Study Title: Optimizing post-allogeneic hematopoietic cell transplant outcomes for lymphoma using ibrutinib

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1. SYNOPSIS

Title	Optimizing post-allogeneic hematopoietic cell transplant outcomes for lymphoma using ibrutinib
Background	Given the emergence of non-hematopoietic cell transplant (HCT) options for this patient population, and the relatively high risk of non-relapse mortality (NRM) associated with HCT, only patients with advanced disease (and thus at a high risk for post HCT relapse) are typically referred for transplant. HCT has become increasingly safe, but *relapse post HCT* and *immune mediated disorders after HCT* (viz. graft-versus-host disease, GVHD) remain the main obstacles to successful outcome. Maintaining control of the neoplasm in the early post HCT period until GVT is established should lead to improved outcomes.
Primary Objective	To study the use of ibrutinib starting between days 60 and day 90 after allogeneic HCT until 12 months post HCT to improve the PFS at 12 months post HCT by 25% compared to historical controls in patients with MCL and CLL.

Secondary Objective:	• CLL/MCL cohort (Cohort A)
	  ○ To increase the incidence of successful outcome (defined as lack of requirement of second line therapy for acute GVHD, lack of NIH severe chronic GVHD, lack of progression or relapse of CLL/MCL, lack of death from disease or non-relapse causes) to at least 60% at 1 y post HCT.
	• To study the safety and tolerability of ibrutinib post HCT in patients enrolled on cohort A (CLL and MCL) and cohort B (follicular center cell lymphoma [FL] and Hodgkin lymphoma [HL]).
	• Acute GVHD
	  ○ To study the incidence of grade 3-4 acute GVHD in the first 6 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	  ○ To study the incidence of second line therapy (systemic only) for acute GVHD in the first 6 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	  ○ To study the incidence of recurrent acute GVHD in the first 6 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	• Chronic GVHD
	  ○ To study the incidence and severity of chronic GVHD in the first 12 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	  ○ To study the incidence of lung involvement with GVHD in the first 12 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	  ○ To study the incidence of sclerotic skin chronic GVHD in the first 12 months post HCT in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined)
	• To study the incidence of infectious deaths not related to GVHD in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined).
	• Correlative studies
	  ○ Cohort A: To study the association of MRD as detected by IgH sequencing prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12

	after HCT. In addition to study the impact of onset of new acute or chronic GVHD on MRD. ○ Cohort A: To study the association of T-cell clonality by T cell receptor (TCR) Vb sequencing prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12 after HCT. In addition to study the impact of onset of new acute or chronic GVHD on TCR sequencing. ○ Cohort A: To study the association of B cell receptor signaling pathways and immune function with response by single cell mass cytometry prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12 after HCT. ○ Cohort A: To study the association of single cell mass cytometry that investigates B cell receptor signaling and its association with new acute or chronic GVHD on BCR signaling.
Inclusion criteria	• Pre-SCT ○ Adult (≥ 18 y) patients undergoing their first T cell replete allo-HCT chronic lymphocytic leukemia (CLL), Hodgkin Lymphoma (HL), or the following subtypes of Non-Hodgkin lymphoma: Mantle cell lymphoma (MCL) and follicular center cell lymphoma (FL) ○ Meeting institutional criteria for allo-HCT. Ejection fraction by echocardiogram or MUGA >40%, pulmonary function test with adjusted DLCO ≥ 60% ○ Matched (8/8) or mismatched (7/8) related, unrelated HCT ○ Stem cell source: bone marrow, peripheral blood stem cell ○ Disease criteria: **Cohort A:** CLL -Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm AND -17 p deletion (detected by any assay) (≥20% of cells involved if assay is conventional cytogenetics or FISH) or NOTCH mutation at any time point during disease course. Patient should have received at least 1 line of therapy. Prior ibrutinib therapy is permitted. OR -Relapsed/refractory CLL ≥ 2 lines of therapy. Prior ibrutinib therapy is permitted MCL -Disease burden: lymph node size <5 cm and/or extra-nodal involvement < 5 cm AND --Relapsed/refractory MCL ≥ 1 line of therapy. Prior ibrutinib therapy is permitted. Prior autologous HCT is permitted OR -MCL blastoid variant in CR1 or MCL being considered for allo HCT in CR1

	Cohort B: FL - Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm AND -Relapsed/refractory FL ≥ 2 lines of therapy. Prior ibrutinib therapy is permitted HD - Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm AND -Relapsed/refractory HD ≥ 2 lines of therapy • Prior to administration of ibrutinib (day 60 to day 90 post HCT) o KPS ≥ 60% o Engraftment of neutrophils (ANC ≥ 1.0 X10^9/L) for 3 days without g-csf support o Platelets ≥100,000/mm^3 or ≥50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation o GFR ≥ 30 ml/min o LFTs (ALT and AST) ≤ 3 X ULN; total bilirubin ≤ 1.5 mg/dL XULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin o Predominant donor chimerisms of ≥ 51% as measured by CD3 and CD33 (or other myeloid marker)
Exclusion criteria	• Pre-SCT o Progression of CLL or MCL or FL or HD at time of transplant o Use of Coumadin (warfarin) or other vitamin-K antagonists for anticoagulation. Non-coumadin anticoagulation is permitted. o Active uncontrolled CNS involvement o Active uncontrolled bacterial or invasive fungal infections o History of malignancy other than the underlying disease unless treated with a curative intent and/or no evidence of disease for at least 3 y OR expected to be cured with SCT o Planned use of post-HCT cyclophosphamide for GVHD prophylaxis o Anticipated planned donor lymphocyte infusion in the first 3 months post-SCT o T cell depleted HCT o Umbilical cord HCT o History of stroke or intracranial hemorrhage within 6 months prior to enrollment. o Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

	• Prior to administration of ibrutinib (day 60 to day 90 post SCT) o In the critical care unit, or use of mechanical ventilation or use of renal replacement therapy at any time post SCT and prior to administration of ibrutinib o Active uncontrolled stage 3-4 acute GI GVHD prior to administration of ibrutinib o Active uncontrolled stage 4 acute liver GVHD prior to administration of ibrutinib o Evidence of progressive disease as compared to pre-SCT (persistence of disease is permitted) o Anticipated planned donor lymphocyte infusion in the first 3 months post-SCT o Active uncontrolled bacterial or invasive fungal infections o Prednisone equivalent of >2mg/kg for treatment of GVHD prior to administration of ibrutinib o Use of second line systemic therapy for treatment of acute GVHD prior to administration of ibrutinib o Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk including the presence of chronic/active HBV and HBC infections and Child-Pugh Class C. o Major surgery or a wound that has not fully healed within 4 weeks of starting ibrutinib o Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon). o Requires chronic treatment with strong CYP3A inhibitors o Vaccinated with live, attenuated vaccines within 4 weeks of starting ibrutinib
Study schedule	Patients will start ibrutinib at a dose of 420 mg by mouth once a day between day 60-90 post HCT and continue until 1 y post HCT. Patients on azoles will start ibrutinib at a dose of 140 mg by mouth once a day between day 60-90 post HCT and continue until 1 year post HCT. Patients using Posaconazole as outlined in section 11.2 will start ibrutinib at a dose of 70 mg by mouth once a day between day 60-90 post HCT and continue until 1 year post HCT.

2. INTRODUCTION

Chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) represent the heterogeneity of B-cell Non-Hodgkin lymphoma, with varying natural histories and pathobiology. Interestingly, targeting the B-cell receptor signaling pathway using ibrutinib, a Bruton tyrosine kinase inhibitor, favorably impacts both of these diseases[1-6]. Despite advances in both cytotoxic and immunotherapeutic approaches, an allogeneic hematopoietic cell transplant (HCT) is the only curative option[7-11]. This is primarily mediated by graft-versus-tumor (GVT) effect[12-14]. Given the emergence of non-HCT options for this patient population, and the relatively high risk of non-relapse mortality (NRM) associated with HCT,

only patients with advanced disease (and thus at a high risk for post HCT relapse) are typically referred for transplant. HCT has become increasingly safe, but *relapse post HCT* and *immune mediated disorders after HCT* (viz. graft-versus-host disease, GVHD) remain the main obstacles to successful outcome. Maintaining control of the neoplasm in the early post HCT period until GVT is established should lead to improved outcomes. Use of conventional cytotoxic agents is not practical in the early post HCT period.

We propose the following primary objective: to study the use of ibrutinib starting between day 60 and day 90 after HCT until 12 months post HCT to improve the progression-free survival (PFS) at 12 months post HCT by 25% compared to historical controls in patients with of CLL and MCL (cohort A).

GVHD is a complex immune phenomenon that is classically defined as acute and chronic and affects a variety of organ systems. The initial phase of GVHD is primarily T cell mediated. Figure 1 shows the various roles of the normal B cell. Adequate pre-clinical and clinical data shows that B-cell dysfunction contributes to chronic GVHD[15-20] . Pre-clinical data shows that part of this dysfunction is due to hyper-responsiveness of the B-cell receptor (BCR), which can be abrogated by disrupting the signaling downstream of the BCR[21]. Thus, it is conceivable that using ibrutinib post HCT may not only lead to effective tumor control but down modulate GVHD. Based on these data, ibrutinib was studied as a single agent for established chronic GVHD (NCT02195869) and approved for chronic GVHD after failure of one or more lines of systemic therapy. It is likely that the effect on GVHD may be prevalent in patients with other lymphomas as well.

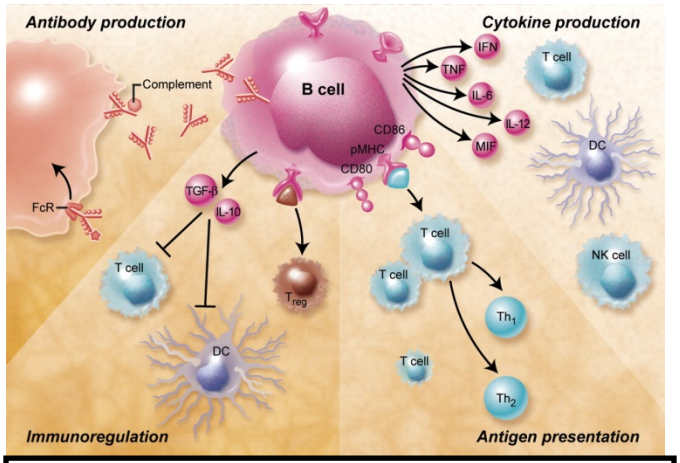


Figure 1: The various functions of the normal B cell in the setting of HCT

Thus, in the *secondary objective: we propose to study the safety, tolerability and impact on acute and chronic GVHD. This aim will encompass diagnoses other than CLL and MCL and will include follicular center cell lymphoma (FL) and Hodgkin lymphoma (HL) (Cohort B).*

3. PRIMARY OBJECTIVE

To study the use of ibrutinib starting between day 60 and day 90 after allogeneic HCT until 12 months post HCT to improve the PFS at 12 months post HCT by 25% compared to historical controls. The sample size is designed to address this primary endpoint.

4. SECONDARY AND EXPLORATORY OBJECTIVES

- CLL/MCL cohort (Cohort A)
    - To increase the incidence of successful outcome (defined as lack of requirement of second line therapy for acute GVHD, lack of NIH severe chronic GVHD, lack of progression or relapse of CLL/MCL, lack of death from disease or non-relapse causes) to at least 60% at 1 year post HCT.

- To study the safety and tolerability of ibrutinib post HCT in patients with non-Hodgkin lymphoma (NHL) and HL (cohort A and B combined)
- Acute GVHD
    - To study the incidence of grade 3-4 acute GVHD in the first 6 months post HCT in patients with NHL and HL (cohort A and B combined)
    - To study the incidence of second line therapy (systemic only) for acute GVHD in the first 6 months post HCT in patients with NHL and HL (cohort A and B combined)
    - To study the incidence of recurrent acute GVHD in the first 6 months post HCT in patients with NHL and HL (cohort A and B combined)
- Chronic GVHD
    - To study the incidence and severity of chronic GVHD in the first 12 months post HCT in patients with NHL and HL (cohort A and B combined)
    - To study the incidence of lung involvement with GVHD in the first 12 months post HCT in patients with NHL and HL (cohort A and B combined)
    - To study the incidence of sclerotic skin chronic GVHVD in the first 12 months post HCT in patients with NHL and HL (cohort A and B combined)
- To study the incidence of infectious deaths not related to GVHD in patients with non-Hodgkin and Hodgkin lymphoma (cohort A and B combined)
- Correlative studies
    - Cohort A: To study the association of MRD as detected by IgH sequencing prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12 after HCT. In addition to study the impact of onset of new acute or chronic GVHD on MRD.
    - Cohort A: To study the association of T-cell clonality by T cell receptor (TCR) Vb sequencing prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12 after HCT. In addition to study the impact of onset of new acute or chronic GVHD on TCR sequencing.
    - Cohort A: To study the association of B cell receptor signaling pathways and immune function with response by single cell mass cytometry prior to starting ibrutinib and compare to post ibrutinib at month 6, 9 and 12 after HCT.
    - Cohort A: To study the association of single cell mass cytometry that investigates B cell receptor signaling and its association with new acute or chronic GVHD on BCR signaling.

5. SCIENTIFIC RATIONALE

5.1 Rationale for Use of Ibrutinib Post HCT-Control of Neoplasm

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream 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. The phosphorylation and activation of BTK by Src family protein kinases (e.g.: LYN, SYK) leads to PLCγ2 phosphorylation, calcium mobilization and activation of downstream pathways (AKT, MAP kinase, NFkB) that leads to changes that promote cell differentiation, proliferation and survival[22;23]. Ibrutinib covalently binds to a cysteine residue in the BTK active site and irreversibly inhibits BCR signaling downstream of BTK. In vivo, ibrutinib reduces the phosphorylation of BTK, PLC γ2, AKT, and ERK pathways[24]. Similar effects were observed in vitro in MCL cells. NFkB downregulation was not limited to peripheral blood but was also noted in bone marrow and lymph nodes. BTK is a member of the Tec kinase family that transmits signals from various cell surface receptors most prominently from the BCR. BTK plays a role in the intermediate stages of BCR signaling cascade and is commonly overexpressed in MCL and CLL[25]. Ibrutinib (IMBRUVICA™) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy and in CLL patients with del 17. In January 2015, it was approved for Waldenstrom's macroglobulinemia. In August 2017, it was approved for chronic GVHD after failure of one or more lines of systemic therapy. Patients undergoing HCT remain at a high risk of relapse post-HCT. Continued post-HCT treatment may be of benefit until GVT has had a chance to eliminate the neoplasm. Thus, patients on the proposed study will start ibrutinib post-HCT, to see if post-HCT use can decrease the risk of relapse or progression. For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib USPI.

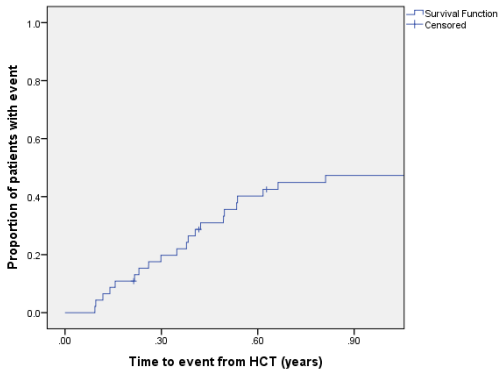


Figure 2: Outcome of 46 patients with CLL/MCL after first HCT at Vanderbilt University Medical Center. Cumulative incidence of failure by 1 y post HCT (defined as requirement of second line therapy of acute GVHD, development of NIH moderate to severe chronic GVHD, death due to relapse/progression, death due to non-relapse causes) was 50%.

5.2 Rationale for Use of Ibrutinib Post HCT-Impact on GVHD Biology

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) and may be a more potent B cell malignancy drug than rituximab[4;26]. BTK is a critical intermediate in BCR signaling [27]. It is a non-receptor tyrosine kinase belonging to the Tec family of kinases (TFKs), and critical for B cell processes effected by the BCR[27]. Individuals who lack functioning BTK lack circulating B cells and are unable to produce immunoglobulins or mount humoral immune responses[28]. BCR ligation leads to BTK activation which subsequently phosphorylates phospholipase Cγ2 (PLCγ2) triggering a series of downstream events including transcriptional regulation involving NF-κB and NFAT[27].BTK appears to regulate B cell survival by triggering the classical pathway in response to BAFF under both BCR and BAFF-R signaling[29]. Ibrutinib is also an irreversible inhibitor of interleukin-2 inducible kinase (ITK). ITK is involved in proximal T-cell receptor (TCR) signaling which activates the signaling cascade that includes NFAT, NFkB, and MAPK pathways resulting in T cell activation. ITK has a dominant role in the activation of Th2 cells, but not in Th1 cells.

GVHD is a complex immune phenomenon that is classically defined as acute and chronic and affects a

variety of organ systems. The initial phase of GVHD is primarily T cell mediated. Figure 1 shows the various roles of the normal B cell. Adequate pre-clinical and clinical data shows that B-cell dysfunction contributes to chronic GVHD[15;17;19;30;31]. Pre-clinical data shows that part of this dysfunction is due to hyper-responsiveness of the B-cell receptor (BCR), which can be abrogated by disrupting the signaling downstream of the BCR[21].

Thus, it is conceivable that using ibrutinib post HCT, may not only lead to effective tumor control but may down modulate GVHD as well. Ibrutinib was studied as a single agent for established chronic GVHD (NCT02195869) and has been approved by the FDA for treatment of chronic GVHD after failure of 1 or more systemic therapies. However, the relationship between early ibrutinib use post-transplantation and the incidence (and severity of) GVHD development has not been examined and may impact NRM. The RP2D in patients with established chronic GVHD is 420 mg.

5.3 Rationale for Duration of Ibrutinib Post HCT

Although the incidence of complete response (CR) in MCL and CLL in the non-transplant population is low[1;4-6] , the incidence of CR post HCT is higher. Also, it is expected that GVT will be the final pathway to effect cure. The role of ibrutinib post HCT is to maintain effective tumor control until GVT is established. In the absence of clinical GVHD, immunosuppressive therapy (IST) is tapered starting at day 100, with a goal of IST cessation by 6 months post HCT. Thus, stopping ibrutinib at 12 months post HCT in patients who have achieved a CR reflects a time point at which one would expect GVT to be established. Also, it is expected that ibrutinib may down modulate chronic GVHD. It is not clear if ibrutinib can facilitate transplantation tolerance. We hypothesize that using ibrutinib starting at day 60-90 post HCT until 12 months post HCT, will increase the incidence of a successful outcome by 25% compared to historical controls. The correlative studies will address molecular monitoring of disease (in cohort A), mechanisms of relapse of disease and development (or lack of) GVHD.

5.4 Rationale for Composite Secondary Endpoint

Typically, IST is continued until day 100 post HCT followed by a planned taper and attempts at IST cessation by day 180-day 270. Recurrent acute GVHD, grade 3-4 acute GVHD and severe chronic GVHD (as defined by NIH criteria)[32] represents the cohort of patients most likely to experience high risk of NRM[33-35].Patients at high risk of early post HCT relapse or persistence of disease at day 30 post HCT are often managed by forced IST tapers to elicit GVT. This often increases the risk of early GVHD and sets the stage for chronic GVHD. Although the *primary objective* of the proposed study is improvement in PFS in patients with MCL and CLL, this endpoint is intertwined with risk of NRM from GVHD. The sample size is designed to address this primary objective and stopping rules have been developed to ensure safety. In addition, we propose a composite secondary endpoint. A successful outcome post HCT is defined as lack of recurrence of the underlying disease with achievement of transplantation immunological tolerance, typically documented as cessation of all immunosuppression without active GVHD and functional immune reconstitution. As these endpoints can be distant, we propose a *composite secondary endpoint to be measured at 12 months post HCT* with success being defined as lack of progression or recurrence of disease, lack of second line therapy for acute GVHD, lack of NIH severe chronic GVHD and lack of death. In review of our single center data (2002-2013) of 46 patients with CLL (N=31) and MCL (N=15) undergoing their first HCT, the cumulative incidence of success at 1 y post HCT (lack of relapse or progression, lack of second line therapy for acute GVHD, lack of NIH moderate to severe chronic GVHD) was only 50% (Figure 2) (unpublished institutional data).

6. IBRUTINIB

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) and interleukin-2-inducible kinase (ITK). Inhibition of BTK blocks downstream 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 patients with the following conditions:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

6.1 Summary of Non-Clinical Data

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib USPI.

6.2 Data on Use of Ibrutinib Post-HCT

NCT02195869 investigated the role of single agent ibrutinib in patients post HCT for established steroid–refractory or dependent chronic GVHD, and a dose of 420 mg orally once a day was established as the recommended dose for chronic GVHD.

Ibrutinib has been used post HCT for CLL and MCL for management of recurrent disease. Coutre et al reported on 16 patients who had received an HCT prior to ibrutinib in studies 1102, 1109, 1112 and 1117 were pooled to consolidate the experience of treating patients with Ibrutinib after HCT failure. Median time since the most recent HCT was 27 months (range, 8-115). Best overall response rate (ORR) was 87.5% and was consistent with results observed in the overall /broader population. The authors concluded that Ibrutinib was well tolerated in patients who had prior HCT, with a safety profile similar to that observed in the overall R/R CLL population. They also presented a case showing a patient who achieved donor chimerism (i.e. full acceptance of the donor B Cells) following ibrutinib treatment, achieved MRD-ve disease and then interrupted for 10 months without relapse to date[36].

Ryan et al reported on 5 patients with CLL relapsing after HCT who were treated with Ibrutinib. All patients responded and 2 patients (11q and 17p) have returned to MRD negative status. Three patients

have achieved donor chimerism. In addition, there was symptomatic improvement in oral and skin chronic GVHD[37].

To date, ibrutinib shows clinically meaningful efficacy with a tolerable safety profile. For additional information, please see the text below, as well as the USPI and Investigator's Brochure.

6.3 Drug Information

6.3.1 Pharmacology

Ibrutinib is a small-molecule inhibitor of BTK and ITK. Ibrutinib is a white to off-white solid, and its molecular formula is C25H24N6O2 and molecular weight is 440.50 g/mole Both tablet and capsule forms are available, and the results of bioequivalence studies may be found in the Investigator's Brochure. Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to inhibition of BTK enzymatic activity; ibrutinib also binds irreversibly to the equivalent cysteine in the ITK pocket BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro* (refer to the current USPI and Investigator's Brochure).

Ibrutinib was designed as a selective and covalent inhibitor of BTK (Pan 2007). 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 (Herman 2011).

For comprehensive information regarding the nonclinical pharmacology and toxicology of ibrutinib, please refer to the current USPI and Investigator's Brochure.

6.3.2 Clinical Pharmacology of Ibrutinib

For the most comprehensive clinical pharmacology information regarding ibrutinib, please refer to the current version of the USPI and the Investigator's Brochure.

6.3.3 Summary of Clinical Safety Data

As of 12 November 2019, ibrutinib has been studied as both a monotherapy and combination therapy in 53 completed (primary or final analyses) and 17 ongoing company-sponsored studies, 9 early access programs (ongoing or completed), and 175 investigator-initiated studies (ongoing or completed). Safety data for completed studies is available for 4,439 subjects, of which, 2,132 were treated with ibrutinib monotherapy (1,600 subjects with hematologic malignancies, 42 subjects with cGVHD, 460 healthy

volunteers, and 30 subjects in a hepatic impairment study). Ibrutinib has been approved in approximately 100 countries for 1 or more indications.

Treatment-emergent AEs and adverse events leading to treatment discontinuation were assessed by performing an integrated analysis of 1600 subjects with hematologic malignancies treated with ibrutinib monotherapy.

Treatment-emergent AEs were observed in 98.8% of subjects taking ibrutinib monotherapy; 86.4% of subjects experienced AEs that were considered to be related to ibrutinib treatment by the assessing investigator. Grade 3 or 4 and serious AEs were experienced by 70.8%, and 52.9% of subjects, respectively, and fatal AEs were reported in 9.9% of subjects.

Treatment-emergent adverse events (observed in >20% of patients) that were considered by the investigator to be related to ibrutinib use were:

- Diarrhea
- Fatigue

The most commonly reported Grade 3 or 4 treatment-emergent AEs (observed in >5% of patients) were:

- Neutropenia
- Pneumonia
- Thrombocytopenia
- Anemia
- Hypertension

The most common serious treatment-emergency AEs (observed in >2% of patients) were:

- Pneumonia
- Atrial fibrillation
- Pyrexia
- Febrile neutropenia
- Sepsis
- Cellulitis

Treatment-emergent AEs that most commonly resulted in death (excluding disease progression) were:

- Pneumonia
- Sepsis
- Richter's syndrome
- Respiratory failure
- Cardiac arrest
- Death (unspecified)

16.8% of patients discontinued ibrutinib due to a treatment-emergent AE. Treatment-emergent AEs that most often lead to discontinuation were:

- Pneumonia (1.7%)
- Sepsis (0.8%)
- Thrombocytopenia (0.7%)
- Subdural hematoma (0.6%)

Treatment-emergent AEs in patients with cGVHD, steroid-dependent or refractory, were similar to those observed in patients with hematologic malignancies. The median and mean duration of ibrutinib treatment was 4.4 months and 9.1 months, respectively. Data from 47 patients was included in the analysis, and all patients were taking ibrutinib in combination with prednisone.

Treatment-emergent adverse events (observed in >20% of patients) that were considered by the investigator to be related to ibrutinib use were:

- Diarrhea
- Fatigue

The most commonly reported Grade 3 or 4 treatment-emergent AEs (observed in >5% of patients) were:

- Pneumonia
- Fatigue
- Diarrhea
- Cellulitis
- Hyperglycemia
- Hypokalemia

The most common serious treatment-emergency AEs (observed in >2% of patients) were:

- Pneumonia
- Cellulitis
- Dyspnea
- Headache
- Septic Shock

Fatal treatment-emergent AEs were observed in 2 subjects (4.8%): bronchopulmonary aspergillosis (considered related) and pneumonia (considered unrelated).

42.9% of patients (18 subjects) discontinued ibrutinib due to at least 1 treatment-emergent AE. The most common treatment-emergent AEs that led to discontinuation were:

- Fatigue (4.8%)
- Pneumonia (4.8%)

For additional information on the clinical safety of ibrutinib, refer to the ibrutinib Investigator's Brochure.

6.4 Formulation/Packaging/Storage

The white opaque 140 mg and 70 mg capsules marked with "ibr 140 mg" or "ibr 70 mg" respectively in black ink are available in white HDPE bottles with a child-resistant closure:

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package until dispensing.

6.5 Dose and Administration

Ibrutinib will be administered at a dose of 420 mg by mouth once a day starting between day 60-90 post HCT and continue until 1y post HCT. Ibrutinib is dispensed as 140 mg capsules and patients will be

instructed to take 3 capsules by mouth once a day. Patients will be instructed to take the drug at approximately the same time every day. Patients will be instructed to swallow the capsules whole with water and not to open, break or chew the capsules.

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

For patients on azoles, the starting dose will be 140 mg by mouth once a day starting between day 60-90 post HCT and continue until 1y post HCT.

Patients using Posaconazole as outlined in section 11.2 will start ibrutinib at a dose of 70 mg by mouth once a day between day 60-90 post HCT and continue until 1 year post HCT.

6.6 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 antidote for ibrutinib. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

7. CORRELATIVE STUDIES (COHORT A ONLY)

7.1 Molecular Monitoring for Minimal Residual Disease

Molecular monitoring using immunoseqMRD testing (refer to Study Schedule) will be done at pre-specified endpoints for CLL and MCL patients (cohort A) and will be considered as standard of care.

7.2 Molecular Monitoring in Presence of Relapse/Progression for CLL and MCL Patients (Cohort A)

Patients suspected of relapse or progression of disease typically undergo histological confirmation. If there is histological presence of disease, these samples from lymph node, BM or other areas will be sent for immunoseqMRD testing to try and identify any clonal shift at time of relapse. This may allow us to gain insight into mechanisms of ibrutinib and escape from GVT effect.

7.3 Molecular Studies for T-cell Repertoire Analyses Using IMMUNOSEQ

Molecular studies for T-cell repertoire analyses using IMMUNOSEQ will be considered a research test and will be done at pre-specified endpoints (refer to Study Schedule). This will be done in all patients in cohort A.

<u>CyTOF Analyses</u>

- For patients in CR (Cohort A): We will employ single-cell mass cytometry to gain a more complete understanding of the impact of ibrutinib on B cell subsets and signalling post SCT

- For patients in CR (Cohort A): We will employ single-cell mass cytometry to gain a more complete understanding of the impact of ibrutinib and GVHD on T cell subsets and signalling post SCT

- For patients with relapse/progression post HCT (cohort A): We will employ single-cell mass cytometry to gain a more complete understanding of the impact of ibrutinib on B cell subsets and identification of signalling pathways that escape BTK inhibition

CyTOF studies will be coordinated by Irish Lab at Vanderbilt University

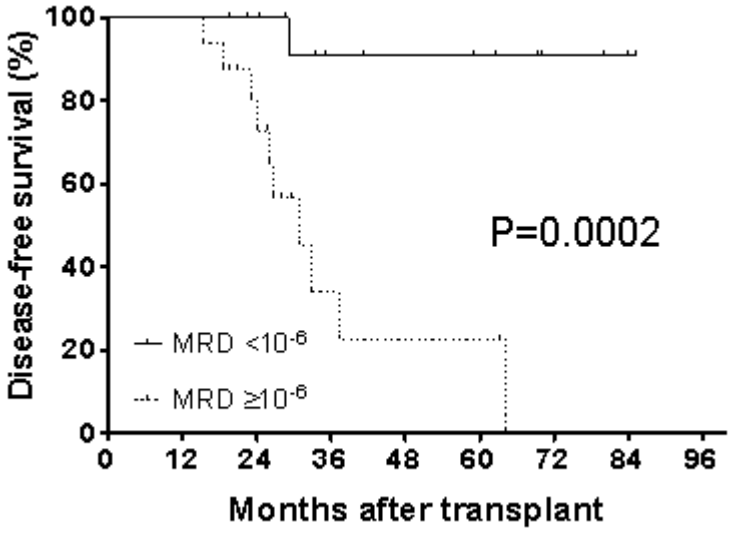
7.4 Correlative Sample Collection and Handling

The actual dates and time and appropriate laboratory parameters must be recorded in the electronic clinical trial database. **See the Laboratory Manual** for appropriate processing and shipping instructions.

8. CORRELATIVE STUDY DESCRIPTION

8.1 immunoseqMRD

immunoseqMRD analysis involves amplification of immunoglobulin heavy chain (IGH) loci using consensus V and J segment primers followed by high-throughput sequencing (HTS) [38], enabling quantification with a detection limit of one cell per million mononuclear cells. Both peripheral blood and marrow aspirate can be used for this assay. This next-generation sequencing method has been used with success for monitoring MRD in multiple lymphoid malignancies[39;40]. immunoseqMRD sequencing-based MRD assessment provides greater sensitivity compared to traditional MRD detection methods, such as flow cytometry and allele-specific oligonucleotide PCR approaches[38]. Moreover, the prognostic value of MRD assessment by sequencing in patients with chronic lymphocytic leukemia[41], multiple myeloma[39], acute lymphocytic leukemia[42] and diffuse large B-cell lymphoma[43] has been demonstrated.



Dr. Miklos and Stanford investigators pioneered immunoglobulin heavy chain high throughput sequencing (IGH-HTS) technologies to provide ultrasensitive CLL MRD detection[44;45]. Minimal Residual Disease (MRD) was quantified by the commercially available CLONOSIGHT method (Sequenta) with a sensitivity of 1 CLL clone in a million blood WBC. Beginning at 9 months post-transplant, MRD detected at 10^{-6} or higher (at least one CLL clone per million PBMC genomes) indicates a significant risk of relapse[46]. As shown in Figure 3, the one-year post allo-HCT detection of CLL by CLONOSIGHT is highly predictive of CLL relapse (p=0.0002).

Figure 3: Disease free survival is predicted by MRD (as detected by ClonoSIGHT) at 1 y post HCT

In patients with chronic GVHD, there is often production of alloreactive antibodies. This has been demonstrated by the Miklos lab, using gender mismatch HCT as a model[30;47;48].

We propose to correlate the presence of HY antibodies with clonal diversity as measured by the Immunoseq assay.

8.2 Immunoseq

ImmunoSeq Assays illuminate the adaptive immune system with controlled Multiplex PCR amplification and high throughput sequencing of T-cell receptors combined with sophisticated bioinformatics.

8.3 CyTOF

Although B cell dysfunction has been implicated in the pathogenesis of chronic GVHD, the role of B-cell dysfunction in acute GVHD remains less well defined. Acute GVHD is typically thought of as a T cell mediated process, with complex interactions through antigen presenting cell (APC) populations, regulatory T cells (T regs), B cell immune response and cytokine secretion. Very recently, a new technology has been developed for the analysis of complex cell subsets, termed single-cell mass cytometry using the DVS CyTOF mass cytometer. Figure 4 shows a schematic of the CyTOF technology. This allows a systems level description of immune response through the simultaneous measurement of more than thirty cell surface marker proteins. The Irish lab has expertise in this technology and has used this assay in single cell interrogation in lymphoma and more specifically in BCR signalling[49-51].

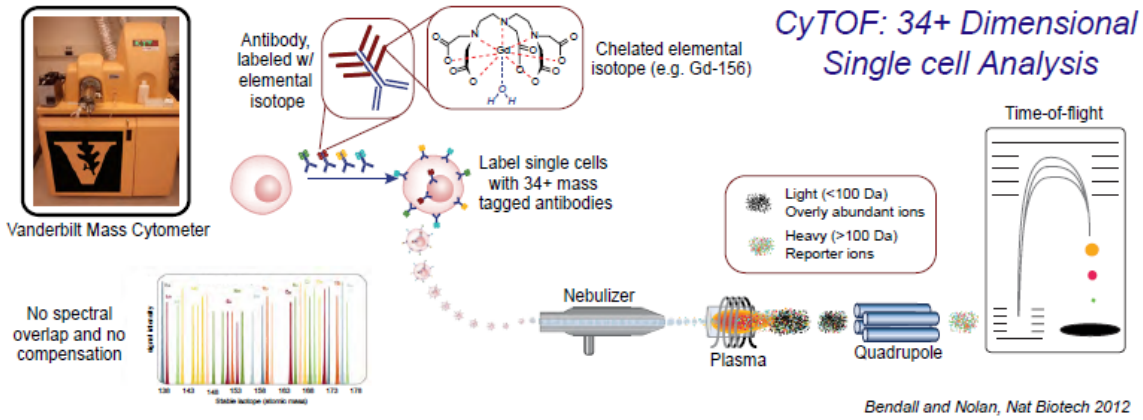


Figure 4: Workflow of CyTOF technology. Cells in single cell suspension are labelled with antibody conjugates tagged to chelated elemental isotope. Each cell can be tagged with 34 probes and thus the output reflects 34+ dimensional single cell analyses. Both surface and intracellular targets can be interrogated.

Appendix 1: Figures 5 to 8 outline the utility of CyTOF in not only dissecting the BCR signaling network but also to generate 2 dimensional heat-maps of 34+ dimensional data. The Irish lab has proven expertise in B cell biology using CyTOF.

- We will employ single-cell mass cytometry to gain a more complete understanding of the impact of ibrutinib on B cell subsets and signalling post SCT

- We will employ single-cell mass cytometry to gain a more complete understanding of the impact of ibrutinib and GVHD on T cell subsets and signalling post SCT

It is anticipated that this may provide novel insights into the changes induced by ibrutinib on the immune system in the early post SCT period.

Samples will be analysed through a collaborative effort with Drs. Dholaria and Irish (both at Vanderbilt University). Single-cell mass cytometry will be used to analyse blood taken from patients prior to administration of ibrutinib, day 100 post SCT, and at month 6 post HCT. If patients develop new onset acute or chronic GVHD while on ibrutinib, an additional sample will be collected. We will objectively assess cellular heterogeneity from single-cell measurement data using an established computational approach, spanning-tree progression analysis of density-normalized events (SPADE) and ViSNE. In this work, we will ensure that all cell surface markers previously implicated in GVHD are included in the analysis. Single-cell mass cytometry will be carried out using the DVS CyTOF mass cytometer in the Flow Cytometry Core facility at Vanderbilt University. Dr. Irish's laboratory has validated a B-cell panel to interrogate B cell dysfunction in the context of lymphoma (see Figures 6-8, Appendix 1). We expect that the same panel of B cell markers to give us adequate insight into the effect of ibrutinib on BCR signaling in the post-HCT period. In addition, we will interrogate cell subsets to include Th1, Th2, Treg, Th17, T effector cells, CD4+ T cell subsets (naïve, effector, memory, and central memory), antigen presenting cells, dendritic cells, and macrophages. Following core hematopoietic surface markers (12) have been validated by the (CD3, CD4, CD8, CD11b, CD19, CD20, CD38, CD45, CD45RA, CD90, CD123, HLADR). In addition, the following 15 markers are available (CD16, CD25, CD27, CD28, CD36, CD39, CD56, CD95, CD103, CTLA4, CD161, CD62L, CD14). Eight intracellular epitopes from mitogen pre-activated cells can be interrogated (IFN-gamma, TNF-alpha, IL-10, IL-17, FoxP3, IL-6, IL-4, and IL-13). This will allow us to get a complete picture of the interaction of ibrutinib on the T cell subsets in the post HCT setting.

9. ELIGIBILITY CRITERIA: INCLUSION

Pre-SCT

1. Adult (≥18 y) patients undergoing their first T cell replete allo-HCT for chronic lymphocytic leukemia (CLL), Hodgkin Lymphoma (HL), or the following subtypes of Non-Hodgkin lymphoma: Mantle cell lymphoma (MCL) and follicular center cell lymphoma (FL)

2. Meeting institutional criteria for allo-HCT. Ejection fraction by echocardiogram or MUGA >40%, pulmonary function test with adjusted DLCO ≥ 60%

3. Matched (8/8) or mismatched (7/8) related, unrelated HCT

4. Stem cell source: bone marrow, peripheral blood stem cell

5. Disease criteria:

Cohort A:

CLL

- Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm

AND

- 17 p deletion (detected by any assay) (≥20% of cells involved if assay is conventional cytogenetics or FISH) or NOTCH mutation at any time point during disease course. Patient should have received at least 1 line of therapy. Prior ibrutinib therapy is permitted.

OR

- Relapsed/refractory CLL ≥ 2 lines of therapy. Prior ibrutinib therapy is permitted

MCL

- Disease burden: lymph node size <5 cm and/or extra-nodal involvement < 5 cm

- Relapsed/refractory MCL ≥ 1 line of therapy. Prior ibrutinib therapy is permitted. Prior autologous HCT is permitted.

- MCL blastoid variant in CR1 or high risk MCL being considered for allo HCT in CR1

Cohort B:

FL

- Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm

  AND

- Relapsed/refractory FL ≥ 2 lines of therapy. Prior ibrutinib therapy is permitted.

HD

- Disease burden: lymph node size <5cm and/or extra-nodal involvement <5 cm

  AND

- Relapsed/refractory HD ≥ 2 lines of therapy

6. Preparative regimen: both reduced intensity and ablative regimens are permitted. Each center will pre-specify the regimen they intend to use during the conduct of the study

7. Donor criteria: HLA ≥ 7/8 related or unrelated donors.

8. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must

agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

9. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

10. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

11. Prior to administration of ibrutinib (day 60 today 90 post HCT)
    - KPS ≥ 60%
    - Engraftment of neutrophils (ANC ≥ 1.0 X10^9/L) for 3 days without g-csf support
    - Platelets ≥100,000/mm^3 or ≥50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation
    - GFR ≥ 30 ml/min
    - LFTs (ALT and AST) ≤3 X ULN; total bilirubin ≤ 1.5 mg/dL X ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
    - Predominant donor chimerisms of ≥ 51% as measured by CD3 and CD33 (or other myeloid marker)

10. ELIGIBILITY CRITERIA: EXCLUSION

Pre-SCT

1. Progression of CLL or MCL or FL or HD at time of transplant

2. Use of Coumadin (warfarin) or other vitamin-K antagonists for anticoagulation. Non-coumadin anticoagulation is permitted.

3. Known CNS involvement

4. Active uncontrolled bacterial or invasive fungal infections

5. History of malignancy other than the underlying disease unless treated with a curative intent and/or no evidence of disease for at least 3 y OR expected to be cured with SCT

6. Planned use of post-HCT cyclophosphamide for GVHD prophylaxis

7. Anticipated planned donor lymphocyte infusion in the first 3 months post-SCT

8. T deplete HCT

9. Umbilical cord HCT

10. History of stroke or intracranial hemorrhage within 6 months of enrollment.

11. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

12. Known HIV

13. Active Hepatitis B or C virus

14. Child-Pugh Class C

Prior to Administration of Ibrutinib (Day 60-Day 90 Post SCT)

1. In the critical care unit, or use of mechanical ventilation or use of renal replacement therapy at any time post HCT and prior to administration of ibrutinib

2. Active uncontrolled stage 3-4 acute GI GVHD prior to administration of ibrutinib

3. Active uncontrolled stage 4 acute liver GVHD prior to administration of ibrutinib

4. Evidence of progressive disease as compared to pre-HCT (persistence of disease is permitted)

5. Anticipated planned donor lymphocyte infusion in the first 3 months post-SCT

6. Active uncontrolled bacterial or invasive fungal infections

7. Prednisone equivalent of >2m/kg for treatment of GVHD prior to administration of ibrutinib

8. Use of second line systemic therapy for treatment of acute GVHD prior to administration of ibrutinib

9. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk including the presence of chronic/active HBV and HBC infections and Child-Pugh Class C.

10. Major surgery or a wound that has not fully healed within 4 weeks of starting ibrutinib

11. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon).

12. Requires chronic treatment with strong CYP3A inhibitors

13. Vaccinated with live, attenuated vaccines within 4 weeks of starting ibrutinib

11. DOSE MODIFICATIONS

11.1 Dose Modifications for Adverse Reactions

Interrupt IMBRUVICA therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA.

The dose of ibrutinib will be modified according to the dose modification guidelines in the table below if any of the following toxicities occur:

Parameter for which dose is being modified	Dose modification duration	Dose restarting parameters	Dose to be restarted	Comments
Grade 3 ANC (<1,000/ µL) with an associated temperature of ≥38.5°C	Hold ibrutinib	Restart after 7 days provided ANC ≥ 1,000/ µL and patient is afebrile for at least 72 hrs.	Level -1	If toxicity is felt to be due to ibrutinib
Grade 4 ANC (<500/µL) for more than 7 days	Hold ibrutinib	Restart after 14 days provided ANC ≥ 500/ µL for at least 7 days	Level -2	If toxicity is felt to be due to ibrutinib
Grade 3 thrombocytopenia (<50,000/µL) in the presence of Grade ≥2 bleeding events	Hold ibrutinib	Restart after 14 days provided platelet count ≥50,000/µL and no bleeding for at least 7 days	Level -2	If patient is on concomitant anticoagulation therapy, stabilize the anticoagulation therapy (if it was restarted) before ibrutinib is restarted
Grade 4 thrombocytopenia (<25,000/µL)	Hold ibrutinib	Restart after 14 days provided platelet count ≥ 50,000/ µL for at least 7 days	Level -2	
Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/ or anti-diarrheal therapy	Hold ibrutinib	Restart after 14 days provided toxicity is at grade 2 or lower for at least 7 days	Level-2	Acute or chronic GVHD may cause nausea, vomiting, diarrhea and needs to be ruled out. If toxicity is attributed to GVHD and resolves drug can be restarted at dose level -1. Similarly, diarrhea can be due to Clostridium difficile colitis-if yes, no dose

Parameter for which dose is being modified	Dose modification duration	Dose restarting parameters	Dose to be restarted	Comments
				reduction may be necessary
Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib	Hold ibrutinib	Discontinue drug (level -3)	Not applicable	None

Dose Levels:

- Dose level 0 = 420 mg po qd
- Dose level -1 = 280 mg po qd
- Dose level -2 = 140 mg po qd
- Dose level -3 =discontinue drug

For patients starting with 140 mg qd (due to concomitant moderate CYP3A inhibitor or azole use as outlined in section 11.2)

- Dose level 0 = 140 mg po qd
- Dose level -1 = 70mg po qd
- Dose level -2 = 70 mg po qod
- Dose level -3 = discontinue

If a patient was on 140 mg po qd (due to concomitant azole use) and then stopped azole, the dose will be increased to 420 mg po qd. This will not be considered a dose escalation.

For patients starting with 70 mg qd (due to concomitant Posaconazole use as out lined in section 11.2)

- Dose level 0 = 70 mg po qd
- Dose level -1 = 70 mg po qod
- Dose level -2 = discontinue

11.2 Dose Modifications for Use with CYP3A Inhibitors

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed.

Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin).

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.

As most post-HCT patients are expected to be on azoles (fluconazole, voriconazole or lower doses of posazconazole as outlined in the table below) until day 100 after HCT, the dose of IMBRUVICA will be 140 mg per day. For patients receiving higher doses of posaconazole as outlined below, the dose of IMBRUVICA will be 70 mg per day. Once these agents are stopped, the dose will be escalated to 420 mg per day.

2.4 Dose Modifications for Use with CYP3A Inhibitors

Recommended dose modifications are described below *[see Drug Interactions (7.1)]*:

Patient Population	Coadministered Drug	Recommended IMBRUVICA Dose
B-Cell Malignancies	• Moderate CYP3A inhibitor • Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Interrupt dose as recommended *[see Dosage and Administration (2.3)]*.
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended *[see Dosage and Administration (2.3)]*.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.

11.3 Dose Modifications for Hepatic Impairment

. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

12. PROHIBITION AND RESTRICTIONS

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

- For any planned 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.

- 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.

- 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.

13. CONCOMITANT MEDICATIONS

13.1 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 other biosimilar GCSF) 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.

13.2 Medications to be Used with Caution

CYP3A Inhibitors/Inducers

Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and strong CYP3A inhibitors should be avoided. In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax and AUC of ibrutinib by 29- and 24-fold, respectively.

Voriconazole and posaconazole can be used concomitantly with ibrutinib, with dose modifications as described above in Section 11.2.

Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided, and an alternative with less CYP3A inhibitory potential should be considered.

For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended.

Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A.

Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John’s Wort). Consider alternative agents with less CYP3A induction.

A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

13.3 Drugs That May Have Their Plasma Levels Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC50 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.

13.4 Antiplatelets and Anticoagulants

Fatal bleeding events have occurred in patients treated with IMBRUVICA includinggrade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage).IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

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 (refer to the Concomitant Medications section).

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. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

13.5 Prohibited Concomitant Medications

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

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.

14. MANAGEMENT OF IMMUNOSUPPRESSION

Participants may be receiving other immunosuppressive therapies (including extra-corporeal photopheresis [ECP]) in addition to glucocorticoids. In addition, due to potential drug-drug interactions with ibrutinib, drug levels for immunosuppressant agents such as cyclosporine, tacrolimus, and/or sirolimus are highly recommended during the clinical trial. The doses for these immune-suppressants should be adjusted per institutional practices based on the measured drug level.

Other strategies of GVHD therapy including PUVA, UVB light therapy, topical use of calcineurin inhibitors (e.g. for ocular GVHD) is permitted.

15. MANAGEMENT OF CORTICOSTEROIDS

Systemic steroids may be decreased at the treating physician's discretion. Non-absorbable oral steroids will be allowed and recorded.

16. PROPHYLAXIS FOR INFECTION

Prophylaxis for infections, including routine monitoring for CMV, EBV will be done per institutional practice. Pre-emptive therapy for CMV will be per institutional practice.

Given the interaction of ibrutinib with azoles, please refer to dose modification section for appropriate dosing guidelines of ibrutinib.

17. USE OF DONOR LYMPHOCYTE INFUSION (DLI)

Use of DLI for mixed chimerism will be at the discretion of the treating physician. Ibrutinib will be held for at least 7 days prior to DLI and resumed at least after 14 days post DLI. Anticipated planned donor lymphocyte infusion in the first 3 months post-HCT is an exclusion criterion.

18. EFFICACY MEASUREMENT

18.1 A review committee led by Nishitha Reddy, MD, MS (Vanderbilt University) will review all response assessments. Cases requiring review of imaging studies will be done in coordination by Dr. Reddy and a radiologist from the individual centers.

18.2 The primary endpoint is to study the use of ibrutinib starting between days 60 to day 90 after allogeneic HCT until 12 months post HCT to improve the PFS at 12 months post HCT by 25% compared to historical controls in patients with MCL and CLL.

18.3 The following established definitions of relapse, recurrence and responses will be used for CLL.[52]

18.3.1 Progressive Disease is Defined if One of the Criteria is Documented[€]:

- The appearance of a new enlarged node >1.5 cm, splenomegaly or hepatomegaly *
- An increase of 50% or more in size if a previously involved site (lymph node, spleen or liver)^

- Richter's transformation documented by lymph node biopsy
- Development of neutropenia, anemia or thrombocytopenia attributable to CLL§

€ The iwCLL definition of PD defined as an increase of 50% or more in the total circulating lymphocyte count with absolute lymphocyte count of >5000/µl or greater has been deleted as patients are to receive the B-cell receptor kinase inhibitor

* Post allogeneic stem cell transplantation, patients may develop adenopathy that can be attributable to other causes (infections, inflammatory state). Adenopathy should be attributable to CLL by the investigator.^

^ A lymph node that was 1 to 1.5 cm previously must increase by 50% or more to a size greater than 1.5 to 2.0 cm in the longest axis

§ Cytopenias cannot be used to determine disease progression in the presence of other immunosuppressive therapies. The cytopenias are defined as a decrease in hemoglobin level by more than 2 g/dl (20g/L) or to less than 10 g/dl (100g/L) or a decrease in platelet count to less than 100,000µl ($100x10^9$/L) in the presence of clonal CLL infiltrates on the bone marrow biopsy.

18.3.2 Complete Remission Requires All of the Following Criteria:

- Absolute lymphocyte count <4000/microL (4×10^9/L).
- No lymph nodes >1.5 cm in diameter.
- No hepatomegaly or splenomegaly.
- No constitutional symptoms attributable to CLL.*
- Bone marrow recovery as demonstrated by ANC >1500/microL (1.5×10^9/L), platelet count >100,000/microL (100×10^9/L), and hemoglobin concentration >11 g/dL (110 g/L) in the absence of transfusion or growth factor support.
- Bone marrow free of clonal CLL cells by conventional flow cytometry and/or immunohistochemistry and without nodular lymphoid aggregates.

* Constitutional symptoms include ≥10% unintentional weight loss within the previous six months, fatigue that interferes with work or usual activities, fevers greater than 100.5°F (>38°C) for ≥2 weeks, or night sweats for >1 month. Note that in our trial, patients are post allogeneic stem cell transplantation and may have these symptoms that are not a result of CLL but attributable as a primary or secondary cause related to allogeneic stem cell transplant. The cause of these symptoms should be documented by the investigator.

18.3.3. Partial Remission: At Least One of These Criteria Must be Documented:

- A decrease in the peripheral absolute lymphocyte count by at least 50% from the level prior to therapy.

- A reduction in previously enlarged nodes by at least 50% with no increase in the size of any single lymph node and no new enlarged lymph nodes. An increase of <25% in a lymph node <2 cm is not considered significant.

- If enlarged prior to therapy, the liver and spleen should be reduced in size by at least 50%.

One of the following hematologic parameters must be met in addition to one of the above criteria in order to qualify for a PR:

- ANC ≥1500/microL (1.5 x 10^9/L) or greater than 50% improvement over baseline (if this value was abnormally low at baseline) without granulocyte colony-stimulating factor support.

- Platelet count ≥100,000/microL (100 x 10^9/L) or at least 50% improvement over baseline (if this value was abnormally low at baseline).

- Hemoglobin concentration ≥11 g/dL (110 g/L) or 50% improvement over baseline (if this value was abnormally low at baseline) without red blood cell transfusions or erythropoietin support.

  Note: Partial remission with Lymphocytosis: PR criteria with the exception of ALC are met is consistent with a PR with lymphocytosis.

18.3.4 Nodular Partial Remission:

Persistent bone marrow nodules on bone marrow biopsy in patients achieving a CR or PR. Lymphoid aggregates should be evaluated with immunohistochemistry to determine whether they are comprised of CLL cells, lymphocytes other than CLL cells, or T cells.

18.3.5 Stable Disease:

Patients, who do not meet the criteria for a complete remission, partial remission, or progressive disease, have stable disease. Stable disease is therapeutically equivalent to a nonresponse (i.e., refractory disease).

18.4 The Following Established Definitions of Relapse, Recurrence and Responses Will Be Used for MCL and FL

18.4.1 Progressive disease or relapse is defined if one of the criteria is documented (either PET/CT or CT can be used).

PET-Based Response:

- Progressive metabolic disease
- Score of 4 or 5 (on a 5-point scale) with an increase in intensity of uptake from baseline and /or
- New FDG-avid foci consistent with lymphoma rather than another etiology (infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.

CT-Based Response:

- An individual node/lesion must be abnormal with an LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir (0.5 cm for lesions ≤ 2 cm, 1.0 cm for lesions > 2 cm)
- In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (for e.g., a 16-cm spleen must increase to > 17.5 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline¥
- New or recurrent splenomegaly
- New or clear progression of preexisting non-measured lesions
- A new node >1.5 cm in any axis
- A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis its presence must be unequivocal and must be attributed to lymphoma.
- Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent Bone marrow involvement

¥ Spleen size baseline 13 cm in vertical length

LDi: longest transverse diameter of a lesion; SDi: Shortest axis perpendicular to LDi; PPD: cross product of LDi and SDi.

18.4.2 Complete remission is defined by the following criteria (should meet all criteria)

PET-Based Response:

- Complete metabolic response with a score of 1, 2 or 3 with or without residual mass on a 5-point scale

CT-Based Response:

- Target nodes/nodal masses must regress to ≤1.5 cm in LDi
- No extralymphatic sites of disease
- Absence of non-measured lesions
- No new lesions
- Bone marrow normal by morphology and if indeterminate, IHC negative

18.4.3 Partial Remission is defined by the following criteria:

PET-Based Response

- Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size

CT-Based Response

- 50% decrease in SPD of up to six target measurable nodes and extranodal sites £

  £ When a lesion is too small to measure on scan, 0.5x0.5 cm is the default value, if no longer visible 0x0 cm, for a node greater than 0.5 x0.5 cm but smaller than normal use the actual measurement for calculation.

- Spleen must have regressed by >50% in length beyond normal

Stable disease:

PET-based response

- No metabolic response with a score of 4 or 5 on the five point scale

CT-based response

- >50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

18.5 The following established definitions of relapse, recurrence and responses will be used for HD

Progressive disease or relapse is defined if one of the criteria is documented (either PET/CT or CT can be used)

PET-Based response:

- Progressive metabolic disease

- Score of 4 or 5 (on a 5-point scale) with an increase in intensity of uptake from baseline

  and /or

- New FDG-avid foci consistent with lymphoma rather than another etiology (infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.

CT based response:

- An individual node/lesion must be abnormal with an LDi > 1.5 cm and Increase by≥ 50% from PPD nadir and an increase in LDi or SDi from nadir (0.5 cm for lesions ≤ 2 cm, 1.0 cm for lesions > 2 cm)

- In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (for e.g., a 16-cm spleen must increase to > 17.5 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline¥

- New or recurrent splenomegaly

- New or clear progression of preexisting non-measured lesions

- A new node >1.5 cm in any axis

- A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis its presence must be unequivocal and must be attributed to lymphoma

- Assessable disease of any size unequivocally attributable to lymphoma

- New or recurrent Bone marrow involvement

¥ Spleen size baseline 13 cm in vertical length

LDi: longest transverse diameter of a lesion; SDi: Shortest axis perpendicular to LDi; PPD: cross product of LDi and SDi.

Complete remission is defined by the following criteria (should meet all criteria)

PET-based response:

- Complete metabolic response with a score of 1, 2, or 3 with or without residual mass on a 5-point scale

CT- based response:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi

- No extralymphatic sites of disease

- Absence of non-measured lesions
- No new lesions
- Bone marrow normal by morphology and if indeterminate, IHC negative

Partial Remission is defined by the following criteria:

PET-based response

- Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size

CT-based response

- >50% decrease in SPD of up to six target measurable nodes and extranodal sites [£]

[£] When a lesion is too small to measure on scan, 0.5x0.5 cm is the default value, if no longer visible 0x0 cm, for a node greater than 0.5 x0.5 cm but smaller than normal use the actual measurement for calculation.

- Spleen must have regressed by >50% in length beyond normal

Stable disease is defined by the following criteria:

PET-based response

- No metabolic response with a score of 4 or 5 on the five-point scale

CT-based response

- >50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met

Footnote: A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response to avoid under treatment

19. REGISTRATION OF PATIENT

Each center will decide at time of study activation their preferred preparative regimens for HCT and complete the preparative regimen selection worksheet. Centers will not be allowed to deviate from their standard during the conduct of the study. Regimens will be stratified as reduced intensity (RIC), myeloablative (MAC) for related (matched and mismatched) and unrelated (matched and mismatched).

Prior to registration, a copy of the IRB approval at the site will be requested and kept on file at the

Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at Coordinating.Center@Vanderbilt.edu to verify slot availability prior to enrollment.

All patients MUST be registered with the VICC prior to the start of the preparative regimen and again prior to start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Central Standard Time Monday through Friday.

1) All sites must email the VICC CTSR Coordinating Center at Coordinating.Center@Vanderbilt.edu to notify of upcoming registration and ensure slot availability. The following information should be included in your email:
   - Study number
   - Patient initials
   - Disease type
   - Anticipated consent date
     Anticipated start date
2) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:
   - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
   - HIPAA authorization form (if separate from the main consent form)
   - VICC Patient Enrollment Form

The Coordinating Center will then provide a subject ID number via email.

3) Email the following documents to the Coordinating Center for eligibility review and patient enrollment (coordinating.center@vanderbilt.edu):
   - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
   - HIPAA authorization form (if separate from the main consent form)
   - VICC Patient Enrollment Form
   - Eligibility supporting documents such as pathology reports, laboratory tests, etc. or EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
   - Tissue Block Registration Form (see the Lab Manual)
   - Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: All study documents should be received 24-48 hours prior to the patient's anticipated start date. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center. Please email the Coordinating Center if enrollment is needed sooner.

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to investigational treatment.

Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin study treatment consistent with the protocol no later than [XXX days/weeks] after registration/enrollment by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact should be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.

Issues that would cause treatment delays should be discussed with the Protocol Chair. Any requests for eligibility exceptions and/or deviations must be approved in writing by the Protocol Chair and the VICC DSMC.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

20. STUDY SCHEDULE

Informed Consent

- The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Performance of procedures considered standard of care within window of screening but prior to consent will be permitted. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA).

- In addition, subjects must sign all approved ICF amendments per the site IRB/IEC guidelines during the course of the study.

Confirm Eligibility

- Eligibility will be confirmed pre-HCT and then second confirmation will be prior to administration of ibrutinib between day 60-90 post-HCT.

- Complete enrollment checklist and submit to coordinating center for review prior to enrollment. Preparative regimen for HCT should not be started until enrollment checklist has been reviewed and approved by coordinating center. A minimum of 48 hour notice will be mandated.

- Second confirmation: Complete enrollment checklist and submit to coordinating center for review and approval prior to start of ibrutinib between day 60-90 post-HCT. Ibrutinib will not be started until enrollment checklist has been reviewed and approved by coordinating center. A minimum of 48 hour notice will be mandated.

Pre-SCT: Screening visit:

All research studies to be completed within 4 weeks of starting preparative regimen unless specified otherwise. Timing of all pre-SCT standard of care assessments may be completed per the institutional practice.

- Standard of care: History and physical including Karnofsky performance status (KPS) (See the Clinical Assessment Manual)

- Standard of care: Transplant evaluation: follow institutional protocol on timing of evaluation prior to HCT and at a minimum will include:

    - Hematology
        - Hematology parameters performed at local laboratory will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, and absolute neutrophil count.

    - Chemistry
        - Serum chemistry parameters performed at local laboratory will include: creatinine, AST, ALT, alkaline phosphatase, and total bilirubin.

    - Coagulation studies
        - Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at local laboratory at Screening.

    - Hepatitis serologies
        - Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody will be evaluated by local laboratory. If Hepatitis B core antibody or Hepatitis B surface antigen is positive, then Hepatitis B PCR to quantitate Hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative prior to enrollment in subjects who are Hepatitis B core antibody positive or Hepatitis B surface antigen positive.

    - Pregnancy test for women of child bearing potential
        - Serum pregnancy tests are required at Screening by local laboratory and only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible.

    - EKG and Echo
        - At baseline, per inclusion criterion patients must have an ejection fraction by echocardiogram or MUGA of ≥ 40%. EKGs should be performed at the investigator's

discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.

- Pulmonary function tests
  - PFT should be done as part of transplant evaluation per institutional criteria and at a minimum report FeV1%, FeV1/FVC ratio and DLCO %. Patients should have a DLCO of ≥ 60% per inclusion criterion.

- Quantitate immunoglobulins including IgG, IgM and IgA

- Peripheral blood T-cell, B-cell and NK cell subsets (CD3+, CD4+, CD8+, CD19+, CD16/56+)

- Standard of care: Disease assessment: Data forms for CIBMTR (CLL Form 2013 R2.0, 10 pages or other lymphomas: Form 2018 Revision 3, 17 pages) will be made available to the coordinating center (see appendix 2 and 3 respectively). Alternatively, detailed disease assessment data will be entered directly into the electronic database.

- Standard of care: DNA sample from recipient and donor to establish allele markers for post HCT chimersim analyses.

- Research: a peripheral blood sample on all patients should be sent for immunoseqMRD analysis (see the Laboratory Manual). This specimen will serve as a baseline to track neoplastic clones post HCT. Diagnostic sample from disease onset (paraffin block of lymph node only is applicable), if available must be sent for immunoseqMRD analyses (See the Laboratory Manual).

- Research: Toxicity assessment will be done to establish baseline severities.

- Research: Peripheral blood sample will be sent to coordinating center for CYTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping.

- Research: BM aspirate in patients with active marrow disease will be sent to coordinating center for CYTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping.

- Research: Complete enrollment checklist and submit to coordinating center for review prior to enrollment. Preparative regimen for HCT should not be started until enrollment checklist has been reviewed by coordinating center

- Research: Toxicity assessment will be done at screening to establish baseline

- Research: concomitant medication data will be obtained to establish baseline

<u>Start of preparative regimen to day +60 post-HCT:</u>

- Standard of care: History and physical and KPS (See the Clinical Assessment Manual.)

- Standard of care: weekly assessment of acute GVHD (and chronic GVHD if applicable) KPS (see the Clinical Assessment Manual). KPS will be recorded every 2 weeks.

- Standard of care: Disease reassessment between day 30 and day 60 will include: appropriate imaging (CT scan and/or PET scan or other imaging) and bone marrow biopsy.

- Standard of care: PB should be sent for chimerism analyses. Ablative transplants will require only % recipient vs. donor. RIC HCT will require sorted chimerism (CD 3: % recipient vs. donor and CD33 [or other suitable myeloid lineage markers]: % recipient vs. donor)

- Research: BM aspirate from patients with active marrow disease will be sent to coordinating center for CyTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping. The BM biopsy and aspiration itself is considered standard of care.

- Research: Toxicity assessment will be done every 2 weeks

- Research: concomitant medication data will be obtained every 2 weeks

Prior to administration of ibrutinib (day 60-90): **(All studies to be done within 2 weeks of starting ibrutinib)**

- Standard of care: Following should be done **within 2 weeks** prior to starting ibrutinib

    - History and physical and KPS (see the Clinical Assessment Manual). KPS will be recorded every 2 weeks during this time period.

    - Hematology
        - Hematology parameters performed at local laboratory will include at a minimum a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, and absolute neutrophil count.

    - Chemistry
        - Serum chemistry parameters performed at local laboratory will include at a minimum: creatinine, AST, ALT, alkaline phosphatase, and total bilirubin

    - Coagulation studies
        - Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at local laboratory at Screening

    - Pregnancy test for women of child bearing potential
        - Serum pregnancy tests are required at Screening by local laboratory and only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible.

    - EKG
        - EKGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea.

    - Quantitative immunoglobulins including IgG, IgM and IgA

- Peripheral blood T-cell, B-cell and NK cell subsets (CD3+, CD4+, CD8+, CD19+, CD16/56+)
- Continue weekly assessment of acute GVHD (see the Clinical Assessment Manual)
- Chronic GVHD assessment (see the Clinical Assessment Manual) using NIH 2015 forms for diagnosis and scoring of chronic GVHD

Please note: For patients who come off study prior to start of Ibrutinib, an End of Study visit should be completed as outlined under "12 Months post HCT or earlier if withdrawing from the study"

Research: Following should be done **within 2 weeks** prior to starting ibrutinib

- Peripheral blood samples on all patients should be sent for Immunoseq for T-cell receptor and for immunoseqMRD analysis. See the Laboratory Manual for sample acquisition, processing and shipping logistics.
- Research: A peripheral blood sample will be collected for CyTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping.
- Research: Complete enrollment checklist and submit to coordinating center for review prior to enrollment. Ibrutinib should not be started until enrollment checklist has been reviewed by coordinating center.
- Research: Toxicity assessment will be done and continued every 2 weeks during this time period weeks
- Research: Concomitant medication data will be obtained and continued every 2 weeks during this time period

Post-ibrutinib (start of ibrutinib until 1 y post HCT). **All studies to be done within +/- 1 week of the planned time-points**

- Standard of care: History and physical including Karnofsky performance status (KPS) (see the Clinical Assessment Manual) will be done monthly until month 6 and then at month 9
- Standard of care: Following should be done **weekly for 4 weeks and then monthly until 6 months post HCT and then at month 9** after starting ibrutinib
    - Hematology
        - Hematology parameters performed at local laboratory will include at a minimum a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, and absolute neutrophil count.
    - Chemistry
        - Serum chemistry parameters performed at local laboratory will include at a minimum: creatinine, AST, ALT, alkaline phosphatase, and total bilirubin.

- Standard of care: To be done at month 6 and 9 post-HCT Peripheral blood T-cell, B-cell and NK cell subsets (CD3+, CD4+, CD8+, CD19+, CD16/56+)

- Research: Following should be done **at month 6 and 9 after** starting ibrutinib

    - A peripheral blood sample on all patients should be sent for Immunoseq for T-cell receptor. See the Laboratory Manual for sample acquisition, processing and shipping logistics.

    - Research: a peripheral blood sample will be collected for CyTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping.

- Toxicity assessment:

    - Research: Toxicity assessment will be done on first day of administration of ibrutinib to establish post-HCT baseline.

    - Research: Toxicity assessment will be done weekly after the start of ibrutinib until day 100 post HCT or at least 4 weeks post-ibrutinib (whichever is longer)

    - Research: Toxicity assessment will be done monthly until 12 months post HCT. Month 7,8, 10, and 11 toxicity assessment can be done telephonically if a patient is unable to travel back to the transplant center. A final toxicity assessment will be conducted 12 months post HCT.

    - Concomitant medication use will be recorded at month 6 and month 9

- Acute GVHD assessment
    - Standard of care: weekly assessment of acute GVHD until day 100 (+/- 1 week) post HCT or at least 4 weeks post-ibrutinib (whichever is longer). See the Clinical Assessment Manual for acute GVHD assessment forms

- Chronic GVHD assessment

    - Standard of care: Assessment at month 6 and 9 post HCT. NIH 2015 diagnosis and scoring forms will be used. See the Clinical Assessment Manual for chronic GVHD assessment forms

    - Research: a peripheral blood sample on all patients (in cohort A only) should be sent for IMMUNOSEQ for T-cell receptor and immunoseqMRD for MRD analyses if a new diagnosis of chronic GVHD is made and ideally before starting new therapy. *This may happen in between the planned assessment time points.* See the Laboratory Manual for collection, processing and shipping details.

    - Research: a peripheral blood sample on all patients (in cohort A only) should be sent for CyTOF analyses if a new diagnosis of chronic GVHD is made and ideally before starting new therapy. *This may happen in between the planned assessment time points.* See the Laboratory Manual for collection, processing and shipping details

- Disease reassessment

    - Standard of care: disease reassessment at month 6 and 9 post HCT per institutional criteria and may include imaging (CT scan and/or PET scan or other imaging) as indicated

    - Chimerism analyses
        - Standard of care: Assessment at months 6 and 9. Peripheral blood should be sent for chimerism analyses. Ablative transplants will require only % recipient vs. donor. RIC HCT will require sorted chimersims (CD 3: % recipient vs. donor and CD33 [or other suitable myeloid lineage markers]: % recipient vs. donor)

    - MRD analyses
        - Research: Assessment at months 6 and 9 post HCT. A peripheral blood sample on all patients should be sent for immunoseqMRD analysis. See the Laboratory Manual.

- Suspected relapse

    - Research: BM aspirate (5 ml in EDTA) in patients with active marrow disease will be sent to the coordinating center. See the Clinical Assessment Manual for detailed instruction on collection, processing and shipping.

    - Research: Tumor biopsy performed for suspected relapse should be collected and sent to coordinating center for CyTOF and IMMUNOSEQ. See the Laboratory Manual for detailed instruction on collection, processing and shipping.

    - Research: Peripheral blood samples on Cohort A patients should be sent for IMMUNOSEQ for T-cell receptor and immunoseqMRD analyses at end of study, only if it has been more than 4 weeks from previous research sample for this assay. See the Laboratory Manual for collection, processing and shipping details.

    - Research: A peripheral blood sample on all patients should be sent for CyTOF analyses only if it has been more than 4 weeks from previous research sample for this assay. See the Laboratory Manual for collection, processing and shipping details.

<u>At the time of new diagnosis of acute or chronic GVHD (from start of ibrutinib until 1 y post-HCT)</u>

- Standard of care: Assessment of acute GVHD (See the Clinical Assessment Manual if applicable.)

- Standard of care: Assessment of chronic GVHD (See the Clinical Assessment Manual if applicable.)

- Research: Peripheral blood samples on all patients (cohort A only) should be sent for IMMUNOSEQ for T-cell receptor and for immunoseqMRD analysis if a new diagnosis of acute or chronic GVHD is made and ideally before starting new therapy. This may happen in between the

planned assessment time points. See the Laboratory Manual for collection, processing and shipping details.

- Research: peripheral blood sample on all patients (cohort A only) should be sent for CyTOF analyses if a new diagnosis of acute or chronic GVHD is made and ideally before starting new therapy. This may happen in between the planned assessment time points. See the Laboratory Manual for collection, processing and shipping details.

<u>12 Months post HCT or earlier if withdrawing from the study (including withdrawal prior to initiation of Ibrutinib)</u>

- Standard of care:
    - History and physical, KPS (see the Clinical Assessment Manual)
    - Hematology
        - Hematology parameters performed at local laboratory will include at a minimum a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, and absolute neutrophil count.
    - Chemistry
        - Serum chemistry parameters performed at local laboratory will include at a minimum: creatinine, AST, ALT, alkaline phosphatase, and total bilirubin
    - Quantitative immunoglobulins including IgG, IgM and IgA
    - Peripheral blood T-cell, B-cell and NK cell subsets (CD3+, CD4+, CD8+, CD19+, CD16/56+)
    - Assessment of acute GVHD (see the Clinical Assessment Manual) if applicable
    - Assessment of chronic GVHD (see the Clinical Assessment Manual) if applicable. NIH 2015 diagnosis and scoring forms will be used.
    - Disease reassessment has to be done for end of study only if prior disease assessment is more than 4 weeks prior to end of study. Disease reassessment will include: appropriate imaging (CT scan and/or PET scan or other imaging) as clinically indicated and bone marrow biopsy. PB should be sent for chimerism analyses. Ablative transplants will require only % recipient vs. donor. RIC HCT will require sorted chimersims (CD 3: % recipient vs. donor and CD33 or lineage specific marker: % recipient vs. donor)
- Research:
    - Peripheral blood samples on all patients should be sent for Immunoseq for T-cell receptor and immunoseqMRD analysis. See the Laboratory Manual for sample acquisition, processing and shipping logistics.
    - Research: A peripheral blood sample will be collected for CyTOF analyses. See the Laboratory Manual for detailed instruction on collection, processing and shipping.

- Research: Toxicity assessment for ibrutinib
    - Research: Toxicity assessment will be done. In addition, toxicity assessment will be done 30 days after cessation of ibrutinib.
    - Concomitant medication use will be recorded

HCT outcome (from 1 yr. post HCT until 2 yr. post HCT)

- Chronic GVHD assessment:
    - Standard of care: assessment per institutional standard.
        - If new diagnosis of chronic GVHD or new organ involvement, coordinating center needs to be informed within 1 month of occurrence. NIH 2014 diagnosis and scoring forms will be used. See the Clinical Assessment Manual for details.
- Disease reassessment:
    - Standard of care: assessment per institutional standard
    - If evidence of progression or relapse, coordinating center needs to be informed within 1 month of occurrence
    - Suspected relapse
        - Research: Although not required by protocol, BM aspirate in patients with active marrow disease will be sent to the coordinating center. See the Laboratory Manual for detailed instruction on collection, processing and shipping.
        - Research: Although not required by protocol, tumor biopsy performed for suspected relapse should be collected and sent to coordinating center. See the Laboratory Manual for detailed instruction on collection, processing and shipping.
- Survival
    - Standard of care: At months 18 and 24 post HCT, coordinating center will be informed of survival status: alive without disease, alive with disease (if new relapse/progression, date of event). If patient died between month 12 and 24, coordinating center will be notified within 2 weeks of event, with date and cause of death (disease or non-relapse)

21. SUBJECT WITHDRAWAL

21.1 Withdrawal from Study Treatment

Study treatment will be withdrawn if:

- Patient experiences relapse or progression of underlying disease while on ibrutinib, and further continuation is not felt to be beneficial.
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration for more than 28 continuous days
- Non-compliance with taking ibrutinib or with following protocol
- Investigator decision
- Withdrawal of consent for treatment by subject
- Subject becomes pregnant
- Study termination by sponsor-investigator

All subjects, regardless of discontinuation of study treatment will undergo end of study visit and be followed for progression and survival until 2 y post HCT by imaging (CT scan and/or PET scan or other imaging) or other modalities per the discretion of the treating physician.

21.2 Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up. Every reasonable effort should be made by the study site personnel to contact the patient and the measures should be document.
- Study termination by Sponsor -investigator
- Death

When a subject withdraws before completing the study, the following information should be documented in source documents:

- Reason for withdrawal
- Whether the subject withdraws full consent (i.e. withdraws consent to treatment and all further contact) or partial consent (i.e. withdraws consent to treatment but agrees to participate in follow-up visits).

22. STUDY TABLE

22.1 Cohort A

Assessment	Within 4 weeks prior to starting preparative regimen for HCT	Start of Prep until day +60 post-HCT (± 1 week)	Day +60 to Day +90 & prior to administration of ibrutinib[13] (± 1 week)	Post-ibrutinib monthly assessment unless stated otherwise (start of ibrutinib until 1 y post HCT) (± 1 week)	At time of suspected relapse/ progression (start of ibrutinib until 1 y post HCT)	At time of new dx of acute or chronic GVHD (start of ibrutinib until 1 yr post HCT)	12M post HCT or EOS[15] (± 2 weeks)	30 Day Follow Up (+ 7 days)
History & Physical Exam	X	X	X	X (monthly until M6, then M9)			X	
KPS (see Clinical Assessment Manual)	X	X (q2 weeks)	X (q2 weeks)	X (monthly until M6, then M9)			X	
Transplant evaluation per institutional criteria	X[1]							
Hematology labs	X		X	X (weekly x 4 weeks, then monthly until M6, then M9)			X	
Chemistry labs	X		X	X (weekly x 4 weeks, then monthly until M6, then M9)			X	
Coagulation studies	X		X					
Hepatitis serology	X							
Pregnancy test (for WOCBP)	X		X					
EKG	X		X					
Echocardiogram	X							
PFT	X							
IgG, IgA, IgM	X		X				X	
Peripheral blood T and B cell subsets	X		X	X (M6, M9 post-HCT)			X	
Disease assessment	X[1]	X[3]		X (M6, M9 post-HCT)	X		X[9]	
DNA banking for subsequent chimerism analyses	X[1]							
Chimerism analyses		X		X (M6, M9 post-HCT)	X		X[9]	

Assessment	Within 4 weeks prior to starting preparative regimen for HCT	Start of Prep until day +60 post-HCT (± 1 week)	Day +60 to Day +90 & prior to administration of ibrutinib[13] (± 1 week)	Post-ibrutinib monthly assessment unless stated otherwise (start of ibrutinib until 1 y post HCT) (± 1 week)	At time of suspected relapse/ progression (start of ibrutinib until 1 y post HCT)	At time of new dx of acute or chronic GVHD (start of ibrutinib until 1 yr post HCT)	12M post HCT or EOS[15] (± 2 weeks)	30 Day Follow Up (+ 7 days)
Bone marrow biopsy	X[10] (active marrow disease)	X[4]			X[4]			
Acute GVHD assessment		X[5]	X[5]	X[12]		X	X	
Chronic GVHD assessment		X[6] (monthly)	X[6] (monthly)	X (M6, M9 post-HCT)		X	X	
Study drug (ibrutinib)			Start between day 60-90 post HCT until 12 months post HCT					
Con meds	X	X	X	X (M6, M9 post-HCT)			X	
PB samples for CyTOF analyses[2]	X		X	X (M6, M9 post HCT)	X (if tumor is biopsied, tumor sample is preferred)	X	X[9]	
Diagnostic sample for immunoseqMRD anlaysis	X[11]							
PB sample for immunoseqMRD analysis **assessment[7]**	X		X	X (M6, M9 post HCT)	X (if tumor is biopsied, tumor sample is preferred)	X	X[9]	
PB Sample for Immunoseq TCR analyses[7]			X[7]	X[7] (M6, M9 post HCT)	X[7]	X[7]	X[7,9]	
Ibrutinib toxicity assessment	X	X	X	X[8] (weekly for first 4 weeks then monthly until M11)			X[14]	X[14]

Between month 12 and month 24: patients will be followed for chronic GVHD, disease status and survival. See section on HCT outcome between 1y and 2y.

Red font is research

1. Transplant evaluation timing is per institutional criteria and does not have to be within 4 weeks of starting HCT
2. Peripheral blood sample for CyTOF analyses. Research sample. See the Laboratory Manual for sample acquisition, processing and shipping logistics
3. Disease reassessment should be done between day 30 and day 60 post-HCT. Imaging (CT scan and/or PET scan or other imaging) as clinically indicated

4. BM biopsy for disease assessment is considered standard of care. If marrow disease is suspected, a research sample for CYTOF analyses is needed. See the Laboratory Manual for sample acquisition, processing and shipping logistics
5. Weekly assessment of acute GVHD ± 3 days. Assessment of acute GVHD may start after engraftment. See the Clinical Assessment Manual.
6. Assessment of chronic GVHD should occur monthly (± 1 week) post-transplant. See the Clinical Assessment Manual.
7. Peripheral blood samples for IMMUNOSEQ analyses for T-cell receptor assay (TCR) and immunoseqMRD analyses. Research samples. See the Laboratory Manual for sample acquisition, processing and shipping logistics
8. Ibrutinib toxicity assessment. Weekly toxicity assessment for first 4 weeks after starting ibrutinib. Subsequently toxicity assessment should be monthly until month 11 post SCT. Toxicity assessment at month 7, 8, 10, 11 can be done over the phone if patient is unable to travel to the transplant center. All other time points for toxicity assessment should be done at the transplant center.
9. Disease reassessment needs to be done at end of study, only if previous disease assessment has been done more than 4 weeks prior to end of study.
10. If BM shows active disease, aspirate will be sent to coordinating center for CyTOF analyses. See the Laboratory Manual for sample acquisition, processing and shipping logistics.
11. Diagnostic sample from disease onset (paraffin block of lymph node only) if available must be sent for immunoseqMRD analyses. See the Laboratory Manual for sample acquisition, processing and shipping logistics.
12. Weekly assessment of acute GVHD: post-ibrutinib, weekly for 4 weeks or until day 100 post HCT whichever is later. See the Clinical Assessment Manual.
13. Please ensure eligibility checklist is complete and has been reviewed by coordinating center prior to the administration of ibrutinib between day 60 and 90 post HCT. All SOC and research studies must be done within 2 weeks of starting ibrutinib.
14. Toxicity assessment should be at the transplant center 30 days after cessation of study drug in addition to end of study.
15. The End of Study visit should be completed even for patients who withdraw from study without initiating Ibrutinib

22.2 Cohort B

Assessment	Within 4 weeks prior to starting preparative regimen for HCT	Start of Prep until day +60 post-HCT (± 1 week)	Day +60 to Day +90 & prior to administration of ibrutinib[12] (± 1 week)	Post-ibrutinib monthly assessment unless stated otherwise (start of ibrutinib until 1 y post HCT) (± 1 week)	At time of suspected relapse/ progression (start of ibrutinib until 1 y post HCT)	At time of new dx of acute or chronic GVHD (start of ibrutinib until 1 yr post HCT)	12M post HCT or EOS (± 2 weeks)[14]	30 Day Follow Up (+ 7 days)
History and Physical Exam	X	X	X	X (monthly until M6, then M9)			X	
KPS (see the Clinical Assessment Manual)	X	X (q2 weeks)	X (q2 weeks)	X (monthly until M6, then M9 post-SCT)			X	
Transplant evaluation per institutional criteria	X[1]							
Hematology labs	X		X	X (weekly for 4 weeks and then monthly until M6, then M9)			X	
Chemistry labs	X		X	X (weekly for 4 weeks and then monthly until M6, then M9)			X	
Coagulation studies	X		X					
Hepatitis serology	X							
Pregnancy test (for WOCBP)	X		X					
EKG	X		X					
Echocardiogram	X							
PFT	X							
IgG, IgA, IgM	X						X	
Peripheral blood T and B cell subsets	X			X (M6, M9 post-HCT)			X	
Disease assessment	X[1]	X[3]		X (M6, M9 post-HCT)	X		X[9]	
DNA banking for subsequent chimerism analyses	X[1]							
Chimersim analyses		X		X (M6, M9 post-HCT)	X		X[9]	
Bone marrow biopsy	X	X			X			

Assessment	Within 4 weeks prior to starting preparative regimen for HCT	Start of Prep until day +60 post-HCT (± 1 week)	Day +60 to Day +90 & prior to administration of ibrutinib[12] (± 1 week)	Post-ibrutinib monthly assessment unless stated otherwise (start of ibrutinib until 1 y post HCT) (± 1 week)	At time of suspected relapse/ progression (start of ibrutinib until 1 y post HCT)	At time of new dx of acute or chronic GVHD (start of ibrutinib until 1 yr post HCT)	12M post HCT or EOS (± 2 weeks)[14]	30 Day Follow Up (+ 7 days)
Acute GVHD assessment		X[5]	X[5]	X[11]		X	X	
Chronic GVHD assessment		X[6] (monthly)	X[6] (monthly)	X (M6, M9 post-SCT)		X	X	
Study drug (ibrutinib)			Start between day 60-90 post HCT until 12 months post HCT					
Con meds	X	X	X	X			X	
Ibrutinib toxicity assessment	X	X	X	X[8] (weekly for first 4 weeks then monthly until M11)			X[13]	X[13]

Between month 12 and month 24: patients will be followed for chronic GVHD, disease status and survival. See section on HCT outcome between 1y and 2y.

Red font is research

1. Transplant evaluation timing is per institutional criteria and does not have to be within 4 weeks of starting HCT
2. Peripheral blood sample for CyTOF analyses. Research sample. See the Laboratory Manual for sample acquisition, processing and shipping logistics
3. Disease reassessment should be done between day 30 and day 60 post-HCT. Imaging (CT scan and/or PET scan or other imaging) as clinically indicated
4. BM biopsy for disease assessment is considered standard of care.
5. Weekly assessment of acute GVHD ± 3 days. Assessment of acute GVHD may start after engraftment. See the Clinical Assessment Manual.
6. Assessment of chronic GVHD should occur monthly (± 1 week) post-transplant. See the Clinical Assessment Manual.
7. Peripheral blood sample for IMMUNOSEQ analyses for T-cell receptor assay (TCR) and for immunoseqMRD analyses. Research sample. See the Laboratory Manual for sample acquisition, processing and shipping logistics
8. Ibrutinib toxicity assessment. Weekly toxicity assessment for first 4 weeks after starting ibrutinib. Subsequently toxicity assessment should be monthly until month 11 post SCT. Toxicity assessment at month 7,8, 10, 11 can be done over the phone if patient is unable to travel to the transplant center. All other time points for toxicity assessment should be done at the transplant center.
9. Disease reassessment needs to be done at end of study, only if previous disease assessment has been done more than 4 weeks prior to end of study.
10. Diagnostic sample from disease onset (paraffin block of lymph node only) if available must be sent for immunoseqMRD analyses. See the Laboratory Manual for sample acquisition, processing and shipping logistics.
11. Weekly assessment of acute GVHD: post-ibrutinib, weekly for 4 weeks or until day 100 post HCT whichever is later. See the Clinical Assessment Manual.

12. Please ensure eligibility checklist is complete and has been reviewed by coordinating center prior to the administration of ibrutinib between day 60 and 90 post HCT. All SOC and research studies should be done within 2 weeks of starting ibrutinib.
13. Toxicity assessment should be at the transplant center 30 days after cessation of study drug in addition to end of study
14. The End of Study visit should be completed even for patients who withdraw from study without initiating Ibrutinib

23. DRUG SHIPMENT

Ibrutinib will be considered as an investigational agent for the purpose of this study. The Vanderbilt Investigational Pharmacy will be the central pharmacy for receiving ibrutinib from Janssen Scientific Affairs and then shipping it to individual site investigational pharmacy. Drug accountability logs will be maintained. All sites will perform IP destruction on site. Each site will send drug destruction and hazardous waste policy to the coordinating center (at Coordinating.Center@Vanderbilt.edu) for review. Study drug destruction at the participating sites will be performed after the approval from the coordinating center. Documentation of the review and approval will be maintained in the study binder and at each participating site. Any drug that has been prepared but not dispensed, returned by the subject, expired, damaged, or otherwise deemed to be unusable will be destroyed on site according to the sites SOP for destruction. Each site will dispose of drug on site according to their SOP for destruction. Please refer to the IP Management Plan for additional details.

24. STATISTICAL ANALYSES PLAN

24.1 Analysis Plan

The statistical analysis plan will address the primary aim: To study the use of ibrutinib starting between day 60 and day 90 after allogeneic HCT until 12 months post HCT to improve the PFS at 12 months post HCT by 25% compared to historical controls. <u>This will be restricted to cohort A which includes the diagnoses of CLL and MCL, only.</u>

- PFS is defined as time to progression, or relapse of the underlying disease for which transplant was undertaken, or death from any non-relapse causes, starting from the date of stem cell transplant (SCT).
- We will estimate the 12-month PFS rate with a 95% confidence interval using the method of Kaplan-Meier and using the Greenwood variance estimator, and we will compare this estimate with the rate in the historical controls.
- Historical data
    - In a study by Sobecks et al[53], the outcomes of patients with CLL after ablative (n=163) and reduced intensity conditioning (RIC) 134 were reported. Outcomes were stratified based on when the HCT occurred (< 2000, or ≥ 2000). We expect the majority of patients with CLL on the proposed study to be undergoing RIC allo HCT, thus relevant data (≥ 2000 and RIC allo HCT) are taken into account for sample size analyses. One year PFS was 62% (95% CI 51-72).
    - In a study by Urbano-Ispizua et al[54], the outcomes of patients with MCL undergoing ablative (n=149) and RIC (n=351) allo-HCT was reported. The 1y PFS for patients with MCL (personal communication, CIBMTR) was 52% (95% CI 47-56)
- The proportion of patients with CLL and MCL enrolling in this study will not be known at the start of the study or be controlled for during the accrual period. Thus, we studied the impact on power of varying proportions of these two diagnoses on outcome for a given effect size.
- We will compare our overall PFS rate with the weighted average of the historical rates in CLL and MCL, using the proportion of our sample with each of these two diagnoses as the weights.

24.2 Sample Size

The following table reflects the power and effect size, if we enroll 65 patients with varying proportion of the diagnoses. **These** calculations **are based on the maximum likelihood estimator (MLE) for the mean survival time assuming exponentially-distributed PFS[53] using the cube-root transformation of the MLE as suggested by Sprott[54]. The one-year survival probability can be calculated once the distribution is specified.** The following test statistic has a standard normal distribution:

$$\frac{\hat{\phi} - \phi}{\left(\hat{\phi}^2/9\hat{Q}\right)^{\frac{1}{2}}} \sim N(0,1),$$

where $\hat{\phi} = \hat{\theta}^{-\frac{1}{3}}$, $\hat{\theta}$ is the MLE for the PFS mean, and $\hat{Q} = \sum(1 - e^{-L_i/\hat{\theta}})$.

This is a single arm phase two study. Patients will be accrued uniformly over two years, and then followed for two years. The power calculations are based on derivations from Lawless[53] with a cube-root trans-formation of the maximum likelihood estimate (MLE), as suggested by Sprott[54] . This is implemented in the online calculator (tool of One Arm Survival) found at https://stattools.crab.org which is provided by the SWOG Statistical Center. Thus, 65 patients will give us at least 84% power to detect an effect size of 25% improvement in progression-free survival at 1 year compared to the estimated historical control rate, for varying proportions of patients with CLL and MCL. The following table reflects the power and effect size, if we enroll 65 patients with varying proportion of the diagnoses.

Table: Power achieved for a sample of 65 patients for different effect sizes using a 2-sided parametric test with level 0.05, assuming on 2 years of uniform accrual and 2 years of follow-up time.

	%CLL	%MCL	1 year PFS Historical Control	1 year PFS Treated	Power
20%	30	70	0.55	0.660	74
	40	60	0.56	0.672	76
	50	50	0.57	0.684	78
	60	40	0.58	0.696	80
	70	30	0.59	0.708	83
25%	30	70	0.55	0.688	91
	40	60	0.56	0.700	92
	50	50	0.57	0.713	93
	60	40	0.58	0.725	95
	70	30	0.59	0.738	96
30%	30	70	0.55	0.715	98
	40	60	0.56	0.728	98
	50	50	0.57	0.741	99
	60	40	0.58	0.754	99
	70	30	0.59	0.767	99

In addition, cohort B will include 10 patients (FL and HD). There is no formal sample calculation for cohort B.

24.3 Safety Analyses

HCT is a complex procedure with varying causes of death post HCT. Patients may die of relapse or progression of disease, development or worsening of acute GVHD after exposure to study drug, development or worsening of chronic GVHD after exposure to study drug, infections in absence of GVHD or other causes (other non-relapse mortality) (includes drug adverse effects).

Both cohort A and B will be at risk for these events and thus will be included in the safety analyses.

In order to safeguard patients, we have set the following limits:

- Development of grade 3-4 acute GVHD by day 180 post HCT for patients who have no acute GVHD prior to starting experimental therapy should not be higher than 30%.

- Development of grade 3-4 acute GVHD for patients with grade1-2 acute GVHD prior to starting experimental therapy should not be higher than 40%.

- Development of grade 3-4 acute GVHD for patients with any grade acute GVHD prior to starting experimental therapy should not be higher than 50%.

- Cumulative incidence of infectious disease mortality (not related to GVHD) should not be higher than 30% at 1 y post HCT

- Cumulative incidence of non-relapse mortality (all cause) at 1 y post HCT should not be higher than 40%

<u>Stopping Rules</u>

Cohort B is an exploratory cohort of 10 patients with diagnoses of follicular lymphoma or Hodgkin disease. Combining cohort, A and B with 75 patients in total, the stopping rules are created based on Bayesian approach to monitor treatment related AEs defined below during the conduct of a clinical trial. We will stop the trial early if the probability that treatment related events of the current regimen exceeds conventional treatment related AE is greater than 80%.

The following tables describe the safety rules. There will be 2 conference calls per month during the conduct of the study to ensure the implementation of the safety rules.

Development of grade 3-4 acute GVHD by day 180 post HCT for patients who have no acute GVHD prior to starting experimental therapy should not be higher than 30%.

Number of patients in complete cohorts of 5 (inclusive)	**Stop the trial if this number of toxicities (inclusive)**
5	3
10	5
15	7
20	8
25	10
30	12

Development of grade 3-4 acute GVHD for patients with grade1-2 acute GVHD prior to starting experimental therapy should not be higher than 40%.

Number of patients in complete cohorts of 5 (inclusive)	**Stop the trial if this number of toxicities (inclusive)**
5	4
10	6
15	8
20	10
25	13
30	15
35	17
40	19

Development of grade 3-4 acute GVHD for patients with any grade acute GVHD prior to starting experimental therapy should not be higher than 50%.

Number of patients in complete cohorts of 5 (inclusive)	**Stop the trial if this number of toxicities (inclusive)**
5	4
10	6
15	8
20	10
25	13
30	15
35	17
40	19

Cumulative incidence of infectious disease mortality (not related to GVHD) should not be higher than 30% at 1 y post HCT.

Number of patients in complete cohorts of 5 (inclusive)	**Stop the trial if this number of toxicities (inclusive)**
5	4
10	6
15	8
20	10
25	13
30	15
35	17
40	19

Cumulative incidence of non-relapse mortality (all cause) at 1 y post HCT should not be higher than 40%.

Number of patients in complete cohorts of 5 (inclusive)	Stop the trial if this number of toxicities (inclusive)
5	4
10	6
15	8
20	10
25	13
30	15
35	17
40	19

24.4 Association Analyses with Correlative Studies

Appropriate methodologies for association analyses of immunoseqMRD,, IMMUNOSEQ, and CYTOF with relevant clinical variables will be undertaken.

25. SAFETY DATA COLLECTION AND REPORTING

25.1 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events, special situations, including pregnancies and product quality complaints will be reported as described in this protocol from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of a product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the use of the study drug.
For the purposes of this study, the J&Jmedicinal product is: Ibrutinib (Imbruvica).

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), and other safety measurements. They will be summarized by descriptive statistics. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned. Exposure to ibrutinib first dose and reasons for discontinuation from study treatment will be tabulated.

25.2 Definitions

25.2.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.

- Any AEs experienced by the patient through the completion of final study procedures.

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with cGVHD that were not present before the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the 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.

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions as measured prior to HCT and prior to administration of ibrutinib.

Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC. is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic AE of Grade 3 or higher*
- Any treatment-emergent SAE of bleeding of any grade
- Any treatment-emergent CNS hemorrhage/hematoma of any grade
- **all hemorrhagic AEs requiring a transfusion of red blood cells should be reported as a Grade 3 or higher AEs per NCI-CTCAE*

Any Adverse Event of Special Interest that is to be reported to Janssen Scientific Affairs, LLC should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of knowledge of the event.**

25.2.2 Serious Adverse Event (SAE)

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

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

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

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in patient death

Adverse Event Reporting Timeframe

Adverse events will be captured from the time of consent until 30 days post cessation of study drug.

Causality (Attribution)

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

- Definite – The AE is clearly related to the study treatment
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment
- Unlikely - The AE is doubtfully related to the study treatment
- Unrelated - The AE is clearly NOT related to the study treatment

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)

- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

25.3 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements:

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a J&Jmedicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- J&J protocol ID

25.4 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product

- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g. autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

25.5 Unlisted (unexpected) Adverse Event/Reference Safety Information

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

https://www.imbruvicahcp.com/

https://www.imbruvicahcp.com/docs/librariesprovider2/pdf-downloads/prescribing_information.pdf

25.6 Special Reporting Situation

Safety events of interest for a J&J medicinal product that expedited reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a J&J medicinal product
- Exposure to a J&J medicinal product from breastfeeding
- Suspected abuse/misuse of a J&J medicinal product
- Inadvertent or accidental exposure to a J&J medicinal product
- Any failure of expected pharmacological action (i.e. lack of effect) of a J&J medicinal product
- Medication error involving a J&J medicinal product (with or without subject/patient exposure to the study drug, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a J&J medicinal product

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events eCRF 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 the Coordinating Center. See the Safety Data Collection and Reporting section for Coordinating Center contact information. Collection of these events will occur from the time the subject signs consent to 30 days after the last dose of study drug.

25.7 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy.

However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to the Coordinating Center within 1 business day of learning of the event. See the Safety Data Collection and Reporting section for Coordinating Center contact information.

All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

All reports of pregnancy from sub-sites must be reported to the Vanderbilt Coordinating Center (Coordinating.Center@vumc.org) by the site within 24 hours of their knowledge of the event using the Janssen Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the J&J medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a J&J medicinal product will be reported to the Vanderbilt Coordinating Center (Coordinating.Center@vumc.org) by the site within 24 hours of their knowledge of the event using the Janssen Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

25.8 Contacting Sponsor-Investigator Regarding Safety

The Sponsor-investigator can be contacted via email (Coordinating.Center@vumc.org)

25.9 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format.

However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

25.10 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for J&J Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a J&J medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a J&J medicinal product.

All (serious and non-serious) adverse events reported for a J&J medicinal product should be followed-up in accordance with clinical practice.

25.11 SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events will be reported from time of consent through 30 days after the last dose of study drug. 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)

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center. All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Janssen SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: Coordinating.center@vumc.org
FAX: (615) 875-0040

If SAE documents are faxed, the Coordinating Center must be notified via email as well. Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication. The

Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

Food and Drug Administration (FDA)

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to study treatment (as determined by the sponsor-investigator) will be reported to the FDA via MedWatch 3500A (available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf. Submissions by the sponsor can be submitted via fax or email and must be addressed to Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

Reporting to Janssen Scientific Affairs, LLC

The Vanderbilt Coordinating Center will report all SAEs, Adverse Events of Special Interest and special situations regardless of causality occurring after exposure to Ibrutinib to Janssen Scientific Affairs, LLC via secure e-mail per the provided instruction manual within 24 hours of becoming aware of the event(s).

Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Event of Special Interest or special situation is required. Collection of these events will occur from the time the subject signs consent to 30 days after the last dose of study drug.

The PRINCIPAL INVESTIGATOR or designee is responsible for ensuring that these cases are complete and if not are promptly followed-up. The Vanderbilt Coordinating Center will follow up with the relevant site until the safety report is complete. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the J&J Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method listed in the Transmission Methods section within 24 hours of such report or correspondence being sent to applicable health authorities.

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in section 25.1 Management of Safety Data.

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a J&J medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR or designee within 24 hours after being made aware of the event. The J&J contact will provide additional information/form to be completed.

If the defect for a J&J medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-J&J Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non J&J medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via J&JSECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

26. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

26.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (e.g., all advertising materials or materials given to the subject during the study) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to the Vanderbilt Coordinating Center as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.
Any changes to site regulatory documents must be submitted by the investigator or designee to the Coordinating Center in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients will begin protocol therapy without formal registration.

Prior to initiating the trial, the investigator will secure and provide to the Coordinating Center essential documents, including but not limited to:

- A signed FDA Form 1572
- A current curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- A copy of the current medical license for all investigators listed on the FDA Form 1572 as applicable (i.e. non licensed personnel listed on the 1572 will not furnish this document).
- A letter from the IRB stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- A copy of the IRB-approved informed consent document
- The current IRB membership list for the reviewing IRB
- A completed financial disclosure form for the investigator and all sub- investigators
- Current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory.

26.2 Informed Consent

The ICF and consent process must comply with US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated

consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

Additionally, information on any change in risk and/or significant change in study procedures must be provided as appropriate to subjects already actively participating in the study, and they must read, understand, and sign the revised ICF confirming willingness to remain in the trial.

26.3 Quality Control and Quality Assurance

The Sponsor, Vanderbilt, shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

26.4 Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the Investigator, or the study site staff. All protocol deviations are required to be reported to the Coordinating Center and submitted to the IRB per institutional guidelines. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

26.5 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to the Informed Consent section), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Vanderbilt and its designees, regulatory agencies, and IRBs/IECs, Janssen Scientific Affairs and its co-development partners. As the study Sponsor, Vanderbilt will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

26.6 Study files and Record Retention

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, documentation of CRF corrections, SAE forms transmitted to Vanderbilt, notification of SAEs and related reports, source documentation, normal laboratory values, curricula vitae for investigators, and all relevant correspondence and other documents pertaining to the conduct of the study.

The Investigator must notify Vanderbilt and obtain written approval from Vanderbilt before destroying any clinical study documents or images (e.g., scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Vanderbilt. Vanderbilt will inform the Investigator of the date that study records may be destroyed or returned to Vanderbilt.

Vanderbilt must be notified in advance of, and Vanderbilt must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the

Investigator and Vanderbilt to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for two years after marketing application approval. If no application is filed, these records must be kept two years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating institution will maintain a copy of all site study records in a safe and secure location. The Sponsor Investigator will inform the Investigator at each site at such time that the records may be destroyed.

26.7 Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (i.e., listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within the required amount of time. At all times, the Investigator has final responsibility for the accuracy and

authenticity of all clinical data.

The CRFs exist within an electronic data capture (EDC) system called REDCap with controlled access managed by Vanderbilt or its authorized representative for this study.

The Vanderbilt University Office of Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). In addition to traditional data capture functionality, REDCap's survey capabilities are a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. All data collection projects rely on a thorough, study-specific data dictionary, defined by all members of the research team in an iterative, self-documenting process. This iterative development and testing process results in a well-planned and individualized data collection strategy.

REDCap servers are housed in a local data center at Vanderbilt, and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Vanderbilt researchers by both our Privacy Office and Institutional Review Board. REDCap has been disseminated for local use at more than 940 other academic/non-profit consortium partners in 75 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at http://www.projectredcap.org/.

Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system.

26.8 Study Monitoring and Audit Requirements

The Sponsor-investigator will monitor this trial continuously until study completion.

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

A Research Compliance auditor under the direction of the DSMC will audit this clinical trial every 6 months for compliance with adverse event reporting, regulatory and studies requirements, and data accuracy and completion. Audit reports detailing the findings are provided to the DSMC. Site visits to ensure compliance will be performed on an ad hoc basis, notably under circumstances of high accrual.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

This study is also subject to other reviews or audits at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. Janssen Scientific Affairs may choose to inspect a study site at any time before, during, or after completion of the clinical study.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/IEC and Vanderbilt and its authorized employees of the appropriate regulatory authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

26.9 Investigator Responsibilities

A complete list of Investigator responsibilities is outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the USPI; will obtain IRB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors, and regulatory agencies adequate and accurate records of study activity and drug accountability for study related monitoring, audits, IRB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/IEC according to the specifics outlined in this protocol;

will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

26.10 Sponsor-Investigator Responsibilities

A complete list of Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols, and promptly inform Investigators and health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

26.11 Financial Disclosure

For this study, each Investigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify the Sponsor Investigator of any relevant changes in financial disclosure information during the conduct of the study and for one year after the study has been completed.

26.12 Protocol Amendments

The Sponsor Investigator is responsible for the development and coordination of all protocol amendments. The Sponsor Investigator will obtain Vanderbilt IRB approval for the protocol amendment and then disseminate the amendment to participating institutions for submission to their IRBs/IECs. Any change to the informed consent document must be reviewed and approved by the Sponsor before being submitted to the IRB/IEC at participating institutions.

Written documentation of IRB/IEC approval must be received by the Sponsor Investigator before the amendment may take effect at each site.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and the Sponsor.

26.13 Publication of Study Results

The sponsor investigator may use the results for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Janssen Scientific Affairs, LLC reserves the right to preview all manuscripts and abstracts related to this study, allowing the Janssen Scientific Affairs, LLC sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors, the Sponsor Investigator and Janssen Scientific Affairs and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

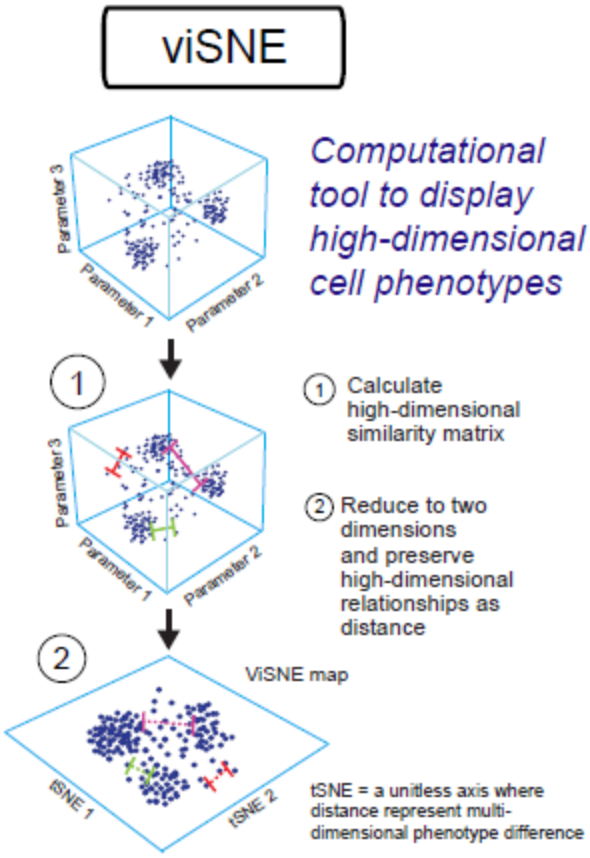
26.14 Study Discontinuation

The Sponsor-investigator reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor-Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor-investigator will assure that adequate consideration is given to the protection of the subjects' interests.

APPENDIX 1: FIGURES 5, 6, 7, 8

APPENDIX 1

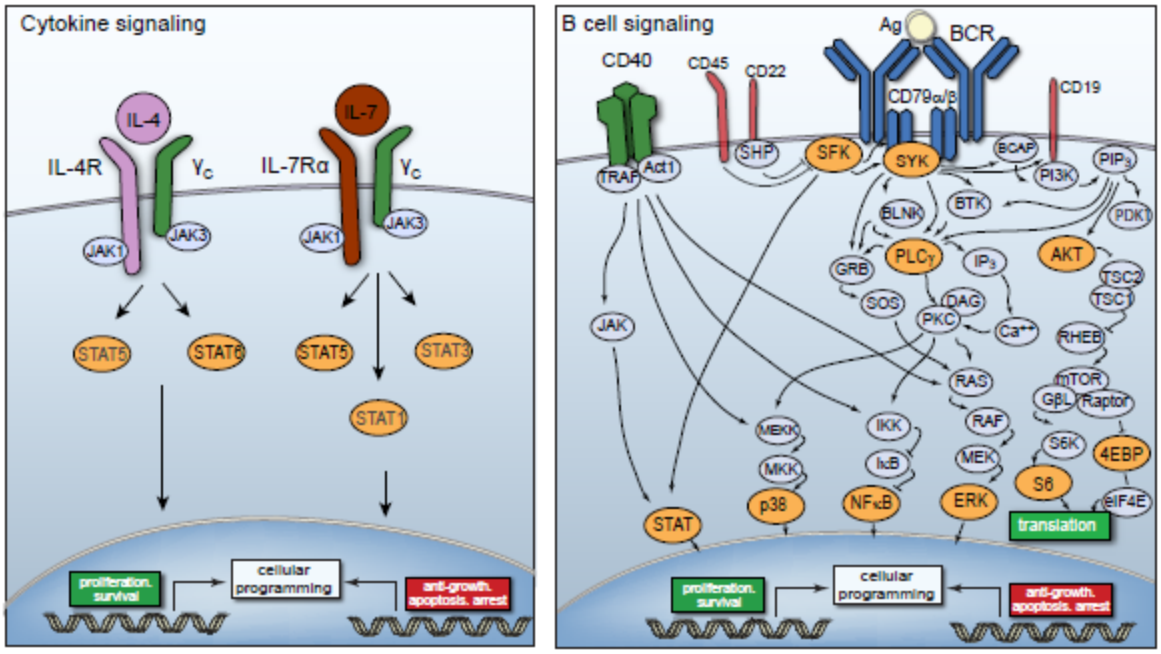
Figure 5: Shows the workflow to develop 2 dimensional plots to reflect the 34 dimensional output using ViSNE.



APPENDIX 1

Figure 6: BCR signaling network: Signaling output (orange circles) that can be measured with CyTOF

Signaling networks

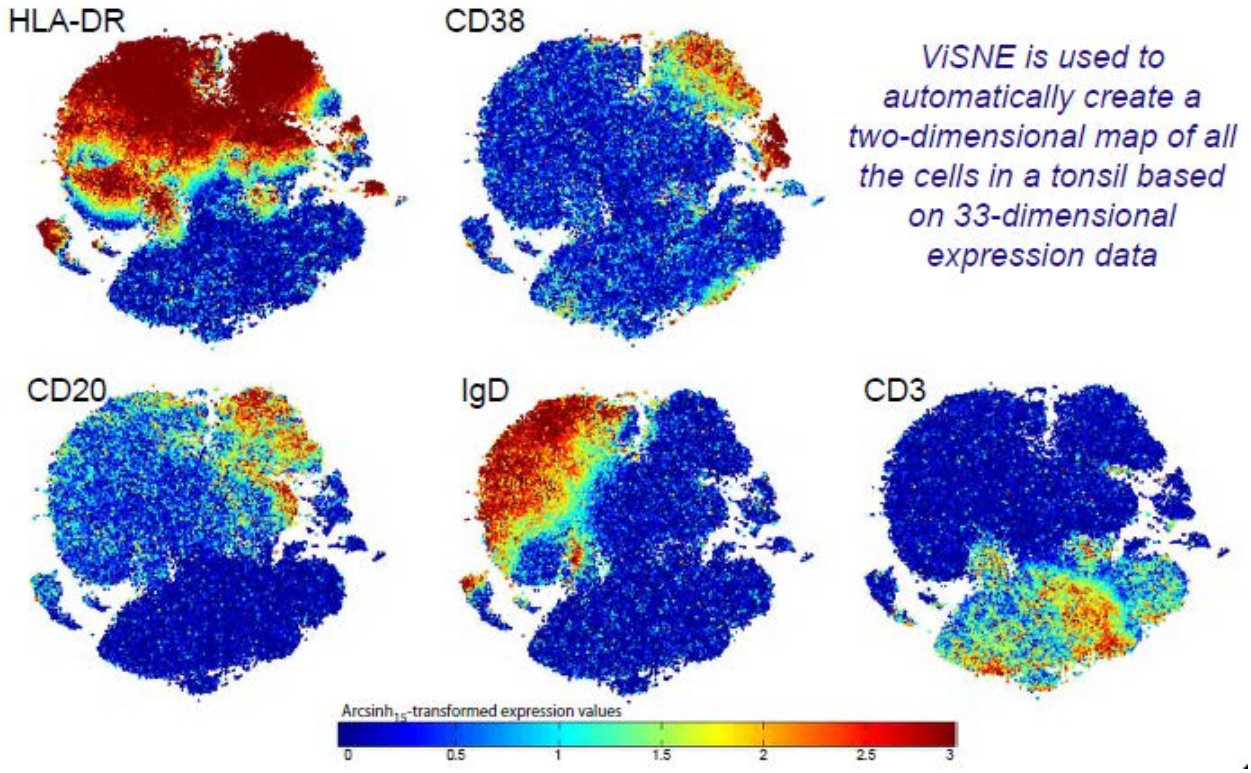


Signaling output

Measured signaling output

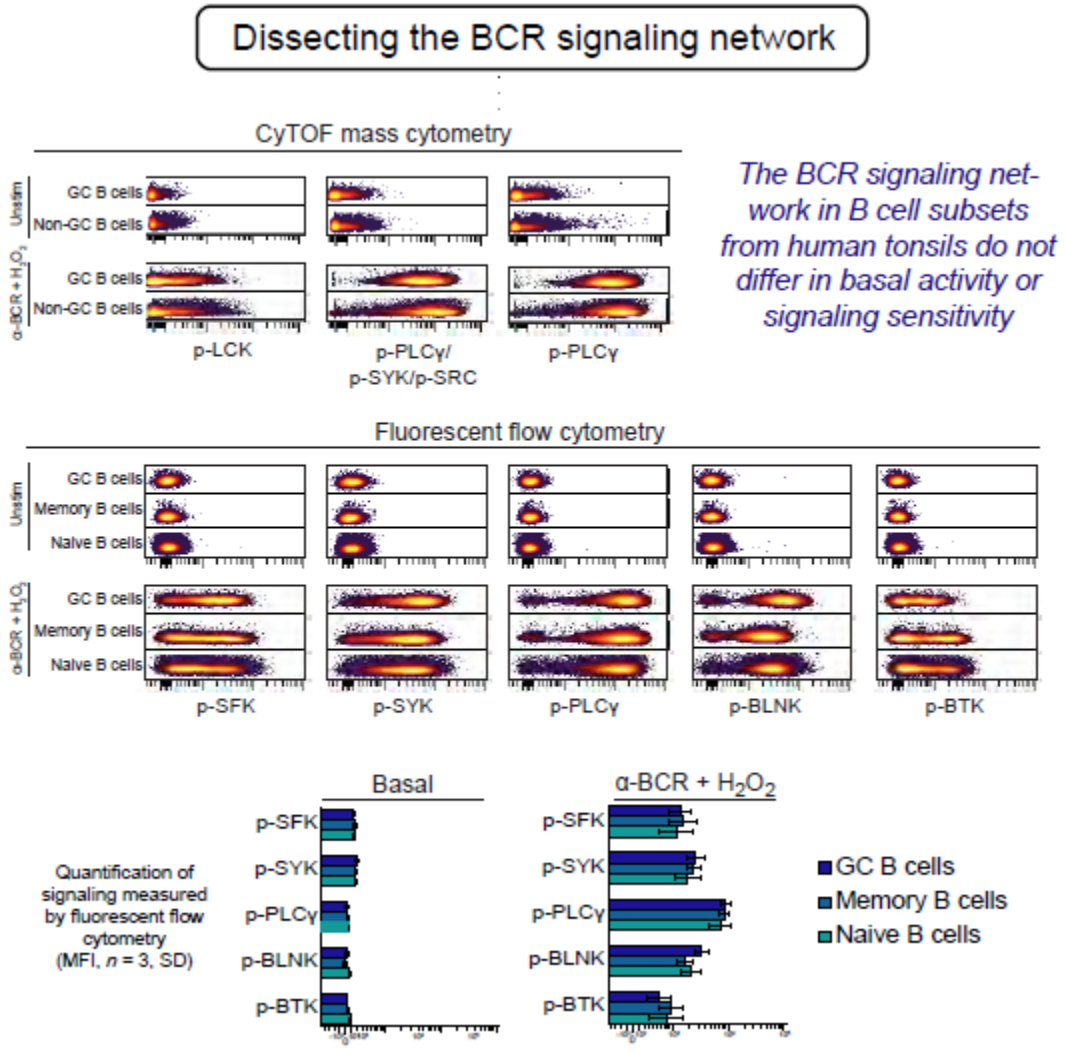
APPENDIX 1

Figure 7: Heat map of the human tonsillar B cell as computed by VISNE



APPENDIX 1

Figure 8: The signaling network of the human B cell as interrogated by CyTOF



APPENDIX 2:

Disease status assessment: Pre HCT: CLL. CIBMTR form 2013, Revision 2.0, 10 pages.

Form 2013 R2.0: Chronic Lymphocytic Leukemia(CLL) Pre-HSCT Data

Center: CRID:

Autoimmune disorder(s) at diagnosis:

9 Immune hemolytic anemia

○ yes ○ no ○ Unknown

10 Immune thrombocytopenia

○ yes ○ no ○ Unknown

11 Positive Coombs' test

○ yes ○ no ○ Unknown

12 Other

○ yes ○ no ○ Unknown

13 Specify other autoimmune disorder: _____

14 What was the Rai stage at diagnosis?

○ low risk - stage 0 - lymphocytosis (>15,000 x 10^9/L) in blood or bone marrow only

○ intermediate risk - stage I- lymphocytosis plus enlarged lymph nodes (lymphadenopathy)

○ intermediate risk - stage II - lymphocytosis plus enlarged liver or spleen with or without lymphadenopathy

○ high risk - stage III - lymphocytosis plus anemia (Hgb < 11 g/dL) with or without enlarged liver, spleen, or lymph nodes

○ high risk - IV - lymphoctyosis plus thrombocytopenia (platelet count < 100 x 10^9/L) with or without anemia or enlarged liver, spleen, or lymph nodes

○ Unknown

15 What was the Binet stage at diagnosis? (Five lymphoid bearing areas are possible: axillary, cervical, inguino-femoral, liver, and spleen.)

○ stage A - two or fewer lymphiod bearing areas enlarged, without anemia or thrombocytopenia

○ stage B - three or more lymphoid bearing areas enlarged, without anemia or thrombocytopenia

○ stage C - presence of anemia (Hgb < 10.0 g/dL) or thrombocytopenia (platelet count < 100 x 10^9/L)

○ Unknown

16 What were the disease symptoms at diagnosis?

○ A - none of the symptoms listed in B below

○ B - unexplained weight loss of >10% of body weight in six months before treatment; unexplained fever > 38°C; or, night sweats

○ Unknown

17 Was there extramedullary and/or extranodal involvement at diagnosis?

○ yes ○ no ○ Unknown

Specify site(s) of involvement:

18 Central nervous system (CNS)

○ yes ○ no

19 Liver

○ yes ○ no

20 Lung

○ yes ○ no

21 Spleen

○ yes ○ no

Form 2013 R2.0: Chronic Lymphocytic Leukemia(CLL) Pre-HSCT Data

Center: CRID:

22 Specify centimeters below costal margin: _____

23 Other site:

○ yes ○ no

24 Specify: _____

If the recipient is 18 years of age or older, complete the Karnofsky Scale. If the recipient is younger than 18 years of age, complete the Lansky Scale.

26 Enter age-appropriate Karnofsky or Lansky score at diagnosis: _____

Laboratory Studies at Diagnosis

Questions: 26 - 80

27 Lymphocytes in bone marrow:

○ Known ○ Not known

_____ %

Peripheral Blood Studies at Diagnosis

28 WBC:

○ Known ○ Not known

29 _____ ○ x 10^9/L (x 10^3/mm^3) ○ x 10^9/L

30 Lymphocytes:

○ Known ○ Not known

31 _____ %

32 Prolymphocytes:

○ Known ○ Not known

33 _____ %

34 LDH:

○ Known ○ Not known

35 _____ ○ U/L ○ µkat/L

36 Upper limit of normal for LDH: _____

37 β^2 microglobulin:

○ Known ○ Not known

38 _____ ○ µg/dL ○ mg/L ○ nmol/L

39 Upper limit of normal for β^2: _____

40 IgG:

○ Known ○ Not known

41 _____ ○ mg/dL ○ g/dL ○ g/L

42 Lower limit of normal for IgG: _____

43 IgA:

○ Known ○ Not known

44 _____ ○ mg/dL ○ g/dL ○ g/L

45 Lower limit of normal for IgA: _____

Form 2013 R2.0: Chronic Lymphocytic Leukemia(CLL) Pre-HSCT Data

Center: CRID:

46 IgM:

○ Known ○ Not known

47 _____ ○ mg/dL ○ g/dL ○ g/L

48 Lower limit of normal for IgM: _____

49 Leukemia cell type: (may be determined at any time after diagnosis)

○ B cell ○ T cell ○ Unknown

Immunophenotype: ***(may be determined at any time after diagnosis)***

50 CD5+

○ yes ○ no ○ Unknown

51 CD19+

○ yes ○ no ○ Unknown

52 CD20+

○ yes ○ no ○ Unknown

53 CD23+

○ yes ○ no ○ Unknown

54 CD38+

○ yes ○ no ○ Unknown

55 sig weakly expressed

○ yes ○ no ○ Unknown

56 Did hypercalcemia occur at any time?

○ yes ○ no

57 Were cytogenetics tested (conventional or FISH)?

○ yes ○ no ○ Unknown

58 Results of tests at diagnosis:

○ Yes abnormalities identified

○ No evaluable metaphases

○ No abnormalities

Specify cytogenetic abnormalities identified at diagnosis:

Trisomy

59 +12

○ yes ○ no

Translocation

60 t(11;14)

○ yes ○ no

61 any translocation of 14

○ yes ○ no

Form 2013 R2.0: Chronic Lymphocytic Leukemia(CLL) Pre-HSCT Data

Center: CRID:

Deletion

82 del(11q)/11q- (ATM)

yes no

83 del(13q)/13q-

yes no

84 del(17p)/17(p53)-

yes no

Other

86 abnormal 6

yes no

88 abnormal 8

yes no

87 Other abnormality

yes no

88 Specify other abnormality: _____

89 Results of tests after diagnosis to prior to preparative regimen:

Yes abnormalities identified

No evaluable metaphases

No abnormalities on any tests after diagnosis and before the preparative regimen

Specify any test result between diagnosis and preparative regimen:

Trisomy

70 +12

yes no

Translocation

71 t(11;14)

yes no

72 any translocation of 14

yes no

Deletion

73 del(11q)/11q- (ATM)

yes no

74 del(13q)/13q-

yes no

76 del(17q)/17(p53)-

yes no

Other

76 abnormal 6

○ yes ○ no

77 abnormal 8

○ yes ○ no

78 Other abnormality

○ yes ○ no

79 Specify other abnormality: _____

80 Is a copy of the cytogenetic or FISH report attached?

○ yes ○ no

Pre-HSCT Treatment for CLL

Questions: 81 - 122

81 Was therapy given between diagnosis and the start of the preparative regimen?

○ yes ○ no ○ Unknown

Line(s) of Therapy (1)

Questions: 82 - 122

Line of Therapy

82 Systemic Therapy

○ yes ○ no

83 Date therapy started: __ __ __ __ - __ __ - __ __

84 Date therapy stopped: __ __ __ __ - __ __ - __ __

85 Number of cycles _____ ☐ Number of cycles unknown/not applicable

Monoclonal antibodies:

86 Alemtuzumab (Campath)

○ yes ○ no

87 Ibritumomab tiuxetan (Zevalin)

○ yes ○ no

88 Rituximab (anti-CD20, Rituxan)

○ yes ○ no

89 tositumomab (Bexxar)

○ yes ○ no

90 other monoclonal antibody

○ yes ○ no

91 Specify: _____

92 Chlorambucil (Leukeran)

○ yes ○ no

93 Cladribine (2-CdA, Leustatin)

○ yes ○ no

94 Corticosteroids

○ yes ○ no

96 Cyclophosphamide (Cytoxan)

yes no

98 Cytarabine (Ara-C)

yes no

97 Doxorubicin (Adriamycin)

yes no

98 Etoposide (VP-16, VePesid)

yes no

99 Fludarabine (Fludara)

yes no

100 Gemcitabine (Gemzar)

yes no

101 Ifosfamide (Ifex)

yes no

102 nitrogen mustard (mustine)

yes no

103 Pentostatin (Nipent)

yes no

104 Vincristine (VCR, Oncovin)

yes no

105 other treatment

yes no

106 Specify: _____

107 Radiation Therapy:

yes no

108 Date therapy started: __ __ __ __ - __ __ - __ __

109 Date therapy stopped: __ __ __ __ - __ __ - __ __

110 Mediastinum

yes no

111 other sites(s)

yes no

112 Specify: _____

113 Surgery:

yes no

114 Date of surgery: __ __ __ __ - __ __ - __ __

115 splenectomy

yes no

116 other site(s)

yes no

117 Specify other site(s) _____

118 Was this line of therapy given for stem cell priming?

yes no

119 Best response to line of therapy

CR Complete response (CR) — no lymphadenopathy; no organomegaly; neutrophils > 1.5 x 10^9/L; platelets > 100 x 10^9/L; hemoglobin > 11g/dL; lymphocytes < 4 x 10^9/L; bone marrow < 30% lymphocytes; absence of constitutional symptoms

NPR Nodular partial response (NPR)-complete response with persistent lymphoid nodules in bone marrow

PR Partial response (PR)->=50% decrease in peripheral blood lymphocyte count from pretreatment value; >= 50% reduction in lymphadenopathy if present pretreatment; >=50% reduction in liver and spleen size if enlarged pretreatment; one or more of the following: neutrophils >= 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, hemoglobin > 11g/dL or 50% improvement over baseline

SD Stable disease (SD)-no change; not complete response, partial response, nor progressive disease

Prog Progressive disease (Prog) — one or more of the following: = 50% increase in the sum of the products of = 2 lymph nodes (= 1 node must be = 2 cm) or new nodes; = 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly; = 50% increase in absolute lymphocyte count to = 5 x 10^9/L; transformation to a more aggressive histology

NA Not assessed (NA)

Unknown

120 Date response established: __ __ __ __ - __ __ - __ __

121 Did disease relapse/progress following this line of therapy?

yes no

122 Date of relapse/progression: __ __ __ __ - __ __ - __ __

Most Recent Disease Assessment Prior to the Start of the Preparative Regimen

Questions: 123 - 137

123 What was the Rai stage immediately prior to the preparative regimen?

Complete Remission

low risk - stage 0 - lymphocytosis (>15,000 x 10^9/L) in blood or bone marrow only

intermediate risk - stage I- lymphocytosis plus enlarged lymph nodes (lymphadenopathy)

intermediate risk - stage II - lymphocytosis plus enlarged liver or spleen with or without lymphadenopathy

high risk - stage III - lymphocytosis plus anemia (Hgb < 11 g/dL) with or without enlarged liver, spleen, or lymph nodes

high risk - IV - lymphoctyosis plus thrombocytopenia (platelet count < 100 x 10^9/L) with or without anemia or enlarged liver, spleen, or lymph nodes

Unknown

124 What was the Binet stage immediately prior to the preparative regimen? (Five lymphoid bearing areas are possible: axillary, cervical, inguino-femoral, liver, and spleen.)

Complete Remission

stage A - two or fewer lymphoid bearing areas enlarged, without anemia or thrombocytopenia

stage B - three or more lymphoid bearing areas enlarged, without anemia or thrombocytopenia

stage C - presence of anemia (Hgb < 10.0 g/dL) or thrombocytopenia (platelet count < 100 x 10^9/L)

Unknown

126 Did the recipient have known nodal involvement immediately prior to the preparative regimen?

yes no

126 Specify the total number of nodes involved:

○ one node ○ two or more nodes

127 Specify the size of the largest nodal mass: _____ cm X _____ cm

128 Did the recipient have known extramedullary and/or extranodal involvement immediately prior to the preparative regimen?

○ yes ○ no

Specify site(s) of involvement:

129 Central nervous system (CNS)

○ yes ○ no

130 Liver

○ yes ○ no

131 Lung

○ yes ○ no

132 Spleen

○ yes ○ no

133 Specify centimeters below costal margin: _____

134 Other site:

○ yes ○ no

135 Specify site: _____

136 Was a direct or indirect Coomb's test performed?

○ yes ○ no

137 Specify the Coomb's test results:

○ negative (normal, no agglutination)

○ postive (abnormal, antibodies present)

Laboratory Studies Prior to the Start of the Preparative Regimen

Questions: 138 - 161

138 Lymphocytes in bone marrow:

○ Known ○ Not known

139 _____ %

140 LDH:

○ Known ○ Not known

141 _____ ○ U/L ○ µkat/L

142 Upper limit of normal for LDH: _____

143 β^2 microglobulin:

○ Known ○ Not known

144 _____ ○ µg/dL ○ mg/L ○ nmol/L

145 Upper limit of normal for β^2: _____

146 IgG:

○ Known ○ Not known

147 _____ ○ mg/dL ○ g/dL ○ g/L

Form 2013 R2.0: Chronic Lymphocytic Leukemia(CLL) Pre-HSCT Data

Center: CRID:

148 Lower limit of normal for IgG: _____

149 IgA: ○ Known ○ Not known

150 _____ ○ mg/dL ○ g/dL ○ g/L

151 Lower limit of normal for IgA: _____

152 IgM:

○ Known ○ Not known

153 _____ ○ mg/dL ○ g/dL ○ g/L

154 Lower limit of normal for IgM: _____

155 Was molecular testing/immunophenotyping performed at the time of disease assessment prior to the preparative regimen?

○ yes ○ no

Specify the testing method(s) used:

156 Immunophenotyping (4 color flow cytometry)

○ yes ○ no

157 Specify the date immunophenotyping was performed: __ __ __ __-__ __-__ __

158 Was disease detected?

○ yes ○ no

159 Heavy chain gene rearrangement (ASO-PCR)

○ yes ○ no

160 Specify the date the heavy chain gene rearrangement testing was performed: __ __ __ __-__ __-__ __

161 Was disease detected?

○ yes ○ no

Disease Status at the Last Assessment Prior to the Preparative Regimen Questions: 162 - 164

162 What was the disease status at the last evaluation prior to the preparative regimen?

○ complete response (CR) - no lymphadenopathy; no organomegaly; neutrophils >1.5 x 10^9/L; platelets > 100 x 10^9/L; hemoglobin > 11g/dL; lymphocytes < 4 x 10^9/L; bone marrow < 30% lymphocytes; absense of constitutional symptoms

○ nodular partial response (NPR) - complete response with persistent lymphoid nodules in bone marrow

○ partial response (PR)- ≥50% decrease in peripheral blood lymphocyte count from pretreatment value; ≥50% reduction in lymphadenopathy if present pretreatment; ≥50% reduction in liver and spleen size if enlarged pretreatment; one or more of the following: neutrophils ≥1.5 x 10^9/L or 50% improvement over baseline, platelets > 100 x 10^9/L or 50 % improvement over baseline, hemoglobin > 11.0 g/dL or 50% improvement over baseline

○ stable disease (SD) - no change; not complete response; partial reponse; nor progressive disease

○ progressive disease (Prog) - one or more of the following: ≥50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 node must be ≥ 2 cm)or new nodes; ≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly; ≥ 50% increase in absolute lymphoctye count to ≥ 5 x 10^9/L; transfromation to a more aggressive histology

○ untreated - no chemotherapy given in the 6 months prior to HSCT

○ Not assessed

163 Date of most recent assessment for disease status prior to the preparative regimen: __ __ __ __-__ __-__ __

First Name: _____ Last Name: _____

Phone number: _____ Fax number: _____

164 E-mail address: _____

APPENDIX 3:

Disease status assessment: Pre HCT: All lymphoma excluding CLL. CIBMTR form 2018, Revision 3, 17 pages.

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

2018: Hodgkin and Non-Hodgkin Lymphoma (LYM) Pre-HCT Data

Registry Use Only
Sequence Number:

Date Received:

Key Fields	

CIBMTR Center Number: ___ ___ ___ ___ ___

CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Date of HCT for which this form is being completed: __ __ __ __ / __ __ / __ __
YYYY MM DD

HCT type (check all that apply) ☐ Autologous ☐ Allogeneic, unrelated ☐ Allogeneic, related

Product type (check all that apply) ☐ Bone marrow
☐ PBSC
☐ Single cord blood unit
☐ Multiple cord blood units
☐ Other product. Specify _____

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Subsequent Transplant	

If this is a report of a second or subsequent transplant for the same disease subtype and this baseline disease insert has not been completed for the previous transplant (e.g. patient was on TED track for the prior HCT, prior HCT was autologous with no consent), begin the form at question one.
If this is a report of a second or subsequent transplant for a different disease, begin the form at question one.

Is this the report of a second or subsequent transplant for the same disease?

☐ yes → Is the second or subsequent transplant for relapse or progression of the same disease?
- ☐ yes - ***Go to question 193***
- ☐ no - ***Go to question 281***

☐ no

Disease Assessment at Diagnosis	Questions: 1-59

1. What was the date of diagnosis? ___ ___ ___ / ___ ___ / ___ ___ (YYYY / MM / DD)

2. What was the lymphoma histology at diagnosis?
   - ☐ 01 Nodular lymphocyte predominant Hodgkin lymphoma
   - ☐ 02 Lymphocyte-rich
   - ☐ 03 Nodular sclerosis
   - ☐ 04 Mixed cellularity
   - ☐ 05 Lymphocyte depleted
   - ☐ 06 Hodgkin lymphoma, not otherwise specified
   - ☐ 07 Splenic marginal zone B-cell lymphoma
   - ☐ 08 Extranodal marginal zone B-cell lymphoma of mucosal associated lymphoid tissue type (MALT)
   - ☐ 09 Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
   - ☐ 10 Follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)
   - ☐ 11 Follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma)
   - ☐ 12 Follicular, predominantly large cell (Grade IIIA follicle center lymphoma)
   - ☐ 13 Follicular, predominantly large cell (Grade IIIB follicle center lymphoma)
   - ☐ 14 Follicular (grade unknown)
   - ☐ 15 Mantle cell lymphoma
   - ☐ 16 Intravascular large B-cell lymphoma
   - ☐ 17 Primary mediastinal (thymic) large B-cell lymphoma
   - ☐ 18 Primary effusion lymphoma
   - ☐ 19 Diffuse, large B-cell lymphoma — NOS
   - ☐ 20 Primary diffuse, large B-cell lymphoma of the CNS
   - ☐ 21 Burkitt lymphoma
   - ☐ 22 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
   - ☐ 23 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin Lymphoma
   - ☐ 24 T-cell/histiocytic rich large B-cell lymphoma
   - ☐ 25 Other B-cell lymphoma - ***Go to question 3***
   - ☐ 26 Extranodal NK/T-cell lymphoma, nasal type
   - ☐ 27 Enteropathy-type T-cell lymphoma
   - ☐ 28 Hepatosplenic T-cell lymphoma
   - ☐ 29 Subcutaneous panniculitis-like T-cell lymphoma
   - ☐ 30 Mycosis fungoides
   - ☐ 31 Sezary syndrome

- ☐ 32 Primary cutaneous CD30+ T-cell lymphoproliferative disorders [Primary cutaneous anaplastic large-cell lymphoma (C-ALCL), lymphoid papulosis]
- ☐ 33 Peripheral T-cell lymphoma (PTCL), NOS
- ☐ 34 Angioimmunoblastic T-cell lymphoma
- ☐ 35 Anaplastic large-cell lymphoma (ALCL), ALK positive
- ☐ 36 Anaplastic large-cell lymphoma (ALCL), ALK negative
- ☐ 37 T-cell large granular lymphocytic leukemia
- ☐ 38 Aggressive NK-cell leukemia
- ☐ 39 Adult T-cell lymphoma/leukemia (HTLV1 associated)
- ☐ 40 Other T-cell/NK-cell lymphoma - ***Go to question 3***

3. Specify other lymphoma: _____
(specify line must be completed for codes 25 or 40)

4. Were immunohistochemical stains obtained? (prior to any transformation)

- ☐ yes →
- ☐ no
- ☐ Unknown

5.	ALK-1 (Anaplastic Lymphoma Kinase 1)	☐ Positive	☐ Negative	☐ Not Done
6.	BCL-2	☐ Positive	☐ Negative	☐ Not Done
7.	BCL-6	☐ Positive	☐ Negative	☐ Not Done
8.	CD5	☐ Positive	☐ Negative	☐ Not Done
9.	CD10	☐ Positive	☐ Negative	☐ Not Done
10.	CD20	☐ Positive	☐ Negative	☐ Not Done
11.	CD23	☐ Positive	☐ Negative	☐ Not Done
12.	CD30	☐ Positive	☐ Negative	☐ Not Done
13.	CD43	☐ Positive	☐ Negative	☐ Not Done
14.	CD103	☐ Positive	☐ Negative	☐ Not Done
15.	Cyclin D1	☐ Positive	☐ Negative	☐ Not Done
16.	Ki-67	☐ Positive	☐ Negative	☐ Not Done
17.	MUM1	☐ Positive	☐ Negative	☐ Not Done
18.	Pax-5	☐ Positive	☐ Negative	☐ Not Done

19. Was flow cytometry (immunophenotyping) performed? (prior to any transformation)

- ☐ yes →
- ☐ no
- ☐ Unknown

20.	CD1	☐ Positive	☐ Negative	☐ Not Done
21.	CD2	☐ Positive	☐ Negative	☐ Not Done
22.	CD3	☐ Positive	☐ Negative	☐ Not Done
23.	CD4	☐ Positive	☐ Negative	☐ Not Done
24.	CD5	☐ Positive	☐ Negative	☐ Not Done
25.	CD7	☐ Positive	☐ Negative	☐ Not Done
26.	CD8	☐ Positive	☐ Negative	☐ Not Done
27.	CD10	☐ Positive	☐ Negative	☐ Not Done
28.	CD19	☐ Positive	☐ Negative	☐ Not Done
29.	CD20	☐ Positive	☐ Negative	☐ Not Done
30.	CD22	☐ Positive	☐ Negative	☐ Not Done
31.	CD23	☐ Positive	☐ Negative	☐ Not Done
32.	CD103	☐ Positive	☐ Negative	☐ Not Done

33.	Cytoplasmic CD3	☐ Positive	☐ Negative	☐ Not Done
34.	Cytoplasmic kappa	☐ Positive	☐ Negative	☐ Not Done
35.	Cytoplasmic lambda	☐ Positive	☐ Negative	☐ Not Done
36.	Kappa	☐ Positive	☐ Negative	☐ Not Done
37.	Lambda	☐ Positive	☐ Negative	☐ Not Done
38.	TCR α-β	☐ Positive	☐ Negative	☐ Not Done
39.	TCR γ-δ	☐ Positive	☐ Negative	☐ Not Done

40. Were cytogenetics tested (conventional or FISH)?

☐ yes → Specify if any of the following cytogenetic abnormalities were identified at diagnosis:

☐ no

☐ Unknown

41.	t(1;14)	☐ yes	☐ no
42.	t(2;5)	☐ yes	☐ no
43.	t(2;8)	☐ yes	☐ no
44.	t(8;14)	☐ yes	☐ no
45.	t(8;22)	☐ yes	☐ no
46.	t(11;14)	☐ yes	☐ no
47.	t(11;18)	☐ yes	☐ no
48.	t(14;18)	☐ yes	☐ no
49.	i(7q)(q10)	☐ yes	☐ no
50.	Was documentation submitted to the CIBMTR? (e.g. cytogenetic or FISH report)	☐ yes	☐ no

51. Were tests for molecular markers performed (e.g. PCR)?

☐ yes →

☐ no

☐ Unknown

52.	BCL-1/Cyclin D1, t(11;14)	☐ Positive	☐ Negative	☐ Not Done
53.	BCL-2, t(14;18)	☐ Positive	☐ Negative	☐ Not Done
54.	BCL-6	☐ Positive	☐ Negative	☐ Not Done
55.	B-cell, Immunoglobulin Heavy (IgH) chain rearrangement	☐ Positive	☐ Negative	☐ Not Done
56.	T-cell receptor (TCR) gene rearrangement	☐ Positive	☐ Negative	☐ Not Done

57. Other molecular marker

☐ Positive →

☐ Negative →

☐ Not Done

58. Specify other molecular marker: _____

Copy questions 57 - 58 if needed for Other Molecular Marker

59. Was documentation submitted to the CIBMTR? ☐ yes ☐ no

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Laboratory Studies at Diagnosis	Questions: 60-71

60. WBC
- ☐ Known → 61. ___ ___ ___ ___ ___ ___ • ___ ☐ x 10^9/L (x 10^3/mm^3) ☐ x 10^6/L
- ☐ Unknown

62. Hemoglobin
- ☐ Known → 63. ___ ___ ___ ___ • ___ ___ ☐ g/dL ☐ g/L ☐ mmol/L
- ☐ Unknown

64. LDH
- ☐ Known → 65. ___ ___ ___ ___ ___ • ___ ___ ☐ U/L ☐ µkat/L
  66. Upper limit of normal for LDH: ___ ___ ___ ___ ___ • ___ ___ ☐ U/L ☐ µkat/L
- ☐ Unknown

67. Serum β2 microglobulin
- ☐ Known → 68. ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L
  69. Upper limit of normal for serum ß2 microglobulin: ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L
- ☐ Unknown

70. Was a gene expression profile performed?
- ☐ yes → 71. Were results considered high risk lymphoma? ☐ yes ☐ no
- ☐ no

Assessment of Nodal and Organ Involvement at Diagnosis	Questions: 72-96

72. Was a PET (or PET/CT) scan performed?
- ☐ yes → 73. Was the PET (or PET/CT) scan positive for lymphoma involvement at any disease site? ☐ yes ☐ no
- ☐ no

74. Did the recipient have known nodal involvement?
- ☐ yes → 75. Specify the total number of nodal regions involved ☐ one nodal region ☐ two or more nodal regions ☐ Unknown
  76. Specify the size of the largest nodal mass: ___ ___ cm x ___ ___ cm
- ☐ no

77. Was there any known extranodal or splenic involvement?
- ☐ yes →
  Specify site(s) of involvement:
  78. Bone ☐ yes ☐ no
  79. Bone marrow ☐ yes ☐ no
  80. Brain ☐ yes ☐ no
  81. Cerebrospinal fluid (CSF) ☐ yes ☐ no
  82. Epidural space ☐ yes ☐ no
  83. Gastrointestinal (GI) tract ☐ yes ☐ no
- ☐ no
- ☐ Unknown

84. Kidney ☐ yes ☐ no
85. Liver ☐ yes ☐ no
86. Lung ☐ yes ☐ no
87. Pleura ☐ yes ☐ no
88. Skin ☐ yes ☐ no
89. Spleen ☐ yes ☐ no
90. Other site
☐ yes → 91. Specify other site: _____
☐ no

92. Stage of organ involvement
☐ I – Involvement of a single lymph node region or of a single extralymphatic organ or site
☐ II – Involvement of two or more lymph node regions on same side of diaphragm or localized involvement of extralymphatic organ or site and one or more lymph node regions on same side of diaphragm.
☐ III – Involvement of lymph node regions on both sides of diaphragm, which may also be accompanied by localized involvement of extralymphatic organ or site, or the spleen, or both
☐ IV – Diffuse or disseminated involvement of one or more extralymphatic organs in tissues with or without associated lymph node enlargement
☐ Unknown

93. Were systemic symptoms (B symptoms) present? (unexplained fever > 38° C; night sweats; unexplained weight loss > 10% body weight in six months before diagnosis)
☐ yes ☐ no ☐ Unknown

94. What scale was used to determine the recipient's functional status?
☐ Karnofsky (recipient age ≥ 16 years) →

95. Karnofsky Scale (recipient age ≥ 16 years):
☐ 100 Normal; no complaints; no evidence of disease
☐ 90 Able to carry on normal activity
☐ 80 Normal activity with effort
☐ 70 Cares for self; unable to carry on normal activity or to do active work
☐ 60 Requires occasional assistance but is able to care for most needs
☐ 50 Requires considerable assistance and frequent medical care
☐ 40 Disabled; requires special care and assistance
☐ 30 Severely disabled; hospitalization indicated, although death not imminent
☐ 20 Very sick; hospitalization necessary
☐ 10 Moribund; fatal process progressing rapidly.

☐ Lansky (recipient age < 16 years) →

96. Lansky Scale (recipient age < 16 years):
☐ 100 Fully active
☐ 90 Minor restriction in physically strenuous play
☐ 80 Restricted in strenuous play, tires more easily, otherwise active
☐ 70 Both greater restrictions of, and less time spent in, active play
☐ 60 Ambulatory up to 50% of time, limited active play with assistance/supervision
☐ 50 Considerable assistance required for any active play; fully able to engage in quiet play

- ☐ 40 Able to initiate quiet activities
- ☐ 30 Needs considerable assistance for quiet activity
- ☐ 20 Limited to very passive activity initiated by others (e.g., TV)
- ☐ 10 Completely disabled, not even passive play

Disease Assessment at Transformation	Questions: 97-158

97. Is the non-Hodgkin lymphoma histology reported at diagnosis (question 2) a transformation from CLL?

- ☐ yes - Also complete Form 2013 - CLL - ***Go to question 193***
- ☐ no →

98. Was histologic transformation (not from CLL) detected at the same time or at any time after the lymphoma diagnosis (question 2)?

- ☐ yes - ***Go to question 99***
- ☐ no - ***Go to question 193***

99. What was the lymphoma histology at transformation?

- ☐ 01 Nodular lymphocyte predominant Hodgkin lymphoma
- ☐ 02 Lymphocyte-rich
- ☐ 03 Nodular sclerosis
- ☐ 04 Mixed cellularity
- ☐ 05 Lymphocyte depleted
- ☐ 06 Hodgkin lymphoma, not otherwise specified
- ☐ 07 Splenic marginal zone B-cell lymphoma
- ☐ 08 Extranodal marginal zone B-cell lymphoma of mucosal associated lymphoid tissue type (MALT)
- ☐ 09 Nodal marginal zone B-cell lymphoma (± monocytoid B-cells)
- ☐ 10 Follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)
- ☐ 11 Follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma)
- ☐ 12 Follicular, predominantly large cell (Grade IIIA follicle center lymphoma)
- ☐ 13 Follicular, predominantly large cell (Grade IIIB follicle center lymphoma)
- ☐ 14 Follicular (grade unknown)
- ☐ 15 Mantle cell lymphoma
- ☐ 16 Intravascular large B-cell lymphoma
- ☐ 17 Primary mediastinal (thymic) large B-cell lymphoma
- ☐ 18 Primary effusion lymphoma
- ☐ 19 Diffuse, large B-cell lymphoma — NOS
- ☐ 20 Primary diffuse, large B-cell lymphoma of the CNS
- ☐ 21 Burkitt lymphoma
- ☐ 22 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- ☐ 23 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin Lymphoma
- ☐ 24 T-cell/histiocytic rich large B-cell lymphoma
- ☐ 25 Other B-cell lymphoma - ***Go to question 100***
- ☐ 26 Extranodal NK/T-cell lymphoma, nasal type
- ☐ 27 Enteropathy-type T-cell lymphoma
- ☐ 28 Hepatosplenic T-cell lymphoma

☐ 29 Subcutaneous panniculitis-like T-cell lymphoma
☐ 30 Mycosis fungoides
☐ 31 Sezary syndrome
☐ 32 Primary cutaneous CD30+ T-cell lymphoproliferative disorders [Primary cutaneous anaplastic large-cell lymphoma (C-ALCL), lymphoid papulosis]
☐ 33 Peripheral T-cell lymphoma (PTCL), NOS
☐ 34 Angioimmunoblastic T-cell lymphoma
☐ 35 Anaplastic large-cell lymphoma (ALCL), ALK positive
☐ 36 Anaplastic large-cell lymphoma (ALCL), ALK negative
☐ 37 T-cell large granular lymphocytic leukemia
☐ 38 Aggressive NK-cell leukemia
☐ 39 Adult T-cell lymphoma/leukemia (HTLV1 associated)
☐ 40 Other T-cell/NK-cell lymphoma - ***Go to question 100***

100. Specify: _____
(specify line must be completed for codes 25 or 40)

101. Was the date of transformation the same as the date of diagnosis?
☐ yes - ***Go to question 193***
☐ no → 102. Date of transformation: __ __ __ / __ __ / __ __
YYYY MM DD

103. Were immunohistochemical stains obtained? (at transformation)
☐ yes → 104. ALK-1 (Anaplastic Lymphoma Kinase 1) ☐ Positive ☐ Negative ☐ Not Done
☐ no
☐ Unknown

105.	BCL-2	☐ Positive	☐ Negative	☐ Not Done
106.	BCL-6	☐ Positive	☐ Negative	☐ Not Done
107.	CD5	☐ Positive	☐ Negative	☐ Not Done
108.	CD10	☐ Positive	☐ Negative	☐ Not Done
109.	CD20	☐ Positive	☐ Negative	☐ Not Done
110.	CD23	☐ Positive	☐ Negative	☐ Not Done
111.	CD30	☐ Positive	☐ Negative	☐ Not Done
112.	CD43	☐ Positive	☐ Negative	☐ Not Done
113.	CD103	☐ Positive	☐ Negative	☐ Not Done
114.	Cyclin D1	☐ Positive	☐ Negative	☐ Not Done
115.	Ki-67	☐ Positive	☐ Negative	☐ Not Done
116.	MUM1	☐ Positive	☐ Negative	☐ Not Done
117.	Pax-5	☐ Positive	☐ Negative	☐ Not Done

118. Was flow cytometry (immunophenotyping) performed? (at transformation)
☐ yes → 119. CD1
☐ no 120. CD2
☐ Unknown 121. CD3

119.	CD1	☐ Positive	☐ Negative	☐ Not Done
120.	CD2	☐ Positive	☐ Negative	☐ Not Done
121.	CD3	☐ Positive	☐ Negative	☐ Not Done
122.	CD4	☐ Positive	☐ Negative	☐ Not Done
123.	CD5	☐ Positive	☐ Negative	☐ Not Done
124.	CD7	☐ Positive	☐ Negative	☐ Not Done
125.	CD8	☐ Positive	☐ Negative	☐ Not Done

126. CD10	☐ Positive	☐ Negative	☐ Not Done
127. CD19	☐ Positive	☐ Negative	☐ Not Done
128. CD20	☐ Positive	☐ Negative	☐ Not Done
129. CD22	☐ Positive	☐ Negative	☐ Not Done
130. CD23	☐ Positive	☐ Negative	☐ Not Done
131. CD103	☐ Positive	☐ Negative	☐ Not Done
132. Cytoplasmic CD3	☐ Positive	☐ Negative	☐ Not Done
133. Cytoplasmic kappa	☐ Positive	☐ Negative	☐ Not Done
134. Cytoplasmic lambda	☐ Positive	☐ Negative	☐ Not Done
135. Kappa	☐ Positive	☐ Negative	☐ Not Done
136. Lambda	☐ Positive	☐ Negative	☐ Not Done
137. TCR α-β	☐ Positive	☐ Negative	☐ Not Done
138. TCR γ-δ	☐ Positive	☐ Negative	☐ Not Done

139. Were cytogenetics tested (conventional or FISH)?
- ☐ yes → Specify if any of the following cytogenetic abnormalities were identified at transformation:
- ☐ no
- ☐ Unknown

140. t(1;14)	☐ yes	☐ no
141. t(2;5)	☐ yes	☐ no
142. t(2;8)	☐ yes	☐ no
143. t(8;14)	☐ yes	☐ no
144. t(8;22)	☐ yes	☐ no
145. t(11;14)	☐ yes	☐ no
146. t(11;18)	☐ yes	☐ no
147. t(14;18)	☐ yes	☐ no
148. i(7q)(q10)	☐ yes	☐ no
149. Was documentation submitted to the CIBMTR? (e.g. cytogenetic of FISH report)	☐ yes	☐ no

150. Were tests for molecular markers performed (e.g. PCR)?
- ☐ yes → 151. BCL-1/Cyclin D1, t(11;14) ☐ Positive ☐ Negative ☐ Not Done
- ☐ no
- ☐ Unknown

152. BCL-2, t(14;18)	☐ Positive	☐ Negative	☐ Not Done
153. BCL-6	☐ Positive	☐ Negative	☐ Not Done
154. B-cell, Immunoglobulin Heavy (IgH) chain rearrangement	☐ Positive	☐ Negative	☐ Not Done
155. T-cell receptor (TCR) gene rearrangement	☐ Positive	☐ Negative	☐ Not Done

156. Other molecular marker
- ☐ Positive →
- ☐ Negative →
- ☐ Not Done

157. Specify other molecular marker: _____

Copy questions 156 - 157 if needed for Other Molecular Marker

158. Was documentation submitted to the CIBMTR? ☐ yes ☐ no

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Laboratory Studies at Transformation	Questions: 159-170

159. WBC
- ☐ Known → 160. ___ ___ ___ ___ ___ ___ • ___ ☐ x 10^9/L (x 10^3/mm^3) ☐ x 10^6/L
- ☐ Unknown

161. Hemoglobin
- ☐ Known → 162. ___ ___ ___ ___ • ___ ___ ☐ g/dL ☐ g/L ☐ mmol/L
- ☐ Unknown

163. LDH
- ☐ Known → 164. ___ ___ ___ ___ ___ • ___ ___ ☐ U/L ☐ µkat/L
  165. Upper limit of normal for LDH: ___ ___ ___ ___ ___ • ___ ___ ☐ U/L ☐ µkat/L
- ☐ Unknown

166. Serum β2 microglobulin
- ☐ Known → 167. ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L
  168. Upper limit of normal for serum ß2 microglobulin: ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L
- ☐ Unknown

169. Was a gene expression profile performed?
- ☐ yes → 170. Were results considered high risk lymphoma? ☐ yes ☐ no
- ☐ no

Assessment of Nodal and Organ Involvement at Transformation	Questions: 171-192

171. Was a PET (or PET/CT) scan performed?
- ☐ yes → 172. Was the PET (or PET/CT) scan positive for lymphoma involvement at any disease site? ☐ yes ☐ no
- ☐ no

173. Was there any known extranodal or splenic involvement?
- ☐ yes →

Specify site(s) of involvement:

174. Bone	☐ yes	☐ no
175. Bone marrow	☐ yes	☐ no
176. Brain	☐ yes	☐ no
177. Cerebrospinal fluid (CSF)	☐ yes	☐ no
178. Epidural space	☐ yes	☐ no
179. Gastrointestinal (GI) tract	☐ yes	☐ no
180. Kidney	☐ yes	☐ no
181. Liver	☐ yes	☐ no
182. Lung	☐ yes	☐ no
183. Pleura	☐ yes	☐ no
184. Skin	☐ yes	☐ no
185. Spleen	☐ yes	☐ no

- ☐ no
- ☐ Unknown

186. Other site
- ☐ yes → 187. Specify other site: _____
- ☐ no

188. Stage of organ involvement at transformation
- ☐ I – Involvement of a single lymph node region or of a single extralymphatic organ or site
- ☐ II – Involvement of two or more lymph node regions on same side of diaphragm or localized involvement of extralymphatic organ or site and one or more lymph node regions on same side of diaphragm.
- ☐ III – Involvement of lymph node regions on both sides of diaphragm, which may also be accompanied by localized involvement of extralymphatic organ or site, or the spleen, or both
- ☐ IV – Diffuse or disseminated involvement of one or more extralymphatic organs in tissues with or without associated lymph node enlargement
- ☐ Unknown

189. Were systemic symptoms (B symptoms) present? (unexplained fever > 38° C: or night sweats; unexplained weight loss > 10% body weight in six months before transformation)
☐ yes ☐ no ☐ Unknown

190. What scale was used to determine the recipient's functional status?
- ☐ Karnofsky (recipient age ≥ 16 years) →

191. Karnofsky Scale (recipient age ≥ 16 years):
- ☐ 100 Normal; no complaints; no evidence of disease
- ☐ 90 Able to carry on normal activity
- ☐ 80 Normal activity with effort
- ☐ 70 Cares for self; unable to carry on normal activity or to do active work
- ☐ 60 Requires occasional assistance but is able to care for most needs
- ☐ 50 Requires considerable assistance and frequent medical care
- ☐ 40 Disabled; requires special care and assistance
- ☐ 30 Severely disabled; hospitalization indicated, although death not imminent
- ☐ 20 Very sick; hospitalization necessary
- ☐ 10 Moribund; fatal process progressing rapidly.

- ☐ Lansky (recipient age < 16 years) →

192. Lansky Scale (recipient age < 16 years):
- ☐ 100 Fully active
- ☐ 90 Minor restriction in physically strenuous play
- ☐ 80 Restricted in strenuous play, tires more easily, otherwise active
- ☐ 70 Both greater restrictions of, and less time spent in, active play
- ☐ 60 Ambulatory up to 50% of time, limited active play with assistance/supervision
- ☐ 50 Considerable assistance required for any active play; fully able to engage in quiet play
- ☐ 40 Able to initiate quiet activities
- ☐ 30 Needs considerable assistance for quiet activity
- ☐ 20 Limited to very passive activity initiated by others (e.g., TV)
- ☐ 10 Completely disabled, not even passive play

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Pre-HCT Therapy	Questions: 193-280

193. Was therapy given?
- ☐ yes →
- ☐ no

194. Systemic therapy
- ☐ yes → 195. Date therapy started
  - ☐ Known → 196. Date started: __ __ __ __/__ __/__ __ (YYYY MM DD)
  - ☐ Unknown
- ☐ no

197. Date therapy stopped
- ☐ Known → 198. Date stopped: __ __ __ __/__ __/__ __ (YYYY MM DD)
- ☐ Unknown

199. Number of cycles
- ☐ Known → 200. Number of cycles: ___ ___
- ☐ Unknown

201. ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	☐ yes	☐ no
202. BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone)	☐ yes	☐ no
203. CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)	☐ yes	☐ no
204. R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone)	☐ yes	☐ no
205. ESHAP (Etoposide, Methylprednisolone, Cytarabine, Cisplatin)	☐ yes	☐ no
206. DHAP (Dexamethasone, Cytarabine, Cisplatin)	☐ yes	☐ no
207. ICE (Ifosfamide, Mesna, Carboplatin, Etoposide)	☐ yes	☐ no
208 R-ICE (Rituximab, Ifosfamide, Mesna, Carboplatin, Etoposide)	☐ yes	☐ no
209. MOPP (Mechlorethamine, Vincristine, Procarbazine, Prednisone)	☐ yes	☐ no
210. Stanford V (Doxorubicin, Vinblastine, Mechlorethamine, Vincristine, Bleomycin, Etoposide, Prednisone)	☐ yes	☐ no
211. Alemtuzumab (Campath)	☐ yes	☐ no
212. Bendamustine	☐ yes	☐ no
213. Bleomycin (BLM, Blenoxane)	☐ yes	☐ no
214. Bortezomib (Velcade)	☐ yes	☐ no
215. Brentuximab	☐ yes	☐ no
216. Carmustine (BCNU, Gliadel)	☐ yes	☐ no
217. Carboplatin	☐ yes	☐ no
218. Cisplatin (Platinol, CDDP)	☐ yes	☐ no
219. Cladribine (2-CdA, Leustatin)	☐ yes	☐ no
220. Corticosteroids	☐ yes	☐ no
221. Cyclophosphamide (Cytoxan)	☐ yes	☐ no
222. Cytarabine (Ara-C)	☐ yes	☐ no
223. Dacarbazine (DTIC)	☐ yes	☐ no

224.	Doxorubicin (Adriamycin)	☐ yes	☐ no
225.	Doxorubicin liposomal (Doxil)	☐ yes	☐ no
226.	Etoposide (VP-16, VePesid)	☐ yes	☐ no
227.	Everolimus (RAD-001)	☐ yes	☐ no
228.	Fludarabine (Fludara)	☐ yes	☐ no
229.	Gemcitabine (Gemzar)	☐ yes	☐ no
230.	Ibritumomab tiuxetan (Zevalin)	☐ yes	☐ no
231.	Ifosfamide (Ifex)	☐ yes	☐ no
232.	Interferon	☐ yes	☐ no
233.	Lenalidomide (Revlimid)	☐ yes	☐ no
234.	Methotrexate (MTX) (Amethopterin)	☐ yes	☐ no
235.	Mitoxantrone (Novantrone)	☐ yes	☐ no
236.	Nitrogen mustard (mustine)	☐ yes	☐ no
237.	Ofatumumab (Arzerra, HuMAX-CD20)	☐ yes	☐ no
238.	Pentostatin (Nipent)	☐ yes	☐ no
239.	Photopheresis	☐ yes	☐ no
240.	Pralatrexate	☐ yes	☐ no
241.	Procarbazine (Matulane)	☐ yes	☐ no
242.	Rituximab (Rituxan, MabThera)	☐ yes	☐ no
243.	Romidepsin	☐ yes	☐ no
244.	Targretin	☐ yes	☐ no
245.	Temsirolimus (Torisel)	☐ yes	☐ no
246.	Tositumomab (Bexxar)	☐ yes	☐ no
247.	Vinblastine (Velban, VLB)	☐ yes	☐ no
248.	Vincristine (VCR, Oncovin)	☐ yes	☐ no
249.	Vinorelbine (Navelbine)	☐ yes	☐ no
250.	Vorinostat	☐ yes	☐ no

251. Other systemic therapy

☐ yes → 252. Specify other systemic therapy:

☐ no

_____

253. Was this line of therapy given for stem cell mobilization (priming)?

☐ yes ☐ no

254. Radiation therapy

☐ yes → 255. Date therapy started

☐ Known → 256. Date started: __ __ __ __/__ __/__ __ (YYYY MM DD)

☐ Unknown

257. Date therapy stopped

☐ Known → 258. Date stopped: __ __ __ __/__ __/__ __ (YYYY MM DD)

☐ Unknown

259. What was the extent of the radiation field?
- ☐ Extended
- ☐ Involved field radiotherapy (IFRT)
- ☐ Involved node
- ☐ Unknown

Specify site(s) of radiation therapy:

260. Abdominopelvic ☐ yes ☐ no
261. Cervical spine ☐ yes ☐ no
262. Inguinal ☐ yes ☐ no
263. Mediastinum/chest ☐ yes ☐ no
264. Other site
- ☐ yes → 265. Specify other site: _____
- ☐ no

266. Dose per fraction: ___ ___ ___ ☐ Gy ☐ cGy

267. Total number of fractions: ___ ___

268. Total dose: ___ ___ ___ ☐ Gy ☐ cGy

269. Specify technique
- ☐ 2 - Dimensional
- ☐ 3D - conformal
- ☐ Electron beam
- ☐ Intensity - modulate radiation therapy (IMRT)
- ☐ Proton
- ☐ Unknown
- ☐ Other → 270. Specify other technique: _____

271. Surgery
- ☐ yes → 272. Date of surgery
  - ☐ Known → 273. Date of surgery: __ __ __ __ / __ __ / __ __ (YYYY / MM / DD)
  - ☐ Unknown
- ☐ no

274. Splenectomy ☐ yes ☐ no

275. Other site(s)
- ☐ yes → 276. Specify other site(s): _____
- ☐ no

277. Best response to line of therapy
- ☐ Complete remission (CR) - complete disappearance of all known disease. For typically FDG-avid lymphoma, a post-treatment residual mass of any size is permitted as long as it is PET negative. For variably FDG-avid lymphomas, all lymph nodes and nodal masses must have regressed via CT to <1.5 cm (for nodes >1.5 cm before therapy) or <1 cm (for nodes 1.1 to 1.5 cm before therapy) - ***Go to question 278***

☐ Partial remission (PR) - ≥50% reductions in greatest diameter of up to six largest dominant nodes or nodal masses and no new sites. For typically FDG-avid lymphomas, post-treatment PET should be positive in at least one site. For variably PET-avid lymphoma, use CT criteria - ***Go to question 278***

☐ Stable disease (SD) - failure to obtain CR, PR, or PD - ***Go to question 278***

☐ Progressive disease (PD) - increase by >50% of previously involved sites from nadir or any new lesion - ***Go to question 278***

☐ Unknown - ***Go to question 279***

☐ Not assessed - ***Go to question 279***

278. Date assessed: __ ___ ___/___/___ (YYYY MM DD)

279. Did disease relapse/progress following this line of therapy?

☐ yes → 280. Date of relapse/progression: __ __ __ __/__ __/__ __ (YYYY MM DD)

☐ no

Copy questions 194 - 280 if needed for Line of Therapy

Disease Assessment at Last Evaluation Prior to the Start of the Preparative Regimen

Questions: 281-323

281. Serum β2 microglobulin

☐ Known →

☐ Unknown

282. ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L

283. Upper limit of normal for serum ß2 microglobulin: ___ ___ ___ • ___ ___ ___ ☐ µg/dL ☐ mg/L ☐ nmol/L

284. Was a PET (or PET/CT) scan performed after the most recent line of therapy or at the time of pre-HCT evaluation?

☐ yes →

☐ no

285. Was the PET (or PET/CT) scan positive for lymphoma involvement at any disease site? ☐ yes ☐ no

286. Were cytogenetics tested (conventional or FISH)?

☐ yes →

☐ no

☐ Unknown

Specify if any of the following cytogenetic abnormalities were identified at the last evaluation prior to start of the preparative regimen:

287. t(1;14)	☐ yes	☐ no
288. t(2;5)	☐ yes	☐ no
289. t(2;8)	☐ yes	☐ no
290. t(8;14)	☐ yes	☐ no
291. t(8;22)	☐ yes	☐ no
292. t(11;14)	☐ yes	☐ no
293. t(11;18)	☐ yes	☐ no
294. t(14;18)	☐ yes	☐ no
295. i(7q)(q10)	☐ yes	☐ no

CIBMTR Center Number: ___ ___ ___ ___ ___ CIBMTR Recipient ID: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

296. Were tests for molecular markers performed (e.g. PCR)?

☐ yes → ☐ no ☐ Unknown

297. BCL-1/Cyclin D1, t(11;14)	☐ Positive	☐ Negative	☐ Not Done
298. BCL-2, t(14;18)	☐ Positive	☐ Negative	☐ Not Done
299. BCL-6	☐ Positive	☐ Negative	☐ Not Done
300. B-cell, Immunoglobulin Heavy (IgH) chain rearrangement	☐ Positive	☐ Negative	☐ Not Done
301. T-cell receptor (TCR) gene rearrangement	☐ Positive	☐ Negative	☐ Not Done

302. Other molecular marker

☐ Positive → ☐ Negative → ☐ Not Done

303. Specify other molecular marker: _____

Copy questions 302 - 303 if needed for Other Molecular Marker

304. Did the recipient have known nodal involvement?

☐ yes → ☐ no

305. Specify the total number of nodal regions involved

☐ one nodal region ☐ two or more nodal regions ☐ Unknown

306. Specify the size of the largest nodal mass: ___ ___ cm x ___ ___ cm

307. Was there any known extranodal or splenic involvement?

☐ yes → ☐ no ☐ Unknown

Specify site(s) of extranodal involvement:

308. Bone	☐ yes	☐ no
309. Bone marrow	☐ yes	☐ no
310. Brain	☐ yes	☐ no
311. Cerebrospinal fluid (CSF)	☐ yes	☐ no
312. Epidural space	☐ yes	☐ no
313. Gastrointestinal (GI) tract	☐ yes	☐ no
314. Kidney	☐ yes	☐ no
315. Liver	☐ yes	☐ no
316. Lung	☐ yes	☐ no
317. Pleura	☐ yes	☐ no
318. Skin	☐ yes	☐ no
319. Spleen	☐ yes	☐ no

320. Other site

☐ yes → 321. Specify other site: _____

☐ no

322. What was the disease status?

- ☐ Disease untreated
- ☐ PIF res - Primary induction failure – resistant: NEVER in COMPLETE remission but with stable or progressive disease on treatment.
- ☐ PIF sen/PR1 - Primary induction failure – sensitive: NEVER in COMPLETE remission but with partial remission on treatment.
- ☐ PIF unk - Primary induction failure – sensitivity unknown
- ☐ CR1 - 1st complete remission: no bone marrow or extramedullary relapse prior to transplant
- ☐ CR2 - 2nd complete remission
- ☐ CR3+ - 3rd or subsequent complete remission
- ☐ REL1 unt - 1st relapse – untreated; includes either bone marrow or extramedullary relapse
- ☐ REL1 res - 1st relapse – resistant: stable or progressive disease with treatment
- ☐ REL1 sen - 1st relapse – sensitive: partial remission (if complete remission was achieved, classify as CR2)
- ☐ REL1 unk - 1st relapse – sensitivity unknown
- ☐ REL2 unt - 2nd relapse – untreated: includes either bone marrow or extramedullary relapse
- ☐ REL2 res - 2nd relapse – resistant: stable or progressive disease with treatment
- ☐ REL2 sen - 2nd relapse – sensitive: partial remission (if complete remission achieved, classify as CR3+)
- ☐ REL2 unk - 2nd relapse – sensitivity unknown
- ☐ REL3+ unt - 3rd or subsequent relapse – untreated; includes wither bone marrow or extramedullary relapse
- ☐ REL3+ res - 3rd or subsequent relapse – resistant: stable or progressive disease with treatment
- ☐ REL3+ sen - 3rd or subsequent relapse – sensitive: partial remission (if complete remission achieved, classify as CR3+)
- ☐ REL3+ unk - 3rd relapse or greater – sensitivity unknown

323. Date assessed: __ ____ __/__ __/__ __
YYYY MM DD

First Name: _____

Last Name: _____

E-mail address: _____

Date: __ ____ __/__ __/__ __
YYYY MM DD

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