurin inhibitor, or resumption of treatment following discontinuation, is not considered as secondary systemic therapy, if the treatment in question was included in the immunosuppressive regimen at study initiation.

A substitution of the systemic immunosuppressant drug (e.g. tacrolimus for sirolimus) for reasons other than cGVHD progression (e.g. toxicity) may be permitted after discussion with the principal investigator and is not considered as secondary systemic therapy.

Topical therapy, including steroid creams, topical tacrolimus, oral budesonide, inhaled steroids and ophthalmic solutions are not considered as secondary therapy.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention (except for emergency procedures) and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

7.1.1.1. ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects in the US must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria until first dose of study drug (Section 4).

7.1.1.3. Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities.

7.1.1.4. Prior and Concomitant Medications

All medications at least 14 days prior to first dose through 30 days after the last dose of study drug will be documented.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event (AE) is provided in Section 11.1. The occurrence of an AE at the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug

until 30 days after the last dose of study drug that meet the AE definition below must be recorded as AEs in the CRF.

- Grade 1 adverse events do not need recorded
- Grade 2 unexpected **and** possibly/probably/definitely related
- Grade 3 requiring hospitalization **and** unexpected/expected regardless of relationship
- Grade 3 unexpected without hospitalization **and** possibly/probably/definitely related
- All grades 4 & 5 regardless of unexpected/expected or relationship

7.1.1.6. Physical Examination

The Screening and follow-up visit physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

7.1.1.7. Karnofsky Performance Status (KPS)

The KPS performance index is provided in Appendix B.

7.1.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate and body temperature.

7.1.2. Laboratory

Laboratory evaluation will be performed per institutional guidelines and include CBC with differential, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, albumin, SGOT(AST), SGPT (ALT), magnesium and calcium. Relevant immunosuppressive drug levels (e.g. sirolimus) will be checked per institutional guidelines.

7.1.3. Diagnostics/Procedures

Radiology (e.g. plain films, CT), pulmonary function tests (PFTs), biopsies (e.g. skin, liver, GI tract) will be performed according to institutional standards.

7.2. Efficacy Evaluations

Formal efficacy assessments will be performed at baseline and post-treatment, monthly x 3 (1, 2, and 3 months), then q3months x 3 (6, 9, and 12 months). See section 8.2.2 for detailed study assessments. All other assessments will be done at the physician's discretion or institutional standards.

7.3. Correlative Blood Collection and Handling

Research blood samples (30-60ml) will be drawn at baseline, prior to ibrutinib dosing, and at each study visit (month 1, 2, 3, 6, 9, 12) for a total of 7 samples. From each blood sample, peripheral blood mononuclear cells (PBMCs) and serum will be collected and cryopreserved for correlative studies.

At each timepoint:

- Serum – draw 10 ml of serum
- PBMCs – If ALC >/= 1000/ul, draw 30ml. If ALC <1,000/ul, draw 50ml

Samples will be frozen in -80^0 C or liquid nitrogen.

8. STUDY PROCEDURES

(See Appendix A for details regarding timing of study procedures and testing.)

8.1. Screening Phase

8.1.1. Screening/Consenting Visit

Required testing for the screening visit:

- Medical History
- Physical examination with vital signs, height, weight
- Schirmer's Test
- Karnofsky Performance Status (Appendix B)
- Serum Pregnancy test
- Hepatitis Serologies (HepBsAg, HepBsAB, HepC)
- Fasting lipid panel
- Laboratory evaluation per institutional guidelines including CBC with differential, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, albumin, SGOT(AST), SGPT (ALT), CRP, CK, calcium, and magnesium.
- IgG level
- Biomarkers (correlative lab studies)

- Pulmonary Function Test
- GVHD assessment form (Appendix E)
- GVHD self-report form (Appendix F)

Eligibility criteria will be verified, and ineligible patients will proceed off study and no further follow-up will be obtained.

8.2. Treatment Phase

8.2.1. Treatment Visits

8.2.1.1. C1D1 Ibrutinib

Required testing for the visit:

- CBC with differential
- Comprehensive metabolic panel

Blood count and hepatic function criteria for dosing will be verified.

8.2.2. Response Follow-up

Required testing for the response follow-up visits (months 1, 2, 3, 6, 9, 12):

- Medical history
- Physical examination, including vital signs, weight, and Karnofsky performance status
- Laboratory evaluation per institutional guidelines including CBC with differential, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, albumin, SGOT(AST), SGPT (ALT), CRP, CK, calcium, and magnesium.
- Biomarkers (correlative lab studies)
- Documentation of concomitant medications
- Completion of institutional GVHD assessment form (see Appendix E)
- Completion of a GVHD patient self-report form (see Appendix F)
- Document cumulative corticosteroid use
- Document any new systemic IST and reason for use

- Document treatment-emergent toxicities and adverse events
- Document any IVIG use
- PFTs (at 3, 6, 9 and 12 month visits only)

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

Patients will be considered to be off study if any new systemic immunosuppressant therapy (including ECP) to treat worsening cGVHD is received. No subsequent adverse or serious adverse event reporting will be done. Further follow up off study will be according to institutional requirements.

Patients will be considered to have completed study follow up at 12 months or 30 days after the last dose of ibrutinib whichever comes last. Further off study follow up will be according to institutional requirements.

9.2. Criteria for Study Discontinuation

Patients may be withdrawn from the study if:

- The patient requests withdrawal
- If the patient develops side effects that are considered life-threatening
- If the patient refuses to have treatment as recommended
- If the patient refuses to have tests that are needed to determine whether the treatment is safe and effective
- If the agents used in this study cease to be available
- If other causes prevent continuation of the study
- For any other reason that the physician feels it may be necessary that the patient discontinue the study

10. STATISTICAL METHODS AND ANALYSES

10.1. Analysis Population

All treated subjects

10.2. Endpoints

10.2.1. Primary Endpoint

The primary endpoint is to estimate the proportion of patients that are alive and off all systemic IST at 12 months following initiation of treatment. To meet this endpoint, patients need to remain off IST for at least 8 weeks after discontinuing systemic immunosuppression (e.g. sirolimus). The use of rituximab and ibrutinib are not considered IST for this endpoint.

10.2.2. Secondary Endpoints

Secondary efficacy endpoints:

To estimate:

- Chronic GVHD response (CR + PR, both individual organ response and overall response, according to 2014 NIH Response Criteria Working Group Report) – See Appendix G.
- Cumulative steroid exposure (total mg methylprednisolone or equivalent).
- Time to discontinuation of systemic immunosuppression (defined as the date that all systemic IST has been discontinued after resolution of all reversible manifestations of cGVHD. Discontinuation of immunosuppressive medications for the purpose of inducing an anti-tumor response after the development of recurrent or secondary malignancy will not be counted as successful discontinuation of IST).
- Failure-free survival (defined as being alive without the requirement for second-line cGVHD therapy). See section 6.3 for definition of second-line cGVHD therapy.
- Non-relapse and overall mortality

Safety endpoints:

To estimate:

- Incidence of grade ≥3 adverse events, possibly or probably related to either ibrutinib and/or rituximab.

10.2.3. Exploratory Endpoints

Biomarkers:

B-cell numbers and subsets, T cell numbers and subsets, T regulatory cells, serum BAFF levels and serum cytokine levels will be measured at baseline, months 1, 2, 3, 6, 9, and 12 to explore biomarkers which predict cGVHD response.

10.3. Sample Size Determination

The study will be powered to detect a clinically meaningful improvement in treatment success at 12 months post-treatment, defined as being alive and off systemic immunosuppression. Experience from our phase II study of rituximab in the upfront treatment of cGVHD found that 56% of patients were alive and off systemic immunosuppression at 12 months post treatment. It is hoped that under this protocol, this rate will be at least 75%. Thus we statistically formalize this study by testing the null hypothesis that p, the treatment success rate is 0.55 or less versus the alternative hypothesis that p is at least 0.75. A sample size of 35 patients gives 80% power with an alpha=0.05, using the formula for a one sample binomial (one-sided) test of a proportion. Replacement of subjects may be possible for those who are lost to follow-up or withdraw from study before 12 months due to non-treatment related reasons, in order to ensure statistical power of the study.

10.4. Efficacy Analysis Methods

This is a phase II trial evaluating the safety and efficacy of ibrutinib and rituximab as primary treatment of cGVHD. Efficacy and safety endpoints will be estimated according to the cumulative incidence and Kaplan-Meier methodology in the presence of competing risks. Outcomes will be compared to historical values based on the Gray's test and log rank test respectively. We plan to enroll 35 patients on this study. Patients will be formally monitored for 12 months to evaluate for outcome and safety endpoints (efficacy/safety visits at the completion of month 1, 2, 3, 6, 9, and 12). All other assessments will be done at the physician's discretion or institutional standards. All patients, responders and treatment failures, will be followed for a period of one year. The primary outcome measure will be the proportion of patients that are alive and off all systemic immunosuppression at 12 months following initiation of treatment. The primary endpoint will be estimated according to the Kaplan-Meier methodology in the presence of competing risks. Outcome will be compared to historical values based on the log rank test. Secondary outcome measures will be cGVHD response, cumulative steroid exposure, time to discontinuation of systemic immunosuppression, requirement for second-line cGVHD therapy, non-relapse and overall mortality, failure-free survival and safety. Secondary survival endpoints will be estimated according to the Kaplan-Meier methodology in the presence of competing risks, and outcomes will be compared to historical values based on the log rank test. Secondary time-to-event endpoints will be estimated according to cumulative incidence methodology, and outcomes will be compared to historical values based on the Gray's test (Gray 1988).

11. ADVERSE EVENT REPORTING

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event (SAE) based on International Conference on Harmonisation (ICH) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and Pharmacyclics LLC is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either Pharmacyclics LLC or the investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) will be used for grading the severity (intensity) of AEs. The CTCAE v5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v5.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. Causality (Attribution)

The investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug(s) caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB 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 study drug under investigation.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, e.g., name confusion)

If any special reporting situation meets the criteria of an AE, it should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E) or designee within 24 hours of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the AEs CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented from the time signed and dated ICF is obtained until 30 days following the last dose of study drug or the start date of a new therapy for cGVHD. SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the CRF from the time of ICF signing. Non-serious AEs will be recorded in the source documents from the time of ICF signing and will be recorded in the CRF from the first dose of study drug(s).

SAEs reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical

signs of disease progression may be reported. (See Section 11.1.1)

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a SAE.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3372) to Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E) or designee, within 24 hours of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject or female partner of a male subject must immediately inform the investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug(s). Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partner of a male subject must be reported from the time of first dose up until 90 days after the last dose of study drug(s). Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E) or designee, per SAE reporting timelines of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

11.4.6. Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E) or designee, within 24 hours of awareness.

11.4.6.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*.
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE v5.0

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Pharmacyclics may request that informed consent documents be reviewed by Pharmacyclics or designee prior to IRB/IEC submission.

12.2. Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

12.3. Protected Subject Health Information Authorization

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from Pharmacyclics or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process.

The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.4. Study Files and Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

12.5. Investigational Study Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Pharmacyclics or a designee or disposal of the drug (if applicable and if approved by Pharmacyclics) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

12.6. Study Monitoring/Audit Requirements

Regulatory authorities, the IEC/IRB and/or Pharmacyclics may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.7. Investigator Responsibilities

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Pharmcyclics and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Pharmacyclics and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

12.8. Protocol Amendments

Any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

12.9. Publication of Study Results

The Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

12.10. Study Discontinuation

Patients may be withdrawn from the study if:

- The patient requests withdrawal.
- If the patient develops side effects that are considered life-threatening
- If the patient refuses to have treatment as recommended.
- If the patient refuses to have tests that are needed to determine whether the treatment is safe and effective.
- If the agents used in this study cease to be available.
- If other causes prevent continuation of the study
- For any other reason that the physician feels it may be necessary that the patient discontinue the study

12.11. Study Completion

The study is expected to be completed approximately 1 year from last subject enrolled, the time point all subjects have exited the study for any reason, or study termination at the Sponsor's discretion, whichever occurs first.

13. REFERENCES

Abou-Mourad, Y. R., B. C. Lau, et al. (2010). "Long-term outcome after allo-SCT: close follow-up on a large cohort treated with myeloablative regimens." Bone Marrow Transplantation 45(2): 295-302.

Bhatia, S., L. Francisco, et al. (2007). "Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study." Blood 110(10): 3784-3792.

Burger, J. A., M. J. Keating, et al. (2014). "Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study." The Lancet. Oncology 15(10): 1090-1099.

Canninga-van Dijk, M. R., H. M. van der Straaten, et al. (2004). "Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host disease." Blood 104(8): 2603-2606.

Champlin, R. E., J. R. Passweg, et al. (2000). "T-cell depletion of bone marrow transplants for leukemia from donors other than HLA-identical siblings: advantage of T-cell antibodies with narrow specificities." Blood 95(12): 3996-4003.

Chang BY, Francesco M, De Rooij MF, et al. Egress of CD19+CD5+ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. Blood. 2013a;122:2412-24.

Chang BY, Francesco M, Steggerda S, et al. Ibrutinib Inhibits Malignant Cell Adhesion and Migration and Reduces Tumor Burden in Lymph Node and Bone Marrow in a Murine Model of Mantle Cell Dissemination and Progression. 2013b AACR: Abstract 923.

Child CG, Turcotte JG. Surgery and portal hypertension. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964;50-64.

Chiodi, S., S. Spinelli, et al. (2000). "Quality of life in 244 recipients of allogeneic bone marrow transplantation." British Journal of Haematology 110(3): 614-619.

Cooke, K. R., L. Luznik, et al. (2017). "The Biology of Chronic Graft-versus-Host Disease: A Task Force Report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease." Biology of Blood and Marrow Transplantation 23(2): 211-234.

Cutler, C., H. T. Kim, et al. (2013). "Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase 2 trial." Blood 122(8): 1510-1517.

Cutler, C., D. Miklos, et al. (2006). "Rituximab for steroid-refractory chronic graft-versus-host disease." Blood 108(2): 756-762.

Dubovsky, J. A., R. Flynn, et al. (2014). "Ibrutinib treatment ameliorates murine chronic graft-versus-host disease." The Journal of clinical investigation 124(11): 4867-4876.

Duell, T., M. T. van Lint, et al. (1997). "Health and functional status of long-term survivors of bone marrow transplantation. EBMT Working Party on Late Effects and EULEP Study Group on Late Effects. European Group for Blood and Marrow Transplantation." Ann Intern Med 126(3): 184-192.

Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31:794-810.

Fraser, C. J., S. Bhatia, et al. (2006). "Impact of chronic graft-versus-host disease on the health status of hernatopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study." Blood 108(8): 2867-2873.

Gray, R. (1988), "A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk," The Annals of Statistics, 16: 1141–1154.

Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117:6287-96.

Higman, M. A. and G. B. Vogelsang (2004). "Chronic graft versus host disease." Br J Haematol 125(4): 435-454.

International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A). March 1995.

International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline: Guidance for Good Clinical Practice (ICH-E6)(R1). June 1996.

Investigator's Brochure. Ibrutinib. Version 10: 29 August 2016. Pharmacyclics LLC; Janssen Research & Development, LLC.

Kiss, T. L., M. Abdolell, et al. (2002). "Long-term medical outcomes and quality-of-life assessment of patients with chronic myeloid leukemia followed at least 10 years after allogeneic bone marrow transplantation." Journal of Clinical Oncology 20(9): 2334-2343.

Koc, S., W. Leisenring, et al. (2002). "Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone." Blood 100(1): 48-51.

Miklos, D., C. S. Cutler, et al. (2017). "Ibrutinib for chronic graft-versus-host disease after failure of prior therapy." Blood 130(21): 2243-2250.

Miklos, D. B., H. T. Kim, et al. (2005). "Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission." Blood 105(7): 2973-2978.

Miklos, D. B., H. T. Kim, et al. (2004). "Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors." Blood 103(1): 353-359.

Okamoto, M., A. Okano, et al. (2006). "Rituximab is effective for steroid-refractory sclerodermatous chronic graft-versus-host disease." Leukemia 20(1): 172-173.

Oken, MM, Creech RH, Tormey DC, et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 5:649-55, 1982.

Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem. 2007;2:58-61.

Pavletic, S. Z., S. L. Carter, et al. (2005). "Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation." Blood 106(9): 3308-3313.

Pugh RN, Murray-Lyon IM, Dawson L, et al. Transection of the oesophagus for bleeding oesophageal varices. The British journal of surgery. 1973;60:646-9.

Ratanatharathorn, V., L. Ayash, et al. (2001). "Chronic graft-versus-host disease: clinical manifestation and therapy." Bone Marrow Transplant 28(2): 121-129.

Ratanatharathorn, V., L. Ayash, et al. (2003). "Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody." Biol Blood Marrow Transplant 9(8): 505-511.

Sauter, C. S., J. N. Barker, et al. (2014). "A phase II study of a nonmyeloablative allogeneic stem cell transplant with peritransplant rituximab in patients with B cell lymphoid malignancies: favorably durable event-free survival in chemosensitive patients." Biol Blood Marrow Transplant 20(3): 354-360.

Schmitz, N., M. Eapen, et al. (2006). "Long-term outcome of patients given transplants of mobilized blood or bone marrow: a report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation." Blood 108(13): 4288-4290.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol. 2006;24:3187-205.

Socie, G., J. V. Stone, et al. (1999). "Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry." N Engl J Med 341(1): 14-21.

Solomon, S. R., C. A. Sizemore, et al. (2015). "Corticosteroid-Free Primary Treatment of Chronic Extensive Graft-versus-Host Disease Incorporating Rituximab." Biol Blood Marrow Transplant.

Stevenson FK, Krysov S, Davies AJ, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood. 2011;118: 4313-20.

Stewart, B. L., B. Storer, et al. (2004). "Duration of immunosuppressive treatment for chronic graft-versus-host disease." Blood 104(12): 3501-3506.

Sullivan, K. M., R. P. Witherspoon, et al. (1988). "Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation." Blood 72(2): 546-554.

Sutherland, H. J., G. M. Fyles, et al. (1997). "Quality of life following bone marrow transplantation: a comparison of patient reports with population norms." Bone Marrow Transplant 19(11): 1129-1136.

Syrjala, K. L., M. K. Chapko, et al. (1993). "Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning." Bone Marrow Transplant 11(4): 319-327.

Vogelsang, G. B. (2001). "How I treat chronic graft-versus-host disease." Blood 97(5): 1196-1201.

Wang, M. L., H. Lee, et al. (2016). "Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial." The Lancet. Oncology 17(1): 48-56.

Wingard, J. R., S. Piantadosi, et al. (1989). "Predictors of death from chronic graft-versus-host disease after bone marrow transplantation." Blood 74(4): 1428-1435.

Zaja, F., A. Bacigalupo, et al. (2007). "Treatment of refractory chronic GVHD with rituximab: a GITMO study." Bone Marrow Transplant 40(3): 273-277.

14. APPENDICES

Appendix A. Schedule of Assessments

Study Day	Screening (within 7 days)	Day 1	Day 7 (+/- 3 days)	Month 1 (+/- 7 days)	Month 2 (+/- 7 days)	Month 3 (+/- 7 days)	Month 6 (+/- 7 days)	Month 9 (+/- 7 days)	Month 12 (+/- 7 days)
Informed Consent	X								
Eligibility Confirmation	X								
Ibrutinib 420mg daily[1]		X		Continuous daily dosing Dispensed on D1 of each cycle through Cycle 12					
Rituximab 375mg/m^2			X[2]			X[3]			
Medical History	X			X	X	X	X	X	X
Physical Exam w/vitals	X			X	X	X	X	X	X
Schirmer's test	X			X	X	X	X	X	X
Karnofsky Performance Status	X								
Serum Pregnancy	X								
Hepatitis serologies	X								
Fasting Lipid Panel	X								
CBC w/differential	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel[4]	X	X	X	X	X	X	X	X	X
IgG level	X					X	X	X	X
CRP	X			X	X	X	X	X	X
CK	X			X	X	X	X	X	X
LDH	X			X	X	X	X	X	X
Biomarkers (Correlative studies)	X			X	X	X	X	X	X
Concomitant Medications	X			X	X	X	X	X	X
GVHD assessment[5]	X			X	X	X	X	X	X
GVHD patient self-report form[6]	X			X	X	X	X	X	X
Pulmonary Function Test	X					X	X	X	X
Calculate cumulative steroid dose				X	X	X	X	X	X
Any new systemic IST				X	X	X	X	X	X
Any IVIG therapy				X	X	X	X	X	X
Adverse Event				X	X	X	X	X	X

[1]Dose reduction required when using strong Cyp 3A4 inhibitors (e.g. voriconazole or posaconazole, see Section 6.2.1, table 4) or with hepatic impairment (see Section 5.1.1.5, table 3).
[2]Rituximab induction 375mg/m^2 Q7days x 4 doses.
[3]Rituximab maintenance 375mg/m^2 q 3months (+/-7days) x 4 doses.
[4]Glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, albumin, SGOT (AST), SGPT (ALT), calcium, magnesium
[5]See appendix E
[6]See appendix F

Appendix B. Karnofsky Performance Status Score

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

Appendix C. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
boceprevir	barbiturates
clarithromycin	efavirenz
cobicistat	glucocorticoids
indinavir	modafinil
itraconazole	nevirapine
ketoconazole	oxcarbarzepine
mibefradil	phenobarbital
nefazodone	phenytoin
nelfinavir	pioglitazone
posaconazole[a]	rifabutin
ritonavir	rifampin
saquinavir	St. John's Wort
suboxone	troglitazone
telaprevir	
telithromycin	
troleandomycin	
Moderate inhibitors:	
amiodarone	
amprenavir	
aprepitant	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir	
diltiazem	
dronedarone	
erythromycin	
fluconazole	
fosamprenavir	
grapefruit juice	
imatinib	
Seville orange juice	
verapamil	
voriconazole[a]	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

a. Classification based on internal data.

Appendix D. Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. Surgery and portal hypertension. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964;50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al. Transection of the oesophagus for bleeding oesophageal varices. The British journal of surgery, 1973;60:646-9.

Appendix E. Chronic GVHD Assessment Form

The Blood Marrow Transplant Program
at Northside Hospital
Atlanta, GA 30342

CHRONIC GVHD NOTE

Patient Name:						MRN:	
DOS:		Current Weight:		Weight Change:		Visit:	CC/OPC-RN/OPC-MD/Input/Restaging
Onset Date:		Day +		BMT Day +:		DLI:	Onset Type:

	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	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SCORE % BSA **Specify skin GVHD features present at diagnosis of Chronic GVHD** *(Scored by BSA):* ☐ Maculopapular rash/Erythema ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No Sclerotic features		☐ Superficial sclerotic features not "hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA) **Check all that apply:**

☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement

☐ *Abnormality present but explained entiredly by non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature 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 the final skin score

MOUTH	SCORE 0	SCORE 1	SCORE 2	SCORE 3
	☐ 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

Lichen planus-like features present: ☐ **Yes** ☐ **No**

☐ *Abnormality present but explained entirely by non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

CHRONIC GVHD NOTE

Patient Name:		MRN:	

EYES	SCORE 0	SCORE 1	SCORE 2	SCORE 3
	☐ No Symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)	☐ Moderate dry eye symptoms 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 (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS

Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist: ☐ **Yes** ☐ **No** ☐ **Not examined**

☐ *Abnormality present but explained entirely by non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

GI Tract	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Specify GI tract GVHD features present at diagnosis of chronic GVHD: ☐ Esophageal web/proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Malabsorption ☐ Abdominal pain/ cramp ☐ Weight loss ≥5%* ☐ 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 significant weight loss within 3 months >15%, 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 non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

** Weight loss within 3 months*

LIVER	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 ULN	☐ Elevated total bilirubin > 3 mg/dL

☐ *Abnormality present but explained entirely by non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

LUNGS**	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Functional Test*** % FEV1: ☐	☐ No Symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of stairs)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring O2)
☐ PFT's Not performed	☐ FEV1 ≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%

☐ *Abnormality present but explained entirely by non-GVHD documented causes (specify):*

☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible.
***FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

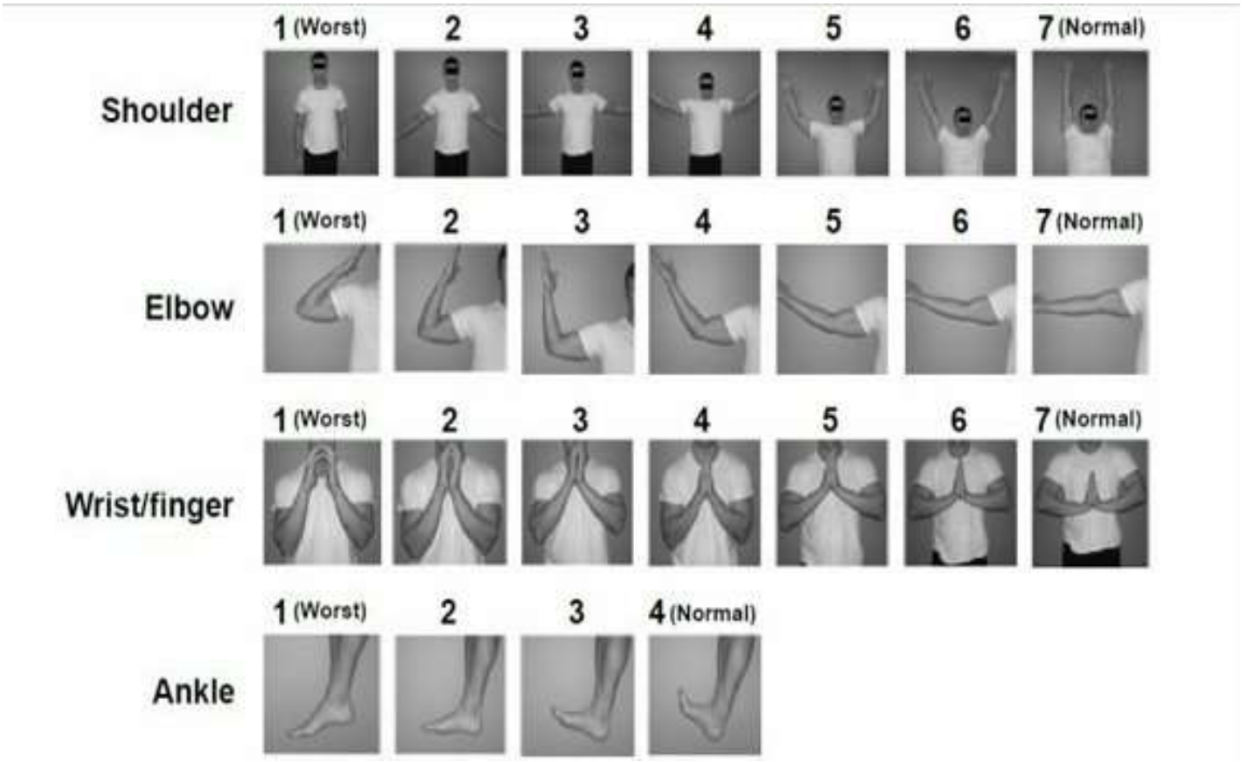
CHRONIC GVHD NOTE

Patient Name:		MRN:	

JOINTS/FASCIA	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):*
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

¤ **Photographic Range of Motion (P-ROM):**



GENITAL TRACT	SCORE 0	SCORE 1	SCORE 2	SCORE 3
☐ Not examined	☐ 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.

Currently sexually active? ☐ Yes ☐ No

☐ *Abnormality present but explained entirely by non-GVHD documented causes (specify):*
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):*

CHRONIC GVHD NOTE

Patient Name:		MRN:	

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)

- ☐ Serositis (e.g. pleural effusion, ascites, pericardial effusion) ☐
- ☐ Peripheral Neuropathy ☐
- ☐ Nephrotic syndrome ☐
- ☐ Alopecia ☐
- ☐ Abnormal slit lamp ☐
- ☐ Oral erythema ☐
- ☐ Musculoskeletal (arthritis, myositis, etc. ☐
- ☐ Myasthenia Gravis ☐
- ☐ Platelets <100,000/µl ☐
- ☐ Weight loss>5%* without GI symptoms ☐
- ☐ Xerophthalmia (dry eyes) ☐
- ☐ Corneal erosion / conjunctivitis ☐
- ☐ Bronchiolitis obliterans ☐
- ☐ Others (specify): ☐
- ☐ Eosinophilia > 500/µl ☐
- ☐ Polymyositis ☐
- ☐ Ulcers (skin) ☐
- ☐ Abnormal Schirmer's test ☐
- ☐ Mucositis /Oral ulcers) ☐
- ☐ Vaginitis / stricture ☐

Biopsy Performed: ☐ **Yes** ☐ **No**

Date: ☐

Organ: Result: ☐ Pos. ☐ Suggestive ☐ Neg. ☐ Inconcl.

Organ: Result: ☐ Pos. ☐ Suggestive ☐ Neg. ☐ Inconcl.

Organ: Result: ☐ Pos. ☐ Suggestive ☐ Neg. ☐ Inconcl.

Where would you rate the severity of this patient's cGVHD 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

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

Current Medications

Medication/Treatment	Start Date	Dose	Comments

Current Status: ☐ None ☐ Acute Active ☐ Acute Quiescent ☐ Acute Resolved ☐ Chronic Active ☐ Chronic Quiescent ☐ Chronic Resolved

Overall Grade: CIBMTR ☐ Limited ☐ Extensive

Overall Severity CIBMTR ☐ Mild ☐ Moderate ☐ Severe **NIH** ☐ Mild ☐ Moderate ☐ Severe

Overall Symptom Score ☐ **Last Evaluation Score:** ☐ **Last Evaluation Date:** ☐

Next C-GVHD Clinic: ☐

GVHD Nurse and/or Attending Physician/Designee Date

Supervisor/Designee Audit Date Data Entry Only Date

Appendix F. Patient Self Report Form

FORM B

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

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

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 **skin and/or joint tightening** at their 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
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	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 this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
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

Appendix G. Chronic GVHD Response criteria

Organ-specific Response Criteria:

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

ULN indicates upper limit of normal.

Source:

1. Lee et al.. Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant 2015; 21:984-999.

Overall Response Criteria:

Complete response (CR): defined as resolution of all manifestations in each organ or site.

Partial response (PR): defined as improvement in at least 1 organ or site without progression in any other organ or site as described above.

Overall response (OR): CR + PR

No response (NR): Defined as no response in any organ, mixed response, or progression.

Stable Disease (SD): Does not meet criteria for CR, PR or disease progression.

Organ improvement: clinically meaningful improvement defined as a decrease of 1 point or more on the 0 to 3 scale for skin, eye, mouth, esophagus, upper or lower GI tract. For joint/fascia, a clinically meaningful improvement is represented by a decrease of at least 1 point on the 0 to 3

scale or increase in the photographic range of motion by at least 1 point for any site. Liver improvement is defined as a 50% decrease in ALT, alkaline phosphatase or total bilirubin. Lung improvement is defined as an increase by 10% of the predicted absolute value of %FEV1 (eg. 50% to 60%).

Organ progression: For skin, eye, mouth, esophagus, upper or lower GI tract, a worsening of 1 point or more on the 0 to 3 scale is considered progression, except a change from 0 to 1, which is considered trivial progression since it often reflects mild, nonspecific, intermittent, self-limited symptoms and signs that do not warrant a change of therapy. For joint/fascia, a worsening of 1 point or more on the 0 to 3 scale is considered progression, even if from 0 to 1. For joints assessed by the photographic range of motion, a worsening of 1 or more points for the 7- point or 4-point scales is considered progression. Worsening of liver GVHD is defined by an increase of 2 or more times the upper limit of normal for the assay for alanine transaminase, alkaline phosphatase, or total bilirubin. For patients with lung involvement, absolute worsening of FEV1 by 10% predicted or more (eg, 50% to 40%) is considered progression.