A Phase 2 Study of Ibrutinib Maintenance After Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia

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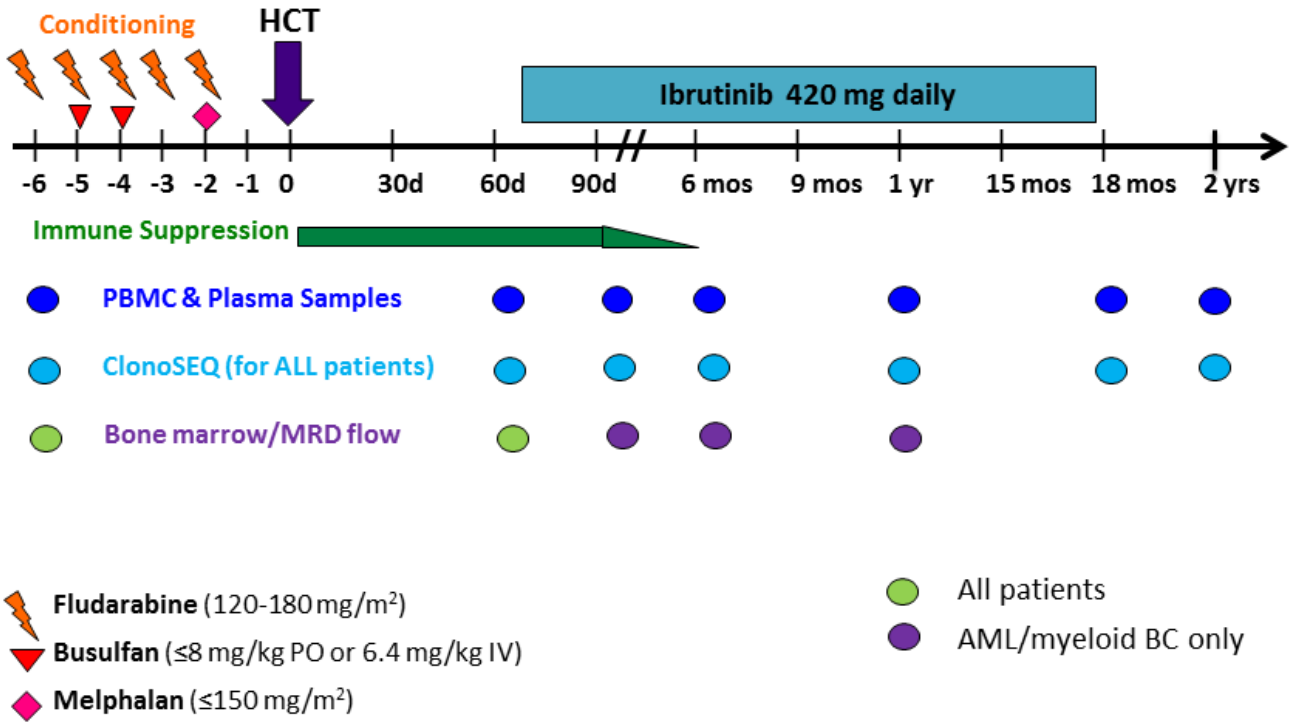
PROTOCOL SYNOPSIS

TITLE	A Phase 2 Study of Ibrutinib Maintenance After Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia
STUDY PHASE	Phase 2
INDICATION	Prevention of relapse in subjects with acute leukemias undergoing reduced-intensity conditioning and allogeneic hematopoietic cell transplantation
INVESTIGATIONAL PRODUCT	Ibrutinib
PRIMARY OBJECTIVE(S)	To reduce the incidence of relapse at 18 months after RIC and allogeneic HCT for AML, ALL, and CML in blast crisis from 45% to 25%
SECONDARY OBJECTIVE(S)	• To study the incidence and severity of post-transplant complications in subjects receiving ibrutinib maintenance after allogeneic HCT. • To study the incidence of infectious complications in subjects receiving maintenance ibrutinib after allogeneic HCT. • To study the impact of ibrutinib maintenance on minimal residual disease after RIC and allogeneic HCT. • To study the impact of maintenance ibrutinib on immune reconstitution and alloreactivity after allogeneic HCT, specifically on Th1/Th2 polarization, T follicular cell number, T- and B-cell repertoire, serum immunoglobulin levels, and alloantibody formation.
INCLUSION CRITERIA	• Diagnosis of acute myeloid leukemia (AML), acute biphenotypic leukemia, or acute lymphoblastic leukemia (ALL). CML transformed to blast crisis is eligible. • Planned allogeneic HCT using FLU/MEL or FLU/BU conditioning (regimens defined in protocol). • Planned GvHD prophylaxis consisting of TAC/MTX or TAC/SRL (regimens defined in protocol). • HLA-identical sibling donor, HLA-matched unrelated donor, or donor mismatched at 1 HLA allele or antigen. • Less than or equal to 5% blasts on bone marrow examination within 60 days of starting conditioning. • Age ≥ 18 years and ≤ 70 years. • Able to give informed consent.

EXCLUSION CRITERIA	• Active involvement of the central nervous system with malignancy (previous CNS involvement is allowed if clearance of CNS disease has been documented prior to enrollment) • Pregnant or breastfeeding • Karnofsky Performance Status < 60% • Active leukemia (> 5% leukemic blasts in peripheral blood or bone marrow) • Non-hematologic malignancy with a life expectancy of < 5 years • Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR-positive will be excluded.* • Known bleeding disorders (eg, von Willebrand's disease) or hemophilia. • History of other malignancies, except: o Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician. o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. o Adequately treated carcinoma in situ without evidence of disease.
TREATMENT SUMMARY	Subjects will be treated with ibrutinib 420 mg orally once daily, starting between Day +60 and Day +90 after allogeneic HCT and continuing until 18 months post-transplant
SAMPLE SIZE	50 subjects enrolled and treated
STATISTICAL CONSIDERATIONS	Screening and enrollment of 50 subjects will provide 84% power to detect a decrease in the incidence of relapse at 18 months post-transplant from 45% to 25%

SCHEMA



Reduced-Intensity Conditioning Regimens:

Fludarabine/Busulfan (FLU/BU)

- Fludarabine (120 to 180 mg/m^2)
- Busulfan (≤ 8 mg/kg PO or 6.4 mg/kg IV)

Fludarabine/Melphalan (FLU/MEL)

- Fludarabine (120 to 180 mg/mg^2)
- Melphalan (≤ 150 mg/m^2)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ALL	Acute lymphoblastic leukemia
AE	Adverse event
AML	Acute myeloid leukemia
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BU	Busulfan
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
FLU	Fludarabine
GvHD	Graft-vs-host disease
GI	Gastrointestinal
HCT	Hematopoietic cell transplantation
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HTN	Hypertensions
IRB	Institutional Review Board
ITK	Interleukin-2-inducible T-cell kinase
IV	Intravenous
MCL	Mantle cell lymphoma
MEL	Melphalan
MTX	Methotrexate
NRM	Non-relapse mortality
OS	Overall survival
PLT	Platelet
PFS	Progression-free survival
PR	Partial response
RIC	Reduced-intensity conditioning
RR	Response rate
SAE	Serious adverse event
SRL	Sirolimus
TAC	Tacrolimus
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1 Primary Objective

- To reduce the incidence of relapse at 18 months after RIC and allogeneic HCT for AML, ALL, and CML in blast crisis from a historical baseline of 45% to 25%, using ibrutinib maintenance therapy.

1.2 Secondary Objectives

- To study the incidence and severity of post-transplant complications in subjects receiving ibrutinib maintenance after allogeneic HCT.
- To study the incidence of infectious complications in subjects receiving maintenance ibrutinib after allogeneic HCT.
- To study the impact of ibrutinib maintenance on minimal residual disease after RIC and allogeneic HCT.
- To study the impact of maintenance ibrutinib on immune reconstitution and alloreactivity after allogeneic HCT, specifically on Th1/Th2 polarization, T follicular cell number, T- and B-cell repertoire, serum immunoglobulin levels, and alloantibody formation.

2. BACKGROUND

2.1 Allogeneic hematopoietic cell transplantation in acute leukemia

Allogeneic HCT is frequently performed with curative intent in patients with AML and ALL. Reduced-intensity conditioning is utilized in older patients, or in those with significant medical comorbidities, in order to reduce the risk of regimen-related toxicity and mortality. However, leukemia relapse after RIC and allogeneic HCT is the most common cause of treatment failure in this patient population. Patients receiving RIC are generally thought to have a higher risk of relapse compared to those receiving high-dose conditioning (1, 2). The incidence of post-transplant relapse in this setting is approximately 45% with current transplant approaches (1-6).

2.2 Ibrutinib

Ibrutinib is a first-in-class, potent, orally-administered, covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. *In vitro*, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases Ibrutinib (Imbruvica) is approved by the U S Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate; 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy; 3) CLL in patients with 17p deletion; and 4) Waldenström macroglobulinemia. Ibrutinib is currently under investigation in various indications. It is not currently approved as a maintenance therapy for acute leukemia following allogeneic HCT, so this clinical trial requires an Investigational New Drug (IND) application.

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell

surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (7).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (8). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (9).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

Pre-clinical data suggest that ibrutinib may have direct anti-tumor activity in AML. The drug's target, BTK, is constitutively activated in many forms of AML, and BTK inhibition with ibrutinib prevents AML blast proliferation in pre-clinical studies (10). Ibrutinib has also been shown to inhibit SDF1/CXCR4 interactions, thus interfering with the migration of leukemic cells and potentially rendering them more vulnerable to cytotoxic chemotherapy or graft--vs-leukemia effects by separating the leukemic cells from their protected niche (11). Given the activity of ibrutinib against B-cells, this compound is also under active investigation for its anti-tumor effects in acute B-lymphoblastic leukemias (12).

Recent studies show that B-cells are key mediators of chronic GvHD. Dysfunctional B-cells have been identified in chronic GvHD, where patients have a relatively higher number of activated memory B-cells, higher levels of B-cell-activating factor of the tumor necrosis family (BAFF), and donor-derived alloantibodies (13). It has been demonstrated that pathogenic antibody deposition occurs in human chronic GvHD, and a network of alloreactive T-helper cells, including Th1, Th2, Th17 and Tfh (T-follicular helper) cells infiltrate tissues and produce effector cytokines thereby causing antibody deposition and tissue fibrosis, similar to autoimmunity. In addition, genetic studies confirmed that ITK and BTK are independently critical for chronic GvHD. Ibrutinib, which hits both targets, showed effectiveness in both T-cell-driven and alloantibody-driven chronic GvHD models. Ibrutinib treatment delayed progression, improved survival and ameliorated clinical and pathological manifestations in mouse models of sclerodermatous and alloantibody-driven chronic GvHD (14).

2.3 Rationale

This study is designed to test the hypothesis that ibrutinib maintenance therapy will reduce the incidence of post-transplant relapse in subjects receiving RIC and allogeneic HCT for AML and ALL. The rationale for the use of ibrutinib in this setting is twofold: ibrutinib may have direct anti-tumor effects against both AML and ALL, as described above; and ibrutinib may potentiate the immunologic graft--vs-leukemia effect driven by donor T-cells after allogeneic HCT. In addition to the BTK-mediated effects of ibrutinib, the compound is known to inhibit ITK, a tyrosine kinase which plays a central role in T-cell differentiation (15). By inhibiting ITK, ibrutinib may drive donor T-cells toward a Th1 phenotype, which is hypothesized to generate more effective graft--vs-leukemia reactions.

2.4 Study Design

This is a treatment, single-group, single-intervention, open-label, non-randomized efficacy trial.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklists in Appendices A & B. Eligibility will be assessed initially before allogeneic HCT, and second confirmation of eligibility will be assessed prior to the administration of ibrutinib, between Day +60 and Day +90 after allogeneic HCT.

3.1 Inclusion Criteria

3.1.1 Inclusion Criteria for enrollment (pre-transplant)

- Diagnosis of acute myeloid leukemia (AML), acute biphenotypic leukemia, or acute lymphoblastic leukemia (ALL). CML transformed to blast crisis is eligible.
- Planned allogeneic HCT using FLU/MEL or FLU/BU conditioning (regimens defined below).
- Planned GvHD prophylaxis consisting of TAC/MTX or TAC/SRL (regimens defined below).
- HLA-identical sibling donor, HLA-matched unrelated donor, or donor mismatched at 1 HLA allele or antigen.
- Less than or equal to 5% blasts on bone marrow examination within 60 days of starting conditioning.
- Age ≥ 18 years and ≤ 70 years.
- Able to give informed consent.

Subjects will be eligible if their planned conditioning regimen for allogeneic HCT consists of one of the two following standard reduced-intensity conditioning regimens:

- FLU/MEL: Fludarabine 120 to 180 mg/m^2; melphalan ≤ 150 mg/m^2
- FLU/BU: Fludarabine 120 to 180 mg/m^2; busulfan ≤ 8 mg/kg orally or ≤ 6.4 mg/kg intravenously

Subjects will be eligible if their planned post-grafting immunosuppression consists of one of the two following regimens:

- TAC/MTX: Tacrolimus (oral or intravenous) and intravenous methotrexate administered according to institutional standard practice.
- TAC/SRL: Tacrolimus (oral or intravenous) and oral sirolimus, administered according to institutional standards of care.

These two regimens of post-grafting immunosuppression have been shown to produce equivalent rates of GvHD, relapse-free survival, and GvHD-free survival in a prospective, randomized controlled trial (16), and we thus view them as equivalent for the purposes of this clinical trial. Immunosuppressant doses and taper schedules will be adjusted based on institutional standard practice and clinical factors, at the discretion of the attending physician, as in previous clinical trials of these regimens (16).

3.1.2 Inclusion criteria (prior to ibrutinib administration)

- Age ≥ 18 years
- Adequate hematologic function, defined as ANC > 0.75 x 10^9/L; platelet count > 50 x 10^9/L; and hemoglobin > 8.0 g/dL without transfusion or growth-factor support for at least 7 days prior to screening (with the exception of pegylated G-CSF and darbopoietin, which require at least 14 days of abstinence prior to screening)
- Adequate hepatic and renal function, as defined by serum AST and ALT ≤ 3.0 x upper limit of normal (ULN); estimated creatinine clearance ≥ 30 mL/min via Cockroft-Gault formula; nd bilirubin ≤ 1.5 x ULN (unless elevated bilirubin is due to Gilbert's syndrome or of non-hepatic origin)
- Adequate coagulation studies, defined as PT/INR and PTT (aPTT) ≤ 1.5 x ULN
- Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon screening.
- Male and female subjects who agree to use both a highly effective method of birth control (eg, implants; injectables; combined oral contraceptives; some intrauterine devices [IUDs]; sexual abstinence; or sterilized partner) and a barrier method (eg, condoms; vaginal ring; sponge; etc) during the period of therapy and for 30 days after the last dose of study drug for females and 90 days after the last dose of the study drug for males.
- Between Day +60 and Day +90 after allogeneic HCT

3.2 Exclusion Criteria

3.2.1 Exclusion Criteria for enrollment (pre-transplant)

- Active involvement of the central nervous system with malignancy (previous CNS involvement is allowed if clearance of CNS disease has been documented prior to enrollment)
- Pregnant or breastfeeding
- Karnofsky Performance Status < 60%
- Active leukemia (> 5% leukemic blasts in peripheral blood or bone marrow)
- Non-hematologic malignancy with a life expectancy of < 5 years
- Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR-positive will be excluded.*
- Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
- History of other malignancies, except:
  - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma *in situ* without evidence of disease.

3.2.2 Exclusion Criteria (prior to ibrutinib administration)

- Active and uncontrolled acute GvHD Grades III or IV
- Use of secondary therapy for acute GvHD at any time (defined as any systemic therapy intended to treat acute GvHD besides corticosteroids)
- Requirement for anticoagulation with warfarin or other Vitamin K antagonists (concomitant use of other anticoagulants is permitted)
- Relapsed leukemia (> 5% leukemic blasts in peripheral blood or bone marrow after allogeneic HCT)
- Karnofsky Performance Status < 60%
- Chemotherapy ≤ 21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 6 weeks prior to first administration of study treatment
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- 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.

- History of stroke or intracranial hemorrhage within 6 months prior to screening
- 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.
- Major surgery within 4 weeks of first dose of study drug.
- Any uncontrolled active systemic infection.
- Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia
- Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction
- Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor (see Appendix E).
- 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).
- Currently active, clinically significant hepatic impairment (Child-Pugh Class B or C)
- Lactating or pregnant
- Uncontrolled cardiac arrhythmias

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

Primary Completion:

The study is expected to complete accrual within 1 year, and to complete treatment within 2 years of opening.

Study Completion:

The study is expected to be completed within 2.5 years of opening.

4. TREATMENT PLAN

Subjects will be assessed for eligibility and enrolled prior to allogeneic HCT, using the pre-transplant inclusion and exclusion criteria above. Eligible and enrolled subjects will then be reassessed prior to the administration of ibrutinib, which may begin at any point between Day +60 and Day +90 after allogeneic HCT, using the pre-ibrutinib inclusion and exclusion criteria above. Ibrutinib will not be initiated until the enrollment checklist has been reviewed by the coordinating center; a minimum of 48 hours' notice is required.

If subjects are deemed ineligible prior to beginning ibrutinib therapy, they may be reassessed for eligibility at any point until Day +90 after allogeneic HCT, and ibrutinib may be initiated if they meet all relevant criteria at any point between Day +60 and Day +90 after allogeneic HCT. Subjects beyond Day +90 will not be eligible to initiate ibrutinib if they have not already done so.

Pre-transplant screening: all studies to be completed within 60 days of beginning conditioning therapy, unless otherwise indicated:

- History and physical examination, including Karnofsky Performance Status (**standard of care**)
- Serologic and/or nucleic-acid testing for HIV, hepatitis B, and hepatitis C according to institutional standard practice (**standard of care**)
- Serum pregnancy testing, for women of childbearing potential (**standard of care**)
- Bone marrow examination, including assessment of minimal residual disease by multiparameter flow cytometry or high-throughput sequencing (**standard of care**)
- Disease assessment (**standard of care**): Data forms for CIBMTR will be made available to the coordinating center. Alternatively, detailed disease assessment data will be entered directly into the electronic database.
- Complete enrollment checklist and submit to coordinating center for review prior to enrollment. Preparative regimen for HCT should not begin until enrollment checklist has been reviewed by coordinating center (**research**).

Start of preparative regimen through Day +60 to Day +90:

- Pre-conditioning blood sample from HCT recipient for high-throughput sequencing, flow cytometry, and CyTOF (**research**)
- Blood sample from HCT donor (related only), as a baseline to investigate development of post-transplant GVL effects (**research**)
- Disease reassessment between Day +28 and Day +60, including bone marrow examination and assessment of minimal residual disease as described above (**standard of care**)

Prior to administration of ibrutinib (Day +60 to Day +90; all studies should be done within 2 weeks of starting ibrutinib):

- Laboratory assessment of hepatic and renal function (**standard of care**)
- Assessment of acute GvHD presence, severity, and therapy history (**standard of care**)

- History and physical, including Karnofsky Performance Status (**standard of care**)
- Assessment of concomitant medications (**standard of care**)
- Collection of peripheral blood samples for mixed lymphocyte reactions, Th1/Th2 assays, and other correlative science endpoints (**research**)

Ibrutinib will be initiated between Day +60 and Day +90, after confirmation that the subject meets all relevant eligibility criteria. The drug will be dosed, and doses modified, as described below. The following assessments will be performed after initiation of ibrutinib:

After start of ibrutinib until 2 years post-transplant (tests should be performed +/- 2 weeks of given time points through Day +180, and +/- 4 weeks of given timepoints after Day +180):

- History, physical examination, and laboratory assessment of hematologic and chemistry tests per institutional standard practice (**standard of care**)
- Acute GvHD assessment weekly through Day +100 (**standard of care**)
- Chronic GvHD assessment at 6 months, 9 months, 12 months, 15 months, 18 months, and 2 years post-transplant (**standard of care**)
- Toxicity assessment at baseline (before starting ibrutinib), weekly through Day +100, monthly until Day +180, and then at 9 months, 12 months, 15 months, and 18 months post-transplant (**research**), unless ibrutinib has been permanently discontinued
- **In subjects with AML, myeloid blast crisis, or biphenotypic leukemia**: bone marrow examination, including assessment of minimal residual disease by multiparameter flow cytometry, at Day +90; Day +180; and 1 year post-transplant (**standard of care**). Please note: Okay to omit Day +90 MRD testing and Day +90 biopsy if previous biopsy (between Day +28 and Day +60) showed no evidence of disease.
- **In subjects with ALL or lymphoid blast crisis**: minimal residual disease testing by peripheral-blood high-throughput sequencing (ClonoSEQ) at Day +90; Day +180; 1 year; 1.5 years; and 2 years post-transplant (**standard of care**)
- Peripheral blood draw for mixed lymphocyte reactions, Th1/Th2 assays, and other correlative science at Day +90; Day +180; 1 year; 1.5 years; and 2 years post-transplant (**research**)

4.1 General Concomitant Medication and Supportive Care Guidelines

Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines. Transfusions may be given in accordance with institutional policy.

Medications to be Used with Caution

CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole; indinavir; nelfinavir; ritonavir; saquinavir; clarithromycin; telithromycin; itraconazole; nefazadone; or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole; erythromycin; amprenavir; aprepitant; atazanavir; ciprofloxacin; crizotinib; darunavir/ritonavir; diltiazem; fluconazole; fosamprenavir; imatinib; verapamil; amiodarone; or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Appendix E Inhibitors and Inducers of CYP3A).
- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix E. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Drugs That May Have Their Plasma Levels Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). 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 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, should be taken at least 6 hours before or after ibrutinib.

QT-prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

Antiplatelet Agents and Anticoagulants

Fatal bleeding events have occurred in subjects treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of subjects. Bleeding events of

any grade, including bruising and petechiae, occurred in approximately half of subjects treated with ibrutinib. The mechanism for the bleeding events is not well understood.

Ibrutinib may increase the risk of hemorrhage in subjects receiving antiplatelet or anticoagulant therapies. See Section 6 (Dose Modification) for recommendations regarding ibrutinib dosing in subjects undergoing surgery or other invasive procedures.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. 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.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib held, and ibrutinib should 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.

Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving study treatment with ibrutinib. Localized, hormonal, or bone-sparing treatment for non-hematologic may be considered with approval of the PI.

The Sponsor-investigator must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with relevant institutional and national guidelines. Transfusions may be given in accordance with institutional policy.

Antimicrobial prophylaxis

All subjects should receive antimicrobial prophylaxis appropriate for allogeneic HCT recipients, according to institutional standard practice. If no institutional standard practice exists, one recommended (although not required) approach is as follows:

- Acyclovir 400 mg TID for 1 year after allogeneic HCT or until discontinuation of all systemic immunosuppressive medication, whichever occurs later.
- Bactrim SS 1 tablet daily for 6 months after allogeneic HCT or until discontinuation of all systemic immunosuppression, whichever occurs later.
- Fluconazole 400 mg daily from start of transplant conditioning until Day +75 after allogeneic HCT.

Antimicrobial prophylaxis should be adjusted according to subject-specific risks, infectious history, institutional susceptibility data, and subjects' clinical condition.

4.2 Criteria for Removal from Study

Ibrutinib will be continued until 18 months post-transplant, or until one of the following occurs: disease relapse; or discontinuation due to adverse events. Subjects with leukemia relapse after allogeneic HCT will discontinue the study drug, and may be treated with any and all appropriate therapies, including investigational agents, at the discretion of the treating physician.

Subjects will be withdrawn from study treatment if one of the following occurs: leukemia relapse; unacceptable toxicity requiring interruption of ibrutinib for more than 28 continuous days; investigator decision; withdrawal of consent by the subject for further treatment and/or follow-up; pregnancy; or study termination. All enrolled subjects, regardless of discontinuation of study treatment, will be followed for leukemia relapse and survival until 18 months after allogeneic HCT unless the subject withdraws consent for follow-up.

Withdrawal from the study will occur under the following conditions: withdrawal of consent for follow-up observation by the subject; loss to follow-up; study termination; or death. When an enrolled subject withdraws from the study, the reason for withdrawal should be documented, as should the subject's willingness to participate in follow-up visits or assessments.

4.3 Alternatives

The alternative to participation on this study is to receive allogeneic HCT on other clinical protocols or treatment plans without the use of maintenance ibrutinib. This alternative will be discussed with subjects during the informed consent process.

5. INVESTIGATIONAL AGENT INFORMATION

5.1 Investigational Agent

The investigational agent utilized in this clinical trial is ibrutinib, administered at a dose of 420 mg orally once-a-day (with dose adjustments for concomitant medications or toxicity as described elsewhere in this protocol) and continued for 1 year, until disease progression, or until discontinuation due to adverse events. **EXCEPTION**: The starting dose for subjects with mild liver impairment (Child-Pugh Class A) is defined to be 140 mg/day.

Ibrutinib capsules are size 0, hard gelatin capsules for oral administration and contain 140 mg of micronized ibrutinib (content may be adjusted for water content and purity) and the following compendial excipients (National Formulary, Pharmacopoeia Europe, Japan Pharmacopoeia): microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; and magnesium stearate. Capsules are packaged in high-density polyethylene bottles with an induction seal and a child resistant screw-top cap. The number of capsules per bottle is indicated on the label.

Ibrutinib capsules should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15° C to 25° C (59° F to 77° F) with excursions permitted to 30° C (86° F). Ibrutinib should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. Ibrutinib must not be taken with grapefruit juice.

There are limited data on the effects of ibrutinib overdose. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). There is no specific antidote for ibrutinib. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

For the most comprehensive information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of Bruton's tyrosine kinase (17). *In vitro*, ibrutinib is a potent inhibitor of Btk activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (18).

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (18). Ibrutinib also inhibited adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (19).

Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QT_c) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell

atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in subjects administered the dose of 420 and 560 mg daily, respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg. Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

Pharmacokinetics and Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15-times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [14C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [14C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in subjects with severe renal impairment or subjects on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

Summary of Clinical Safety

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below in Table 1.

Table 1. Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs > 10%	Most frequently reported Grade 3 or 4 TEAEs > 2%	Most frequently reported Serious TEAEs > 1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

For more detailed information refer to the current version of the IB.

Risks

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion; epistaxis; and petechiae; and some major hemorrhagic events including gastrointestinal bleeding; intracranial hemorrhage; and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (> 400,000/μL) may confer increased risk. Consider temporarily holding ibrutinib. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count > 5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with mantle cell lymphoma (MCL)

treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, > 400,000/μL) has been observed in some subjects. Lymphocytosis was not commonly observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6).

Cytopenias

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

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. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 6).

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in subjects treated with ibrutinib. Cases of hepatitis E, which may be chronic, have occurred in patients treated with ibrutinib. Subjects should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting and jaundice, and abnormal liver function tests) and appropriate therapy should be instituted as indicated.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count > 5,000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL

treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, > 400,000/μL) has been observed in some subjects. Lymphocytosis was not observed in subjects with WM treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

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.

Rash

Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study 1112. Most rashes were mild to moderate in severity.

Tumor lysis syndrome (TLS)

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities

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. Should symptoms develop, follow the protocol dose modification guidelines (see Section 6).

5.2 Availability

Ibrutinib will be provided for this clinical trial by its manufacturer, Pharmacyclics.

5.3 Agent Ordering

Each study site will order their drug stock through Pharmacyclics. Ibrutinib will be requested from the research pharmacy at each study site.

5.4 Agent Accountability

Ibrutinib will be kept secure according to institutional guidelines and will be processed and dispensed by Investigational Drug Services at Stanford University and by analogous services at outside collaborating centers.

Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in subjects. 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 1,680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1,680 mg. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 7.2 for further information regarding AE reporting.

6. DOSE MODIFICATIONS

The study dose levels of ibrutinib are defined as follows.

Dose level 0: 420 mg orally once a day.
Dose level -1: 280 mg orally once a day.
Dose level -2: 140 mg orally once a day.
Dose level -3: Discontinue ibrutinib.

The dose of ibrutinib should be modified according to the dose modification guidelines in Table 2 if any of the following toxicities occur and are considered to be due to ibrutinib.

Hematologic Adverse Events

- Grade 3 ANC (< 1,000/ μL) with an associated temperature ≥ 38.5°C
- Grade 4 ANC (< 500/μL) for more than 7 days
- Grade 3 thrombocytopenia (< 50,000/μL) in the presence of Grade ≥ 2 bleeding events
- Grade 4 thrombocytopenia (< 25,000/μL)

Non-Hematologic Adverse Events

- 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 toxicity attributed to ibrutinib

Table 2: Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥ 750 or platelets > 25,000 with no evidence of Grade ≥ 2 bleeding; may restart at original dose level
Second	Withhold ibrutinib until recovery to an ANC ≥ 750 or platelets > 25,000 with no evidence of Grade ≥ 2 bleeding; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to an ANC ≥ 750 or platelets > 25,000 with no evidence of Grade ≥ 2 bleeding; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib [a]
Non-Hematologic Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib [a]

[a] If ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

Dose changes must be recorded. At the Investigator's discretion, the dose of ibrutinib may be re-escalated after 8 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

Dose modifications for use with CYP3A inhibitors

Concomitant use of strong CYP3A inhibitors which would be taken chronically (eg, ritonavir; indinavir nelfinavir; saquinavir; boceprevir; telaprevir; nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (eg, antifungals and antibiotics) either reduce ibrutinib dose to 140 mg daily or withhold ibrutinib therapy until the CYP3A inhibitor is no longer needed.

Reduce ibrutinib dose to 140 mg orally once daily if a moderate CYP3A inhibitor must be used (eg, fluconazole; darunavir; erythromycin; diltiazem; atazanavir; aprepitant; amprenavir; fosamprevir; crizotinib; imatinib; verapamil; and ciprofloxacin). Subjects taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

As most study subjects are expected to be receiving azoles (fluconazole; voriconazole; posaconazole) until at least Day +75 after allogeneic HCT, the dose of ibrutinib will be 140 orally once daily while on such medications. Once these agents are stopped, the dose may be escalated to 420 mg once daily.

Dose modifications for hepatic impairment

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh Class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose reduction for ibrutinib is to 140 mg daily (1 capsule). Subjects who develop moderate or severe hepatic impairment (Child-Pugh Class B or C) will have study drug withheld until resolved to mild impairment (Child-Pugh Class A) or better. Subjects who completely resolve liver impairment may re-initiate ibrutinib treatment according to Table 2. Subjects who resolve liver impairment to mild (Child-Pugh Class A) may re-start ibrutinib treatment at 140 mg daily (1 capsule). Continue to monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Table 2).

Dose modifications for planned surgery or invasive procedures

The following recommendations should be considered during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

a. For any planned major surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention 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 serosanguineous drainage or the need for drainage tubes.

b. For planned minor procedures (such as a central line placement, needle biopsy, 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 for these procedures.

c. For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator.

Ultimately, the management of ibrutinib in conjunction with invasive procedures depends upon the perceived bleeding risk, the subject's clinical situation, and the urgency of the procedure.

6.1 Treatment Discontinuation

Study treatment with ibrutinib will be permanently discontinued for any subject if any of the following occur.

- Grade 4 treatment related (ie, possibly-, probably-, or definitely-related) non-hematologic toxicity
- Grade 4 neutropenia lasting > 21 days
- Grade 4 thrombocytopenia lasting > 21 days or associated with clinically significant bleeding (requiring > 3 units of packed red blood cells within 24 hours

to replace loss OR bleeding from a site which in the Investigator's opinion is a potential life-threatening source irrespective of blood loss)

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Please see "Risks" in Section 5.1 above for a full description of known risks and toxicities associated with ibrutinib.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

An adverse event (AE) will be defined as any medical change in the subject's baseline or pre-treatment condition (occurring during the course of the clinical study) after receiving the study drug (ibrutinib), whether considered treatment-related or not. Adverse events will be monitored spontaneously by the subject or will be discovered as a result of general questioning by the investigator or by physical examination. All adverse events will be recorded. As far as possible, each adverse event will be described by its duration (start and end dates), frequency (single episode, intermittent, continuous), severity (mild, moderate, severe) and assessment of its cause (the underlying study indication, co-existing disease, concomitant medication, investigational drug, or other), relationship to investigational drug (unrelated, unlikely, possibly, probably, definitely), whether it influenced the course of treatment, whether it required specific therapy and what is expected or unexpected. All adverse events will be graded on a three point scale of increasing severity. Serious adverse events will be reported to the IRB and appropriate regulatory agencies.

An adverse event is any significant medical occurrence in a subject treated on this protocol both during treatment and follow-up period, regardless of causality assessment. This includes adverse clinical or laboratory findings, inter-current illness, or an exacerbation or progression of a condition present at the time of study initiation. An adverse event is considered serious if it fulfills one of the following criteria:

a. Results in death
b. Life-threatening (subject at risk of death at the time of the event)
c. Requires inpatient hospitalization or prolongation of existing hospitalization
d. Results in persistent or significant disability
e. Other medical events that may not be immediately life-threatening or result in death or hospitalization by may jeopardize the subject or require intervention to prevent one of the outcomes listed above

Study subjects will be instructed to report any adverse events to investigators and subjects will be evaluated for adverse events at every clinic visit. All adverse events will be documented by investigators and will contain the following information, if known:

a. Medical diagnosis of the event
b. Date and time of onset of event
c. Date and time of resolution of event
d. Severity of the event according to the National Cancer Institute (NCI) Common Toxicity Criteria and Adverse Events (CTCAE) criteria, version 4.0
e. Frequency of the event
f. Intervention
g. Outcome
h. Likelihood of association between the event and the study drug

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 informed consent form 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.

Serious adverse events (SAEs) CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences. If complete information is not available at the time, the investigator must provide follow-up information as soon as it is known.

Adverse events that are serious and unexpected suspected adverse reactions, and are possibly, probably, or definitely related to the study drug ibrutinib (SUSAR per 21CFR§312.32), will be reported to the FDA via IND Safety Report [21CFR§312.32]

within 14 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction.

In addition, all serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Report Form from Pharmacyclics and sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (for instance, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

Hematopoietic cell transplantation (HCT) is an aggressive therapy for the treatment of a number of life-threatening malignant and non-malignant disorders. Individuals considered for HCT have generally exhausted other avenues of effective therapy. The non-relapse mortality (NRM) associated with a sibling-donor myeloablative allogeneic transplant is approximately 20% and the NRM for an unrelated-donor myeloablative allogeneic transplant ranges from 20-50%. In the setting of reduced-intensity conditioning and allogeneic HCT, the NRM is approximately 10% with a sibling donor and 20% with an unrelated donor.

As an aggressive therapy, HCT is associated with a large number of AEs and SAEs. The toxicities associated with HCT are related to the following: 1) the underlying disease; 2) therapy antecedent to HCT; 3) the health status of the transplant recipient, including co-existing conditions; 4) the preparative regimen employed before transplant; 5) therapies directed at reducing transplant-related complications (eg, immunosuppressants for the prevention of GvHD); and 6) the treatment of complications of HCT.

The use of toxicity grading scales such as the NCI CTC is a standard in the medical community for the reporting of AEs and SAEs in the investigation of new drugs or devices. The use of this type of scale is less helpful in the evaluation of AEs and SAEs associated with a treatment, such as HCT. In an effort to report to regulatory agencies the toxicities that are relevant and meaningful for the evaluation of risks and benefits to potential HCT recipients, the following guidelines will serve to determine which events are reported as AEs and SAEs.

The following SAEs require reporting to the Stanford Cancer Institute Data Safety Monitoring Board for subjects on research protocols. If the event is unexpected, serious, and harmful, then it will also require reporting to the IRB:

1) Deaths

All deaths:

- while the subject is receiving treatment on a protocol
- up to 60 days (autologous) or 90 days (allogeneic) after last dose of protocol treatment
- or any death that occurs more than 60 days (autologous) or 90 days (allogeneic) after protocol treatment has ended that is felt to be treatment related.

Reports will include deaths from the common and expected Grade 4 toxicities noted below. Deaths that occur outside of Stanford will be reported whenever possible. It must be noted that obtaining detailed information on the cause and circumstances of a death occurring at another institution can be difficult. Excludes deaths related to relapse of underlying disease, which will reported to the IRB at the time of protocol renewal.

2) All serious and unexpected toxicities

Defined as those toxicities not identified in the transplant literature, product inserts, or study consent form.

The following will be *recorded*, but generally will **not** be *reported* as AEs or SAEs, unless also considered related to the study drug.

1) Hospitalizations

Approximately 50% of allogeneic transplant recipients will be readmitted to the hospital. The most common indications for readmission of an allogeneic HCT recipient are fever, failure to maintain nutritional status, and GvHD. NOTE: Events that result in hospitalization or extend hospitalization will still be considered SAEs.

2) Relapse of disease

Relapse unfortunately remains a significant problem following both autologous and allogeneic HCT. The risk of relapse is influenced by both subject and disease variables. The risk of relapse following allogeneic transplant is extremely dependent on the disease being treated but ranges from 10% (for subjects with severe aplastic anemia) to 80% (for subjects with refractory acute leukemia).

3) Common and expected toxicities of HCT ≤ Grade 4 that are well-described in transplant literature, the product inserts, or study consent form and do not result in death.

In general, these toxicities are considered reversible. The specific reporting requirements are found in the protocol. These Grade 4 toxicities include, but are not limited to, alopecia, anemia, anorexia, bleeding requiring transfusions, cardiac arrhythmias , central venous catheter infections, constipation, diarrhea, edema, fatigue, febrile episodes, gastritis, graft failure, graft versus host disease, hematuria , hypertension, hypotension, hypoxia, incontinence, infections, insomnia, laboratory abnormalities, mental status changes, mood alterations, mucositis, nausea , neutropenia, pain, pleural effusion, pneumonitis, rash, seizures, sepsis, sinusoidal obstructive syndrome, tachycardia, thrombocytopenia, thrombotic microangiopathy, tremor, vomiting. For IND studies, SAEs that are SUSARs per 21CFR§312.32 will be reported as IND Safety Reports (see above).

4) Acute and chronic GvHD

Acute and chronic GvHD are major complications of HCT and account for most non-relapse mortality. The incidence of GvHD will be reported as part of the secondary outcomes and to the IRB at the time of the protocol annual review.

5) Secondary Malignancies

The occurrence of secondary malignancies and associated mortality is a known risk of cancer therapies. The occurrence of secondary malignancies will be reported to the IRB at the time of the protocol annual review.

6) Special reporting situations which 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)

Occurrence of any special reporting situation should be recorded in the CRF. If any special reporting situation meets the criteria for an adverse event, it should be recorded on the adverse events CRF. If the adverse event is considered serious, it should be recorded on the adverse events CRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 15 days of awareness.

Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. The following events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per SAE reporting timelines.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events 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 v4.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest.

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 ([redacted]@pcyc.com) or fax (408-215-3500) to Pharmacyclics Drug Safety, or designee, within 15 days of

the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events 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)

8. CORRELATIVE/SPECIAL STUDIES

We propose a series of correlative laboratory studies using blood samples collected from study participants, with the aim of elucidating the impact of ibrutinib on immune reconstitution after allogeneic HCT and on the development of alloreactivity, graft--vs-tumor effects, and GvHD.

Background

Alloreactive T- and B-cells play a crucial role in development of both beneficial graft-vs-tumor effects and harmful GvHD after allogeneic HCT. In chronic GvHD, T follicular helper cells (TFH), Th2, and Th17 T-cells activate B-cells and elicit fibrotic cascades underpinned by alloantibody production and collagen deposition. To understand the impact of ibrutinib on alloreactivity after allogeneic HCT, we will perform global B- and T-cell immune phenotype analysis using multiplexed CyTOF analysis, focused on quantifying Th2 subversion and cytotoxic T-cell preservation, T follicular cell composition, and T-cell functional activation. These laboratory assays will be correlated with clinical evidence of GvHD and GVL effects (quantified by measuring minimal residual disease via sequencing of T- and B-cell immune receptors with clonoSEQ technology (in subjects with ALL) and via multi-parameter flow cytometry (in subjects with AML).

T- and B-cell repertoire reconstitution will be monitored via immune receptor high-throughput sequencing (HTS) and H-Y alloreactive B-cell phenotyping. We will determine the effect of ibrutinib on serum immunoglobulin levels, cytokine quantification, protective anti-EBV and anti-tetanus immunity, and allogeneic H-Y antibody responses after allogeneic HCT.

Minor histocompatibility antigens expressed on the Y chromosome are called H-Y antigens and are frequently targeted by female donor lymphocytes when male subjects undergo sex-mismatched transplantation (F→M HCT). Dr Miklos' lab has demonstrated that H-Y specific B-cells and antibodies are associated with chronic GvHD following F→M HCT. We hypothesize that ibrutinib will preferentially target and deplete

alloreactive B-cell. While H-Y antigen provides a model system to study antigen-specific alloimmunity, H-Y can only be studied in male subjects with female donors (F→M HCT). Recognizing this limitation for H-Y antigen studies, as well as limitations in the number of PBMC available for research per subject, we have decided to dedicate F→M HCT subject samples to H-Y B-cell analyses while using samples from all other donor and recipient sex combinations (not F→M) for T-helper cell and functional T-cell analyses as shown in Table 3 below. Historically, F→M allotransplants account for 35-40% of cases of chronic GvHD.

Sample collection

As in the PCYC 1129 protocol, 50 mL of blood will be collected in five 10 mL heparinized green-top tubes before the start of conditioning therapy; before ibrutinib intiation; and then again at Day +180, 1 year, and 1.5 years after allogeneic HCT. We will also obtain blood samples from the HCT donor. The 50 mL aliquots of recipient blood will be processed on-site at Stanford University, providing three vials of 1.5 mL plasma and five 1 mL vials of viably frozen peripheral blood mononuclear cells (PBMC) separated by Ficoll gradient centrifugation as described in the PCYC1129 laboratory manual. PBMC cell yields will be recorded and evenly distributed into five vials irrespective of cell quantity. Plasma will be stored at -80° C and PBMC will be stored in liquid nitrogen on-site. Comprehensive multiplexed B- and T-cell phenotype analysis will be performed on all samples at all time points using CyTOF. In addition, B- and T-cell repertoire analyses will be determined using immune receptor high-throughput sequencing (HTS). We plan to reserve a single vial of PBMC and 1 mL plasma per subject in central storage, in case trial investigators identify additional informative studies later.

Table 3. Schedule of correlative laboratory studies.

		Pre-HCT	Pre-Ibrut.	6 m	12 m	18 m
CyTOF B- and T-cell phenotyping (PBMC 1)	Res.	All	All	All	All	All
T-cell repertoire analysis by immune receptor sequencing (PBMC 2)	Res.	All	All	All	All	All
B-cell repertoire analysis by immune receptor sequencing (PBMC 2)	ALL SOC AML Res					All
IgG & IgM quantification	SOC	All	All	All	All	All
Cytokine Analysis and BAFF (plasma 1)	Res.	All	---	---	All	All
T-Follicular quantification (PBMC 3)	Res.	All but F→M	All but F→M	All but F→M	All but F→M	All but F→M
H-Y alloreactive Antibodies (Plasma 2)	Res.	F→M only	F→M only	F→M only	F→M only	F→M only
H-Y specific B-cell characterization (PBMC 4)	Res.	F→M only	F→M only	F→M only	F→M only	F→M only

Abbreviations: HCT, hematopoietic cell transplantation; Ibrut, ibrutinib; m, months; Res, research; SOC, standard of care; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; F->M, female-donor-to-male-recipient; PBMC, peripheral blood mononuclear cells

Preliminary data

We performed immune phenotyping on peripheral blood samples collected from 12 subjects who underwent allogeneic HCT for chronic lymphocytic leukemia and who were treated with ibrutinib for post-transplant relapse. In these subjects, ibrutinib rapidly depleted pre-germinal-center B-cells ($CD19^+CD38^+CD27^+IgD^+$), which have previously been associated with development of chronic GvHD. In contrast, memory B-cells ($CD19^+CD27^+IgD^-CD38^-$) persisted, and total serum IgG levels were maintained despite ibrutinib treatment. Subset analysis of T-cells showed a 75% reduction in GATA3-expressing Th2 cells, while Tbet-expressing Th1 cells remained unaffected. T follicular cells ($CD4^+CXCR5^+BCL6^+$) were likewise depleted rapidly from the circulation by ibrutinib treatment (Figure 1). Taken together, these preliminary results support the hypothesis that ibrutinib treatment after allogeneic HCT will result in Th1 polarization of the T-cell repertoire, preservation of CD8+ T-cells, and depletion of T follicular cells, all of which would be expected to reduce GvHD risk while maintaining beneficial anti-tumor alloreactivity. Of note, these preliminary data were obtained in subjects treated with ibrutinib for relapse, while the proposed study herein attempts to elucidate the role of maintenance ibrutinib on immune reconstitution and GvHD.

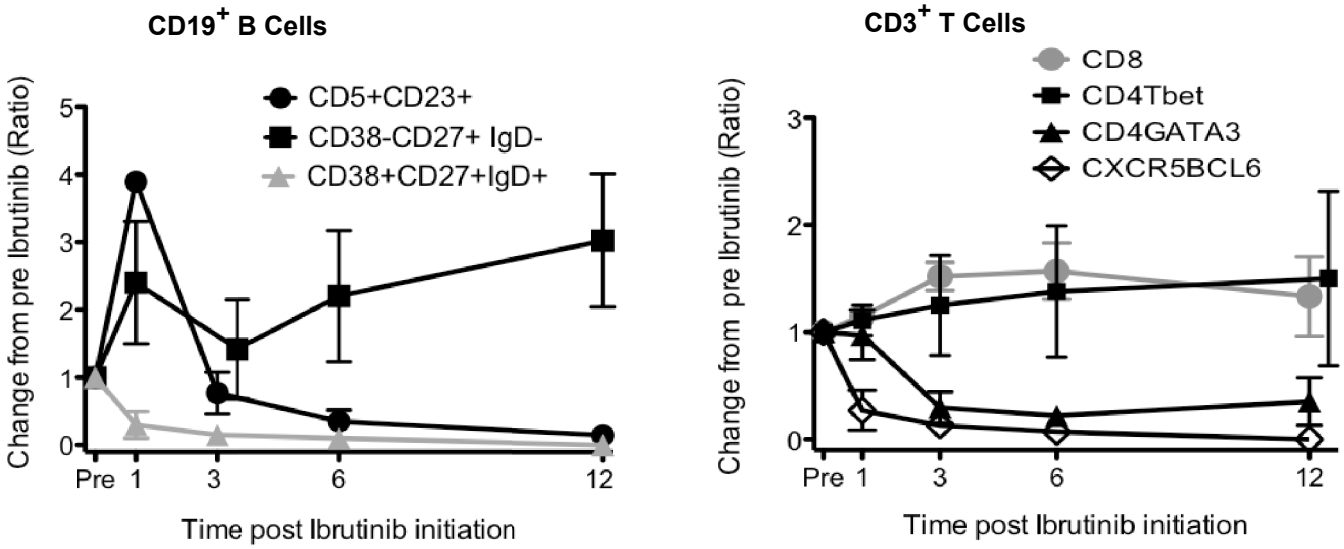


Figure 1. Changes in peripheral B-cell and T-cell subsets after treatment with ibrutinib in subjects with relapsed CLL after allogeneic HCT

Correlative science aims

1. Perform immunophenotyping of peripheral-blood B- and T-cells before and after initiation of maintenance ibrutinib.
   a. Evaluate Th1 polarization, effect on T follicular cells, and $CD8^+$ cytotoxic T lymphocytes
   b. Evaluate B-cell reconstitution by quantifying transitional, naïve, memory, and activated plasmablast fractions

   c. Determine concentrations of Th1 and Th2 cytokines in plasma

2. Characterize the B- and T-cell repertoire during and after ibrutinib maintenance using immune receptor high-throughput sequencing to assess clonal expansion of donor cytotoxic T-cells and follicular T-cells.
   a. Compare to results from patients transplanted at our institution without maintenance ibrutinib
   b. Quantify EBV-specific T-cell reconstitution
3. Assess B-cell function before and after initiation of maintenance ibrutinib
   a. Evaluate for presence of alloreactive B-cells and H-Y antibodies in F->M allogeneic HCT
   b. Quantify total serum immunoglobulin levels
   c. Quantify protective anti-EBV and anti-tetanus antibodies
   d. Assess levels of BAFF before, during, and after ibrutinib maintenance treatment

These laboratory studies will be correlated with clinical data (including onset, severity, and response of chronic GvHD and minimal residual disease detection of leukemia).

9. STUDY CALENDAR

Studies shown in italics are research studies, while evaluations shown in black represent clinical standard of care.

	Within 60 days of starting conditioning	Between Day +28 and Day +60	Start of ibrutinib (between Day +60 and Day +90)	Day +90	Day +180	9 months	1 year	15 months	18 months	2 years	Off Study
Eligibility determination	*X*	*X*									
History & physical	X	X	X	X	X	X	X	X	X	X	X
KPS assessment	X	X	X	X	X	X	X	X	X	X	X
Laboratory testing of hepatic and renal function	X	X	X	X	X	X	X	X	X	X	X
Transplant evaluation per institutional criteria	X										
Electrocardiogram (ECG)	X										
Hepatitis and HIV testing	X										
Pregnancy test (for women of childbearing potential)	X										
Bone marrow aspiration and/or biopsy with assessment of minimal residual disease	X	X		AML only*	AML only		AML only				
Minimal residual disease detection by peripheral-blood high-throughput sequencing (ClonoSEQ)	X	X		X*	X		X		X	X	
Assessment of concomitant medications	X	X	X	X	X	X	X	X	X		X
Acute GvHD assessment		X		X							
Chronic GvHD assessment				X	X	X	X	X	X	X	X
Ibrutinib (study drug)				*X* ----------*X*							
Adverse event evaluation				*X*----------*X*							
Blood draw for biological studies	*X*		*X*	*X*	*X*		*X*		*X*	*X*	
Blood sample from HCT donor (related only)	*X*										

For the Day +90 and Day +180 timepoints, the relevant evaluations may be performed within +/- 2 weeks of the specified timepoint. For the 9-month, 1-year, 15-month, and 18-month timepoints, the relevant evaluations should be performed within +/- 4 weeks of the specified timepoint.

* Please note: Okay to omit Day +90 MRD testing and Day +90 biopsy if previous biopsy (between Day +28 and Day +60) showed no evidence of disease.

10. MEASUREMENTS

10.1 Primary and Secondary Outcome measures

The primary outcome measure is the incidence of relapsed leukemia at 18 months after allogeneic HCT. This is an efficacy endpoint.

Secondary endpoints include the incidence of acute GvHD Grades II–IV and III–IV at Day +180 after allogeneic HCT, the incidence of chronic GvHD at 18 months after allogeneic HCT, and the incidence of detectable minimal residual disease at 1 year after allogeneic HCT.

10.1.1 Relevant Subsets

The primary and secondary outcomes will be measured on all enrolled subjects.

10.1.2 Measurement Definition

For the primary outcome measure, relapsed leukemia is defined as > 5% leukemic blasts detected in bone marrow or peripheral blood. Subjects will also be considered to have relapsed leukemia if they receive any active treatment for progressive leukemia after allogeneic HCT, even if they have <5% leukemic blasts. Withdrawal of immunosuppression alone is not considered an active treatment for progressive disease.

For the secondary outcome measures, acute GvHD will be graded and scored according to standard criteria (Appendix C). Chronic GvHD will be graded and scored according to the 2014 NIH consensus criteria (Appendix D). Minimal residual disease will be assessed by high-throughput sequencing (ClonoSEQ) for subjects with ALL, and by high-sensitivity flow cytometry for subjects with AML or acute biphenotypic leukemia. Minimal residual disease will be considered present if > 1 x 10^{-6} leukemic clones are detected by ClonoSEQ (20), or if any aberrant blasts matching the original leukemic immunophenotype are detected by high-sensitivity flow cytometry (21).

10.1.3 Measurement Methods and Time Points

The primary outcome will be measured by bone marrow examination at Day +90; Day +180; and 1 year after allogeneic HCT in subjects with AML or myeloid leukemias, and by peripheral-blood high-throughput sequencing on Day +90; Day +180; 1 year; 18 months; and 2 years post-transplant in subjects with ALL. Minimal residual disease detection by high-throughput sequencing is not itself diagnostic of relapse, but should prompt a bone marrow examination to assess definitively for relapse. Routine monitoring of peripheral blood counts and differential will also be performed according to clinical standards of care, with bone marrow examination performed in response to any concerning findings to assess for relapse.

The secondary outcomes will be measured as follows: acute GvHD will be scored weekly (if returning to the transplant center that frequently) from initiation of ibrutinib through Day +100 using the criteria described above. Chronic GvHD will be assessed at Day +180, at 9 months, at 1 year, at 15 months, and at 18 months after allogeneic

HCT, using the criteria described above. Minimal residual disease will be assessed as described above on Day +90; Day +180; 1 year; and 18 months after allogeneic HCT.

For the Day +100 and Day +180 timepoints, the relevant evaluations may be performed within +/- 2 weeks of the specified timepoint. For the 9-month; 1-year; 15-month; and 18-month timepoints, the relevant evaluations should be performed within +/- 4 weeks of the specified timepoint.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

Primary internal data monitoring will be performed by the Overall Protocol Director at Stanford and site investigators and their research staff. The Protocol Director will review data to assure the validity of data, as well as the safety of the subjects. The Protocol Director will also monitor the progress of the trial. The Protocol Director will be responsible for maintaining the clinical protocol, reporting adverse event, assuring the consent is obtained and documented, reporting of unexpected outcomes and reporting the status of the trial in the continuing renewal report submitted annually to the IRB and SRC.

A safety monitoring committee (SMC) will be composed of the Protocol Director and research staff, including other site principal investigators. The SMC will conduct regular teleconferences on at least a quarterly basis or more frequent communication between the Protocol Director and research staff may occur via email or teleconference as necessary.

The data will be monitored continuously over the accrual and follow up periods by the investigators and the study coordinators. The Protocol Director will be responsible for maintaining the clinical protocol, reporting adverse event, assuring the consent is obtained and documented, reporting of unexpected outcomes and reporting the status of the trial to the IRB and the Stanford University Cancer Center Data Safety Monitoring Board (DSMB).

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific electronic Case Report Forms (eCRFs) will document treatment outcomes for data analysis. The RedCAP database system will be used and maintained by the PI and/or his designees. The eCRFs will be secured via confidential username and password access to the research team.

11.4 Confidentiality

Subjects may be referred to this clinical trial from outside of Stanford. Therefore, study subjects will be assigned a unique study identification (ID) number. Referring physicians will be sent letters by the BMT physicians updating them on their subject's status, including information regarding the expected side effects of the treatment, necessary precautions and also the appropriate follow-up. Specific information regarding the study would not be routinely shared with the referring physician.

Subjects will be assigned a study-specific identification number (a unique number) and their data are entered into a secure database. Access to the database is password-restricted and limited to study personnel.

Research records will be maintained in a secure BMT office, and electronic data will be maintained in a study-specific, secure database. In addition, information from the main Stanford BMT database may be uploaded into the study-specific database.

All study staff will be required to complete HIPAA training. All research staff must complete the IRB human subjects research training. The study subject data are identified by a unique study ID number in the research documents. Access to the research database is limited to approved clinical and research staff. The code is maintained by the Stanford's BMT Database System Administrator, and kept in a secure location.

Study subjects will not be directly identified in any publications, presentations or correspondence.

Private Health Information (PHI) is collected and recorded at the time of the subject's first consultation with the BMT program. Additional information is collected when the subject is enrolled in a clinical trial. PHI may include some or all of the following:

1. Names and initials
2. Telephone numbers
3. Addresses including ZIP code
4. Dates, including date of birth
5. Age; sex; race; and ethnicity
6. Email addresses
7. Identification numbers, including Medical record numbers (MRNs) and Stanford Patient Number (SPN)
8. Relevant medical history as it pertains to their BMT history, malignancy for which they received their BMT, acute and chronic GvHD history, past treatments for GvHD, vital signs, diagnostic test results, laboratory values, physical exam findings, past medical history, including relevant family medical history (eg, coronary heart disease, diabetes, hypertension, etc) that may place them at risk for side effects, medication history/current medications, interval history since last clinic visit, current health complaints, GvHD assessment, and treatment plan.

Other outside agencies that may receive information include:

- Pharmacyclics LLC, its affiliates or collaborators (eg, Janssen Biotech, Inc.) or their representatives

- The Office for Human Research Protections (OHRP) in the US Department of Health and Human Services (DHHS)
- The Food and Drug Administration
- The US Centers for Medicare & Medicaid Services (CMS), the agency responsible for administration of the Medicare program
- Other federal and/or regulatory agencies as required
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Institutes of Health (NIH) / National Cancer Institute (NCI) / National Heart, Lung, and Blood Institute (NHLBI)
- Stanford Data Safety Monitoring Board
- Other Stanford investigators with IRB-approved projects (researchers outside of the BMT program will not have access to subject's identity or personal protected health information (PHI). The data will be managed using a database program. Data sets may be generated to share with investigators outside the program by de-identifying the data).

Samples will be identified by the Subject ID number. Research records are kept in a locked office. Access to the office is limited to key access. Only study personnel within the research program have access to the electronic database, the research records, or the code linking the samples to subject's identifying information.

11.5 Reporting Mechanisms

The study Protocol Director (or designee) will be responsible for the coordination and development of all protocol amendments. Any changes to the protocol or consent will be made in the form of an eProtocol modification, and will be approved prior to implementation. Any amendments to the Protocol or Informed Consent Form protocol must be sent to Pharmacyclics for review and approval prior to submission to the IRB. This process will be included in the monitoring plan. Changes or amendments to the protocol or consent will be reported to the IRB, FDA and NHLBI. All IRB actions will be reported to the DSMC, NHLBI and FDA.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design, Effect Size, and Sample Size

This study is designed as a single-arm efficacy trial using historical published controls. This study's primary endpoint is the incidence of relapse at 18 months after allogeneic HCT for AML/ALL. Baseline relapse rates after reduced-intensity conditioning for these diseases in the published literature vary from 40–60% (1-6). For the purposes of study design, we will use a relatively conservative baseline relapse risk of 45%. This study is designed to detect a decrease in relapse rate from 45% to 25%. Therefore, in the power analysis we will assume that the true relapse rate in the study population is 25%, while the null hypothesis holds that the relapse rate is 45%. Under these conditions, using intent-to-treat analysis, a sample size of 50 enrolled subjects will provide 84% power to conclude that the relapse rate is lower than 45% at the two-sided significance level of 0.05. Conservatively assuming that 45 of these 50 subjects meet the secondary criteria to continue to ibrutinib treatment (Appendix B) and are treated with ibrutinib, a subgroup analysis restricted to these 45 subjects will have 78% power to conclude that the relapse rate is < 45% with a significance level of 0.05.

12.2 Interim analyses

We will monitor major adverse event rates as described above, in particular serious bleeding complications (hemorrhage Grade 3 or 4, as defined by CTCAE v4.0). We will monitor and estimate the incidence rate of serious bleeding in study participants, and report all occurrences and corresponding analytic summaries (such as the estimated incidence rate with 95% confidence intervals) to the DSMB to assist in decision-making regarding early termination for safety.

Allogeneic HCT is an intensive therapy with many associated side effects and toxicities related to the transplant conditioning regimen; the ensuing immunosuppressed status; adverse effects of standard post-transplant medications; and graft-vs-host interactions or GvHD. Toxicities, including Grade 4 toxicities, are relatively common. Non-relapse mortality (NRM) is a definitive endpoint which captures fatal effects of any aspect of the transplant process outside of disease relapse, and thus represents the most accurate and reproducible measure of the toxicity and safety of the allogeneic HCT process.

The baseline cumulative incidence of NRM after allogeneic HCT for acute leukemia with FLU/MEL conditioning was estimated in a recent large cohort study at 20% (22).
In order to ensure that patients are not harmed by the study intervention, the formal stopping rule below monitors that the study intervention does not increase the risk of NRM in participants.

The stopping rule is based on the incidence of NRM at 1 year after allogeneic HCT. Patients will be evaluable with regard to the stopping rule if they die or if they reach 1 year post-transplant, whichever occurs first. The stopping rule will be tested every increment of 5 evaluable patients. The stopping rule will be triggered if any of the following conditions are met:

Number of evaluable patients	Number of patients with NRM
5	3
10	5
15	6
20	8
25	9
30	10
35	12
40	13

If the stopping rule is triggered, the study will be terminated, and FDA so notified. This stopping rule provides 80% power to detect an increase in NRM with a type I error rate of 0.05. The stopping rule was constructed using the Pocock boundary with the same significance level for all looks at the data. The rule was created using R v.3.1.3 and the clinfun package.

12.3 Analysis Population

Subjects who are enrolled but never treated with ibrutinib (eg, due to failure to meet the secondary criteria to continue to ibrutinib treatment) will be included in the primary analysis, which will be performed as an intention-to-treat analysis. However, they will not be counted toward the overall accrual goal of 45 subjects. A planned subset analysis will be performed testing the primary and secondary endpoints in the subset of subjects who receive at least 1 dose of ibrutinib on study.

12.4 Accrual estimates

We performed 36 reduced-intensity allogeneic HCT for AML/ALL at Stanford in calendar year 2014. We will also plan to open this study at UCSF (with Dr Aaron Logan) and City of Hope (with Dr Alex Herrera). We anticipate accruing 10 to 15 subjects annually at UCSF and 20 subjects annually at City of Hope, based on their historical transplant patterns. We therefore expect that study accrual will take 1 year to complete.

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APPENDICES

APPENDIX A: Pre-Transplant Eligibility Checklist

Protocol Title:	A Phase 2 Study of Ibrutinib After Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia
Protocol Number:	**IRB-38934 / BMT302**
Principal Investigator:	Andrew R Rezvani, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC-Approved ☐ IRB-Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Pre-transplant screening: all studies to be completed within 60 days of beginning conditioning therapy, unless otherwise indicated:

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Diagnosis of acute myeloid leukemia (AML), acute biphenotypic leukemia, or acute lymphoblastic leukemia (ALL). (CML transformed to blast crisis is eligible).	☐	☐	
2. Planned allogeneic HCT using FLU/MEL or FLU/BU conditioning (as defined in protocol).	☐	☐	
3. Planned GvHD prophylaxis with TAC/MTX or TAC/SRL (regimens defined in protocol).	☐	☐	
4. HLA-identical sibling donor, HLA-matched unrelated donor, or donor mismatched at 1 HLA allele or antigen.	☐	☐	
5. Less than or equal to 5% blasts on bone marrow examination within 60 days of starting conditioning.	☐	☐	
6. Age ≥ 18 years and ≤ 70 years.	☐	☐	
7. Able to give informed consent.	☐	☐	

Exclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Active involvement of the central nervous system with malignancy (previous CNS involvement is allowed if clearance of CNS disease has been documented prior to enrollment)	☐	☐	
2. Pregnant or breastfeeding	☐	☐	
3. Karnofsky Performance Status <60%	☐	☐	
4. Active leukemia (> 5% leukemic blasts in peripheral blood or bone marrow)	☐	☐	
5. Non-hematologic malignancy with life expectancy < 5 years	☐	☐	
6. HIV positivity, active hepatitis C virus infection, or active hepatitis B virus infection. (Subjects positive for HBV surface antigen or HBV core antibody are eligible if they have a negative HBV PCR before enrollment. Those who are PCR-positive are not eligible)	☐	☐	
7. Known bleeding disorder (eg, von Willebrand's disease, hemophilia)	☐	☐	
8. History of other malignancies, except: o Malignancy treated with curative intent and with no known active disease for at least 3 years before the first dose of study drug, and felt to be at low risk of recurrence by treating physician o Adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease o Adequately treated carcinoma in situ without evidence of invasive disease	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Appendix B: Secondary criteria to continue to ibrutinib treatment

Protocol Title:	A Phase 2 Study of Ibrutinib After Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia
Protocol Number:	**IRB-38934 / BMT302**
Principal Investigator:	Andrew R Rezvani, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC-Approved ☐ IRB-Approved ☐ Contract signed ☐

IV. Continuation Criteria

Continuation Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Between Day +60 and Day +90 after allogeneic HCT	☐	☐	
2. Age ≥ 18 years	☐	☐	
3. Adequate hematologic function, defined as ANC > 0.75 x 10^9/L, platelet count > 50 x 10^9/L, and hemoglobin > 8.0 g/dL without transfusion or growth-factor support for at least 7 days prior to screening (with the exception of pegylated G-CSF and darbepoietin, which require at least 14 days of abstinence before screening)	☐	☐	
4. Adequate hepatic and renal function, defined by serum AST and ALT ≤ 3x upper limit of normal (ULN); estimated creatinine clearance ≥ 30 mL/min by Cockroft-Gault equation; and bilirubin ≤ 1.5 x ULN (unless elevated bilirubin is due to Gilbert's syndrome or of non-hepatic origin)	☐	☐	
5. Adequate coagulation studies, defined as PT/INT and PTT (aPTT) ≤ 1.5 x upper limit of normal	☐	☐	
6. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon screening.	☐	☐	

Continuation Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
7. Male and female subjects who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) and a barrier method (eg, condoms, vaginal ring, sponge, etc) during the period of therapy and for 30 days after the last dose of study drug for females and 90 days after the last dose of the study drug for males.	☐	☐	

Withdrawal Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Active and uncontrolled acute GvHD Grades III or IV	☐	☐	
2. Use of secondary therapy for acute GvHD at any time (defined as any systemic therapy intended to treat acute GvHD besides corticosteroids)	☐	☐	
3. Requirement for anticoagulation with warfarin or other Vitamin K antagonists (concomitant use of other anticoagulants is permitted)	☐	☐	
4. Relapsed leukemia (> 5% leukemic blasts in peripheral blood or bone marrow at any point after allogeneic HCT)	☐	☐	
5. Karnofsky Performance Status <60%	☐	☐	
6. Chemotherapy ≤ 21 days prior to first study drug dose and/or monoclonal antibody ≤ 6 weeks prior to first study drug dose	☐	☐	
7. Vaccinated with live, attenuated vaccine within 4 weeks of first study drug dose	☐	☐	
8. Currently active, clinically significant cardiovascular disease (eg, NYHA Class III or IV heart failure, uncontrolled arrhythmia, or acute coronary syndrome within 6 months of first study drug dose)	☐	☐	
9. History of stroke or intracranial hemorrhage within 6 months of first study drug dose	☐	☐	
10. Any life-threatening illness, medical condition, or organ dysfunction that, in the investigator's judgement, could compromise the subject's safety or put the study outcomes at undue risk.	☐	☐	
11. Major surgery within 4 weeks of first study drug dose	☐	☐	
12. Active, uncontrolled systemic infection	☐	☐	

Withdrawal Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
13. Unresolved toxicities from prior anti-cancer therapy (not resolved to CTCAE v4 Grade 1 or less, or to the levels described in these criteria, except alopecia)	☐	☐	
14. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction	☐	☐	
15. Requiring treatment with strong CYP3A inhibitor (see Appendix E)	☐	☐	
16. Unwilling or unable to participate in all required study evaluations and procedures	☐	☐	
17. 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).	☐	☐	
18. Lactating or pregnant	☐	☐	
19. Uncontrolled cardiac arrhythmias	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Continuation Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Appendix C: Grading of acute graft--vs-host disease

Organ	Stage	Description
Skin	1	Maculopapular rash over <25% of body area
	2	Maculopapular rash over 25–50% percent of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0–3.0 mg/dL; SGOT 150–750 IU
	2	Bilirubin 3.1– 6.0 mg/dL
	3	Bilirubin 6.1–15.0 mg/dL
	4	Bilirubin > 15.0 mg/dL
Gut	1	Diarrhea > 500 mL/day; or upper-gut symptoms with positive histology
	2	Diarrhea > 1000 mL/day
	3	Diarrhea > 1500 mL/day
	4	Diarrhea > 2000 mL/day; or severe abdominal pain ± ileus

Glucksberg Grade:

I Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0

II Stage 1–3 skin involvement; Stage 1 liver or gut involvement; ECOG PS 1

III Stage 2–3 skin, liver, or gut involvement; ECOG PS 2

IV Stage 1–4 skin involvement; Stage 2–4 liver or gut involvement; ECOG PS 3

Abbreviations: SGOT: serum glutamic oxaloacetic transaminase; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Appendix D: Assessment of chronic graft--vs-host disease

Assessment of chronic GvHD will be performed using the 2015 NIH consensus criteria (23). The diagnosis of chronic GvHD requires at least 1 diagnostic manifestation of chronic GvHD or at least 1 distinctive manifestation plus a pertinent biopsy, laboratory, or other tests (eg, pulmonary function tests [PFT], Schirmer's test), evaluation by a specialist (ophthalmologist, gynecologist), or radiographic imaging showing chronic GvHD in the same or another organ, unless stated otherwise.

The follow table describes the diagnostic, distinctive, other features, or features common to both acute and chronic GvHD:

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)	Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and chronic GVHD)
Skin	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures		
Females	Vaginal scarring or clitoral/labial agglutination	Ulcers		
Males	Phimosis or urethral/meatus scarring or stenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children
Liver				Total bilirubin, alkaline phosphatase > 2 × upper limit of normal ALT > 2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease‖	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper-gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

ALT indicates alanine aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

* In all cases, infection, drug effect, malignancy, or other causes must be excluded.
† Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
‡ Common refers to shared features by both acute and chronic GVHD.
§ BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).
‖ Pulmonary entities under investigation or unclassified.
¶ Diagnosis of chronic GVHD requires biopsy.

Assessment of chronic GvHD will be performed only if a subject has a diagnosis of chronic GvHD. Organ systems will be scored as outlined in the following table:

	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, capabl of self-care, >50% of waking hours ou 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 % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic 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 entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ 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
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >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 cause (specify):*_____				
LIVER	☐ 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 cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

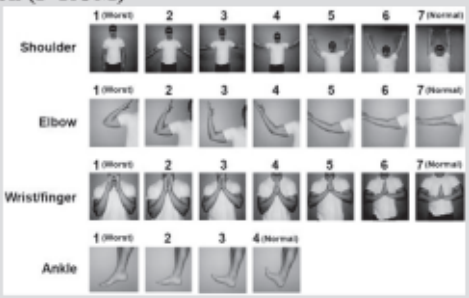
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **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):*_____				
GENITAL TRACT (*See Supplemental figure*[†]) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs[‡] and females with or without discomfort on exam	☐ Moderate signs[‡] and may have symptoms with discomfort on exam	☐ Severe signs[‡] with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

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

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



Mild chronic GVHD
1 or 2 Organs involved with no more than score 1 *plus*
Lung score 0
Moderate chronic GVHD
3 or More organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1
Severe chronic GVHD
At least 1 organ with a score of 3
OR
Lung score of 2 or 3
Key points:
In skin: higher of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix E: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	

Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Appendix F. Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34 to 50 (2 to 3)	> 50 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 to 35 (2.8 to 3.5)	< 28 (< 2.8)
PT INR	<1.7	1.71 to 2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I or II (or suppressed with medication)	Grade III or 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. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R. "Transection of the oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60:646-649.