PROTOCOL

A Pilot Study of Single-Agent Ibrutinib in Relapsed or Refractory Transformed Indolent B-Cell Non-Hodgkin Lymphoma

Trial of the Fred Hutchinson Cancer Center (FHCC) and the University of Washington (UW)

Supported in part by Janssen Scientific Affairs, LLC

Protocol Version Date: 07/18/2022
Previous Version Date: 04/23/2020

SPONSOR-INVESTIGATOR:

Ajay K Gopal, MD
Professor, UW
Member, FHCC
Fred Hutchinson Cancer Center
825 Eastlake Ave. E.
Seattle, WA 98109
Telephone: (206) 606-2037

Lead Sub-Investigator:
Solomon A Graf, MD
Acting Instructor, UW
Fred Hutchinson Cancer Center
825 Eastlake Ave. E.
Seattle, WA 98109
Telephone: (206) 277-6829

PROTOCOL ACTIVITY

Accrual Activated:

Protocol Revision Record:

Original Version:	Version 3, Dated 06/17/2014
Amendment #1:	Version 4, Dated 10/23/2015
Amendment #2:	Version 5, Dated 02/27/2019
Amendment #3:	Version 6.0, Dated 04/23/2020
Amendment #4:	Version 7.0, Dated 07/18/2022

SCHEMA

Registration

Ibrutinib 560 mg PO taken daily continuously on a 21-day cycle

Continued until intolerance, progressive disease, or the discretion of patient / clinician

Stop ibrutinib

Routine clinical follow-up for up to 5 years

TABLE OF CONTENTS:

1.0 OBJECTIVES

1.1 Primary objectives

1.1.1 Perform a preliminary assessment of the efficacy of single-agent ibrutinib, based on overall response rate, in subjects with relapsed or refractory transformed indolent B-cell non-Hodgkin lymphoma (R/R TIL).

1.2 Secondary objectives

1.2.1 To determine the tolerability of chronic ibrutinib therapy in this patient population.

1.2.2 To determine the disease control rate of this regimen.

1.2.3 Evaluate the complete response rate, overall survival, and progression-free survival to single-agent ibrutinib in this patient population.

1.2.4 Determine response rate relative to the underlying B-cell histology.

2.0 BACKGROUND

2.1 Transformed indolent B-cell non-Hodgkin lymphoma

Indolent B-cell non-Hodgkin lymphomas are comprised of several histologic subtypes, including follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), and marginal zone lymphoma (MZL). As a disease class, it is incurable short of allogeneic transplantation and shows a variable natural history. The course is typically slowly progressive at the outset and responsive to cytotoxic and immunologic therapies. Most patients eventually relapse with a disease phenotype that is increasingly resistant to treatment, with shorter intervals of response, over time [1, 2]. At a rate of approximately 3% per year, indolent B-cell non-Hodgkin lymphomas transform into more aggressive malignancies that share a clonal relationship with the original disease [3].

Transformed indolent B-cell non-Hodgkin lymphoma (TIL) is classically diagnosed with histologic demonstration of an increased proportion, compared with the original specimen, of large neoplastic cells. Though typically transformation is to DLBCL, other subtypes, including to unclassifiable B cell lymphoma (BCLU), lymphoblastic lymphoma, and acute lymphocytic leukemia (ALL) also occur [4]. Clinically, transformation is often reflected by a rapid rise in LDH, discordant localized nodal growth, or new B-type symptoms [4, 5]. Treatment paradigms for TIL are dictated by prior therapies and patient characteristics. High dose therapy (HDT) followed by consolidation with autologous stem cell transplantation (ASCT) appears to benefit select patients, with estimates of 5-year overall survival ranging from 37 – 65% [6-9], but this procedure is generally limited to a subset of patients with chemotherapy-sensitive disease and in good physical condition. Involved-field radiotherapy is beneficial in the subset of patients with early stage disease. For cases of relapsed or refractory TIL (R/R TIL), few therapeutic strategies of proven benefit are available. Radioimmunotherapy has activity in a subset of patients with R/R TIL and is approved for this indication; however its role is not yet clearly defined [10].

2.2 Ibrutinib in lymphoma

The B-cell antigen receptor (BCR) transmits proliferation signals during normal B cell development and its signaling activity has been shown to play a role in a variety of B cell malignancies, including follicular lymphoma [11, 12]. The Bruton's tyrosine kinase (BTK) is an essential component of the BCR pathway; its absence results in the arrest of normal peripheral B cell maturation and, consequently, low levels of circulating immunoglobulin [13, 14]. Ibrutinib (PCI-32765) is a small molecule that selectively and covalently inhibits BTK and has shown activity in several B cell malignancies, including previously treated mantle cell lymphoma and chronic lymphocytic leukemia, for which its administration is FDA approved [15]. Early data also suggest a benefit in FL, with an overall response rate in 6 of 11 patients treated on PCYC-04753, and in DLBCL [16]. Ibrutinib is not currently FDA approved for these diseases nor for RR/TIL. Ibrutinib has been shown to modulate B-cell chemotaxis and migration and promote apoptosis [17]. It is taken orally and, to date, has demonstrated a very good safety profile with reported adverse events mostly grade 1 and 2 in severity and typically self-limited in duration [15, 18].

2.3 Summary

R/R TIL presents a great therapeutic challenge and requires novel strategies. Ibrutinib has shown significant promise in treating several B-cell malignancies, and its oral administration and favorable toxicity profile make it an especially attractive candidate in advanced, previously treated disease. We hypothesize that its use will achieve significant and durable responses in a subset of patients with R/R TIL, thus adding to the limited selection of therapeutic options for this disease.

3.0 DRUG INFORMATION

3.1 General Information

Ibrutinib is an orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase, currently being co-developed by Pharmacyclics, Inc. and Janssen Scientific Affairs, LLC in B-cell malignancies.

3.2 Administration

Each capsule contains 140 mg of ibrutinib. The capsules are to be taken once daily around the same time each day. They should be swallowed whole and should not be opened, broken, or chewed. 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.

3.3 Toxicity

3.3.1 Adverse events

Refer to the current FDA-approved package insert or the *Physician Desk Reference*.

The most common adverse reactions (≥20%) in patients with MCL were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal

pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.

The most common adverse reactions (≥20%) in patients with CLL were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness.

3.3.2 Hemorrhage

Five percent of patients with MCL and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Overall, 4 bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 63% of patients with CLL treated at 420 mg daily. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding.Subjects in the current study will be monitored closely for hemorrhagic adverse events. Guidance on use of antiplatelet agents and anticoagulants is provided in Section 3.4.3.

3.3.3 Other Malignancies

Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with ibrutinib. Four percent of patients with MCL, had skin cancers and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.It is not clear whether or not these events are attributable to ibrutinib.

3.4 Drug Interactions

3.4.1 Metabolism

Ibrutinib is metabolized primarily by CYP3A. In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg). Avoid concomitant administration of ibrutinib with strong or moderate inhibitors of CYP3A. 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 ibrutinib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the ibrutinib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Administration of ibrutinib with strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and
St. John's Wort). Consider alternative agents with less CYP3A induction. Appendix C outlines some of the inhibitors and inducers of CYP3A.

3.4.3 Concomitant Use of Ibrutinib and Antiplatelet Agents and Anticoagulants
There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Also, patients with congenital bleeding diathesis have not been studied. Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 5.3). Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. It is possible that treatment with ibrutinib may increase the risk of bruising or bleeding, particularly in subjects receiving antiplatelet agents or anticoagulants. Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding and ibrutinib should be held in the event of major bleeding events defined as adverse event of special interest (Section 12).

3.5 Lymphocytosis

MCL:
Upon initiation of ibrutinib a temporary increase in lymphocyte counts (ie >= 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) occurred in 33% of patients in the MCL study. The onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks.
Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.
CLL:
Upon initiation of ibrutinib a temporary increase in lymphocyte counts (ie >= 50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) in 77% of patients in the CLL study. The onset of isolated lymphocytosis occurs during the first month of ibrutinib therapy and resolves by a median of 23 weeks (range 1 - 104+ weeks).

3.6 Supplier

Ibrutinib used under this study will be provided by Janssen Scientific Affairs and will be identical to the commercially marketed product.

3.7 Drug Accountability

The sponsor-investigator, or a responsible party designated by the sponsor-investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received for this study using the study specific Investigational Agent Accountability Record form or NCI Drug Accountability form.

Return of unused ibrutinib

Patients will be instructed to return unused ibrutinib to the SCCA pharmacy. All unused drug will be destroyed per Investigational Drug Services policy.

4.0 STAGING CRITERIA

4.1 When applicable, the Ann Arbor staging criteria (see Appendix A) will be used; staging should be the highest stage established, either at diagnosis or relapse of disease.

4.2 For patients from whom data are available, the international prognostic score at the time of diagnosis and enrollment will be documented as detailed below:

1. Age > 60 years
2. Ann Arbor stage III or IV
3. Elevated serum LDH
4. ECOG PS (see Appendix B) > 1
5. More than 1 extra-nodal side of disease

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Patients must have histologically confirmed transformed indolent B-cell non-Hodgkin lymphoma that is relapsed or refractory to at least one line of therapy.

5.1.2 Patients must have a CT (preferred) or MRI scan of the chest, abdomen, and pelvis within 28 days of enrollment.

5.1.3 Patients must have measurable disease defined as lesions greater than 1.5 cm that can be accurately measured in two dimensions by CT (preferred), or MRI.

5.1.4 Patients must have a PET scan within 56 days of enrollment.

5.1.5 Patients must have an ECOG performance status of 0 to 2 (See Appendix B).

5.1.6 Patients must be 18 years of age or older.

5.1.7 Hematology values must be within the following limits independent of growth factor or transfusion support:

5.1.7.1 Absolute neutrophil count (ANC) ≥ 1000/mm^3 or ≥ 750/ mm^3 in the setting of marrow involvement by disease.

5.1.7.2 Platelets ≥50,000/mm^3 or ≥ 30,000 /mm^3 in the setting of marrow involvement by disease or splenomegaly due to disease.

5.1.8 Biochemical values within the following limits:

5.1.8.1 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)

5.1.8.2 Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

5.1.8.3 Creatinine clearance (Clcr) > 25 mL/min

5.1.9 Patients must be anticipated to complete 2 cycles of therapy in the opinion of the treating physician.

5.1.10 Women of childbearing potential and men who are sexually active must affirm they are 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 or 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 the study drug.

5.1.11 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.

5.1.12 Sign (or their legally-acceptable representatives must sign) an informed consent document in accordance with institutional and federal guidelines indicating that they understand the investigational nature of and procedures required for the study, including biomarkers, and are willing to participate in and comply with the guidelines of the study.

5.2 Exclusion Criteria

5.2.1 Known history of human immunodeficiency virus (HIV) or active Hepatitis C Virus or active Hepatitis B Virus infection or any uncontrolled active systemic infection.

5.2.2 Major surgery or a wound that has not fully healed within 4 weeks of initiation of therapy.

5.2.3 Known central nervous system lymphoma.

5.2.4 History of stroke or intracranial hemorrhage within 6 months of screening.

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

5.2.6 Requires chronic treatment with strong CYP3A inhibitors.

5.2.7 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.

5.2.8 Vaccinated with live, attenuated vaccines within 4 weeks of initiation of therapy.

5.2.9 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.

5.2.10 Patients with other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, breast or cervical cancer *in situ*, or other cancer from which the patient has been disease-free for 5 years or greater, unless approved by the protocol Sponsor-Investigator / Lead-Sub-Investigator.

5.2.11 Patients that previously were treated with ibrutinib for > 7 days.

5.2.12 Previous chemotherapy, immunotherapy, biologically targeted therapy, other investigational agent, or radiation therapy within 3 weeks of initiation of ibrutinib therapy or radio-immunotherapy within 12 weeks of initiation of ibrutinib therapy.

5.2.13 Prior allogeneic transplant with GVHD requiring immunosuppressive therapy.

5.3 Restrictions: The following guidance should be considered during the perioperative period for subjects who require surgical intervention (including oral surgery) or an invasive procedure while receiving ibrutinib:

5.3.1 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.

5.3.2 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.

5.3.3 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.

6.0 REGISTRATION

6.1 Patients must be registered prior to the start of protocol therapy. A completed eligibility checklist with source documentation, a copy of the signed consent form and a signed HIPAA authorization are required for registration. All of the eligibility requirements according to Section 5.0 must have been met.

7.0 TREATMENT PLAN

7.1 For treatment or dose-modification related questions, please contact Dr. Graf at (206) 606-2195 or Dr. Gopal at (206) 606-2037. (MedCon may also be used to contact MDs at 206-543-5300.)

7.2 Administration of ibrutinib. Ibrutinib is taken orally at a dose of 560 mg daily.

Drug	**Dose**	**Route**	**Days**	**Duration**
Ibrutinib	560 mg	PO	Once daily	Until disease progression, intolerance, or decision of patient or treating physician
Post Protocol Follow-up				
Long-term follow-up will assess survival and disease progression; subjects will be contacted until death, subject withdrawal of consent, lost to follow-up, or study termination by the sponsor-investigator, whichever occurs first.				

7.3 Prophylaxis
No prophylaxis is needed for ibrutinib and supportive care should be administered as needed.

7.4 Criteria for removal from protocol treatment:

7.4.1 Documented progression of disease (see section 10.6).

7.4.2 Development of any related non-hematologic grade ≥ 4 toxicity or other serious adverse event as defined in section 12.0 will qualify for consideration from removal from protocol treatment

7.4.3 Development of any other unacceptable toxicity

7.4.4 Delay of treatment for more than 21 days due to adverse events.

7.4.5 The patient may withdraw from the treatment at any time for any reason.

7.4.5 Taking prohibited medications concurrent with ibrutinib therapy may result in removal from protocol treatment.

7.5 Continuation of therapy after disease progression

Anecdotal reports indicate that cessation of ibrutinib in patients with B-NHL may contribute to rapid tumor progression. Consequently, it may be beneficial for patients to begin a new treatment regimen after a minimal interval off ibrutinib. To facilitate this, ibrutinib may be continued for up to 4 weeks after documentation of disease progression provided that all other criteria for continuation of treatment re met. Ibrutinib must be stopped at least 24 hours prior to the initiation of the new B-NHL treatment regimen.

8.0 DOSAGE MODIFICATIONS

8.1 Dose Modification and Dose Delay

Treatment with ibrutinib should be held for any of the toxicities listed below:

8.1.1 Grade 4 neutropenia (ANC < 500/mm3)

8.1.2 Grade 3 thrombocytopenia (platelets < 50,000/mm3) in the presence of significant bleeding (≥ Grade 2 bleeding)

8.1.3 Grade 4 thrombocytopenia (platelets < 25,000/mm3)

8.1.4 Grade 3 or Grade 4 nausea, vomiting or diarrhea (if persistent despite optimal antiemetic or antidiarrheal therapy) or any other Grade 4 or unmanageable Grade 3 drug-related toxicities.

The following actions should be taken for drug-related toxicities:

Occurrence of the Same Adverse Event	Action
First	Hold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Hold ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (420 mg daily)
Third	Hold ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
Fourth	Discontinue ibrutinib

Ibrutinib may be held for a maximum of 21 consecutive days. Ibrutinib should be discontinued if the treatment cannot be resumed within 21 days. Once the ibrutinib dose is reduced because of toxicity, it cannot be re-escalated. No dose escalation of ibrutinib (above 560 mg) is allowed in this study. Refer to section 3.4 for subjects requiring the initiation of anticoagulants while receiving study

drug and for instructions on dose modification or temporary hold during concomitant administration of CYP3A inhibitors or inducers. Refer to section 5.3 for guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

If there is a rapid increase in disease burden leading to an "apparent" response of PD after the study drug has been held for at least 7 consecutive days, an assessment response of tumor flare may be assigned instead of PD. Should this occur the patient may remain on study drug if they otherwise meet criteria to continue until the next restaging exam unless there is ongoing evidence of progressive disease before that time despite ongoing treatment. If there is further documented PD on or before the next restaging evaluation the patient will be considered to have PD and the date of PD will be assigned to the initial date tumor flare.

8.2 Dose Modifications for Adverse Reactions

For adverse reactions listed in Table 1, interrupt IMBRUVICA therapy. Once the adverse reaction has improved to Grade 1 or baseline (recovery), follow the recommended dosage modifications.

Table 1. Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction[a,b]	**Occurrence**	**Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg**	**Dose Modification for CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg**
Grade 2 cardiac failure	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]
	Second	Restart at 280 mg daily[c]	Restart at 140 mg daily[c]
	Third	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]
	Second	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue IMBRUVICA	Discontinue IMBRUVICA
Other Grade 3 or 4 non-hematological toxicities[d] Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First	Restart at 420 mg daily	Restart at 280 mg daily
	Second	Restart at 280 mg daily	Restart at 140 mg daily
	Third	Discontinue IMBRUVICA	Discontinue IMBRUVICA

[a] See *Warnings and Precautions.*
[b] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL/SLL.
[c] Evaluate the benefit-risk before resuming treatment.

[d] For Grade 4 non-hematologic toxicities, evaluate the benefit-risk before resuming treatment. These updated dosage modification recommendations may reduce the occurrence of additional serious events and are intended to improve tolerability for continued Imbruvica treatment.

Summary of updated dosage modification recommendations:

- Resume ibrutinib treatment at a reduced dose for patients who experience specific non-hematologic and hematologic adverse drug reactions, including Grade 2 cardiac failure and Grade 3 cardiac arrhythmias, as outlined in *Table 1*
- Evaluate the benefit-risk before resuming ibrutinib treatment following Grade 2 cardiac failure, Grade 3 cardiac arrhythmias, or other Grade 4 non-hematological adverse reactions
- Discontinue treatment for patients who experience adverse drug reactions of Grade 3 or 4 cardiac failure or Grade 4 cardiac arrhythmia

8.3 Concomitant Therapy

8.3.1 Medications used during the course of the study should be documented.

8.3.2 *Prohibited Concomitant Therapy*:
The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Radiation therapy is also prohibited.

8.3.3 Patients should be strongly discouraged from taking any “alternative” or “naturopathic” medications since these agents may interact with study treatment. Any use of these medications should be at the judgment of the treating physician and should be documented in the patient’s medical record.

8.3.4 Hematopoietic growth factors and transfusions are allowed.

9.0 STUDY CALENDAR

Required Studies	Screening (within 4 weeks of initiation of treatment)	During treatment	Post Therapy	Follow-up
Physical				
Medical History	X			
Physical Exam	X	X[4]	X[6]	X[7]
Performance Status	X	X[4]	X[6]	
Clinical Disease Assessment	X	X[4]	X[6]	
Adverse Event Assessment	X	X[4]	X[6]	
EKG	X			
Lab				
CBC and differential	X	X[4]	X[6]	
Serum creatinine, total bilirubin, SGOT (AST), electrolytes, glucose	X	X[4]	X[6]	
Albumin, LDH	X		X[6]	
Bone marrow studies	X[1]	X[1]		
Pregnancy test	X[2]			
Pathologic studies	X			
Radiology				
CT (preferred) or MRI Chest, abdomen and pelvis	X	X[5]	X[6]	
FDG-PET (skull base to proximal femur)	X[3]	X[5]		

[1] Bone marrow studies include aspirate and unilateral or bilateral biopsy and should be performed at screening unless approved by the Sponsor-Investigator or Lead Sub-Investigator. If all bone marrow studies are negative at screening, these do not need to be repeated. If bone marrow status is unknown or positive at screening, patients will need to a have bone marrow study to confirm a suspected CR.

[2] Pregnancy test is only required in women of childbearing potential.

[3] May be obtained up to 8 weeks in advance of initiation of therapy (provided no additional anti-cancer therapies are administered during the interval). A Deauville score should be assigned [19].

[4] At the beginning of therapy (within 3 days), on completion of every cycle (+/- 3 days) during first 9 cycles, then on completion of every 4 cycles (+/- 6 days thereafter. For the first day of therapy, pre-entry H&P, PS, disease assessment, and adverse event assessment may be used (these do not need to be repeated within 3 days) and labs done within 14 days are acceptable.

[5] During treatment restaging CT (preferred) or MRI will be performed on completion of every 3 cycles of therapy (+/- 6 days) during the first 9 cycles and on completion of every 8 cycles of therapy (+/- 12 days) thereafter, or as indicated to evaluate clinical suspicion of disease progression. Restaging PET/CT will be performed once during therapy on completion of the first 6 cycles (+/- 6 days). A Deauville score should be assigned [19] when restaging PET is performed.

[6] Post therapy studies should be done within 28 days after the last dose of ibrutinib. A CT (preferred) or MRI will be obtained if prior imaging was > 21 days of therapy's completion.

[7] Routine, long-term follow-up should be done approximately every 3 months or as clinically indicated. This can be done in conjunction with the patient's local MD; patients do not need to return to the SCCA. Long-term follow-up will assess survival and disease progression for up to 5-years after completion of treatment; subjects will be contacted until death, subject withdrawal of consent, lost to follow-up, or study termination by the sponsor-investigator, whichever occurs first.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be based on standard criteria for lymphoid malignancies .

10.1 Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  Abnormal lymph nodes are those that are either

  >15 mm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or

  > 10 mm in short axis diameter regardless of long axis
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

10.2 PET Scans

Visual assessment currently is considered adequate for determining whether a PET scan is positive. A Deauville score should be reported. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology.

10.3 Response Criteria

For measurement of response, standard 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used (see Appendix D) [20].

10.4 If a subject who had radiological evidence of PD is clinically stable or improving or exhibiting signs of tumor flare without confirmation of PD by PET or biopsy, the subject may continue treatment with ibrutinib upon approval by the sponsor-investigator.. If tumor flare is suspected, the PI may continue ibrutinib and obtain additional radiological and clinical evaluation at a subsequent disease evaluation visit within 6 weeks, with a determination as to whether ibrutinib should be discontinued (in subjects with evidence of further progression at repeat evaluation) or further treatment provided (in subjects with signs of subsequent tumor shrinkage or stable disease without clinical deterioration).

10.5 Progression-free survival (PFS): PFS will be measured as time from first study drug administration to the first occurrence of disease progression or death from any cause. Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative

anticancer therapy. The estimates will be formed using the all treated population. Progression-free survival will be calculated using assessments by investigators. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).

10.6 Assessment inadequate, objective status unknown: Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

10.7 Bone Marrow Status: Bone marrow status is evaluated as follows:

Positive: Unequivocal cytological or architectural evidence of malignancy.

Negative: No aggregates or only a few well-circumscribed lymphoid aggregates.

Indeterminate: Does not qualify for either Positive or Negative Status. *Note this typically consists of increased number or size of aggregates without cytological or architectural atypia.

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary objective is to gain a preliminary (pilot) assessment of the efficacy of this regimen based on overall response rate (ORR) (see section 10.2). Analyses of secondary endpoints will be primarily descriptive. Patients with R/R TIL have a poor prognosis and short median survival; therefore an ORR of ≥ 30%, a disease control rate of ≥ 50% (defined as ORR plus stable disease, as defined in section 10.2), or a median PFS of ≥ 6 months will be considered a success.

11.2 Anticipated accrual: We anticipate that accrual will take 1-2 years.

11.3 Estimated* distribution of study population by gender and race and ethnicity:

Ethnic Category	Females	Males
American Indian/Alaska Native		
Asian	1	1
Native Hawaiian or Other Pacific Islander		
Black or African American	1	1
White	8	8
More than one race		
Unknown or not reported		
Racial Categories: Total of all subjects	10	10

*The exact sample size is not known since it is dependent on the number of evaluable patients, but we estimate the total enrollment will be 20.

11.4 If treatment efficacy meets predefined success rate of 30% overall response rate (combined CR + PR) then a recommendation may be made to expand the study to accrue an additional 20 patients.

12.0 STUDY MONITORING AND REPORTING PROCEDURES

12.1 Adverse Event Reporting

Complete and timely reporting of adverse events (AEs) is required to ensure the safety of patients. Reporting requirements are determined by the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event, and whether the event is *of interest* to Janssen Scientific Affairs. The guidelines outlined in this section, as well as the specific direction on each report form must be followed. The NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) will be used to classify and grade toxicities.

12.2 Definitions and descriptions of terms used in adverse event reporting.

12.2.1 ***Adverse Event (AE)***
An *adverse event* is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure.

12.2.2 ***Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR)***
A *Serious Adverse Event* or *Adverse Drug Reaction* means any AE/ADR occurring at any dose that results in:

- Death;
- A life-threatening AE/ADR (i.e, the patient/subject was, in the view of the initial reporter/investigator, at immediate risk of death from the AE as it occurred. It does not refer to an AE that hypothetically might have caused death if more severe);
- Inpatient hospitalization or prolongation of existing hospitalization (i.e, hospitalization was required to treat or diagnose the AE/ADR: excludes hospitalization for unrelated reasons (e.g., social reasons such as pending placement in long-term care facility) OR surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, 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;

- A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions;

- A congenital anomaly/birth defect;

- An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);

- Any suspected transmission via a medicinal product of an infectious agent.

Sponsor-Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

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.

12.2.3 ***Adverse Events of Special Interest***

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities. These events will be reported to Janssen Scientific Affairs within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection. Specific adverse events of interest include:

1. Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

2. Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

3. Other Malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for

the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

12.2.4 ***Pregnancy***

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the study-site personnel within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported as a Serious Adverse Event. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event.

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

12.2.5 ***Grade***

Grade is defined as the severity of the adverse event. The CTCAE Version 4.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

12.2.6 ***Attribution***

Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- *Unrelated* The adverse event is *clearly NOT related* to therapy
- *Unlikely* The adverse event is *doubtfully related* to therapy
- *Possible* The adverse event *may be related* to therapy
- *Probable* The adverse event is *likely related* to therapy
- *Definite* The adverse event is *clearly related* to therapy

12.2.7 ***Unexpected Adverse Event***

An adverse event is considered unlisted (unexpected) if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure and US package insert.

12.2.8 ***Product Quality Complaint***

A product quality complaint may allege an injury or malfunction associated with the use of the drug product. It may involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product. It may also involve any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product.

12.2.9 ***J&J Medicinal Product***

J&J medicinal product includes the specific drug under study and other J&J medicinal product.

12.3 Routine Reporting

Routine reporting is required for all adverse events.

All applicable adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until30 days following the last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document.

The sponsor-investigator assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to Janssen Scientific Affairs all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The sponsor must report these events to the appropriate IRB that approved the protocol unless otherwise required and documented by the IRB.

12.4 Expedited Reporting

All unexpected adverse events, serious adverse events, and adverse events of interest which may be due to study treatment or intervention, must be reported to the Sponsor-Investigor as soon as possible. Expedited reporting will be conducted

in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations, and agreements with Janssen Scientific Affairs.

Expedited reporting additionally applies to any death occurring during protocol therapy or within 30 days of completing protocol therapy and any death that occurs more than 30 days after completing protocol treatment that is thought to be treatment-related and is not due to disease recurrence. Expedited reporting further applies to the occurrence of pregnancy or, new diagnosis of cancer during treatment or within 30 days of the last dose of study drug, or overdose of study drugs (regardless of adverse outcome).

12.5 Follow-up of serious adverse events

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)

12.6 Reporting to Janssen Scientific Affairs

All serious adverse events and adverse events of interest occurring during the study must be reported to Janssen Scientific Affairs by the sponsor-investigator within 24 hours of learning of the event.

The Sponsor-Investigator will initially notify Janssen Scientific Affairs within 24 hours, by facsimile or e-mail, upon learning of the occurrence during the Study of:

- All serious AE/ADRs, regardless of causality (see 12.2);
- AEs of special interest (see 12.2.3, 12.2.4);
- Special reporting situations (see 12.11);
- Product quality complaints (see 12.13);
- Any exposure of a pregnant Study participant to the Study Drug within thirty (30) days of exposure;
- A female partner of a male Study participant becoming pregnant within thirty (30) days of exposure;
- Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study.

All such occurrences listed in this section shall be reported in final form to Janssen Scientific Affairs using a MedWatch form. An aggregate listing of all SAEs and AEs will also be sent yearly and at the end of the study to Janssen Scientific Affairs electronically.

In the event the IRB requests additional safety information from the investigator, the investigator shall notify Janssen Scientific Affairs of such request within one (1) business day of learning of the request.

12.7 Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase as well as the end of the follow-up phase of the Study, the Sponsor-Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary.

12.8 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Sponsor-Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. The Sponsor-Investigator will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, the Sponsor-Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

12.9 Dissemination of Safety Information from Janssen Scientific Affairs to theSponsor-Investigator

Janssen Scientific Affairs will provide to the Sponsor-Investigator IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the Janssen Scientific Affairs for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

12.10 Reporting to the IRB

Guidelines of the local IRB will be followed for reporting serious adverse events in a timely manner.

12.11 Special Reporting Situations

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the

serious adverse event page of the CRF. Safety events of interest on a Johnson & Johnson medicinal product that may require expedited reporting and/or safety evaluation include, but are not limited to:

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

12.12 Data Safety and Monitoring Plan

All serious adverse events are communicated to the study Sponsor-Investigator, and regulatory agencies as described above. A status report including accrual, adverse events, and death information will be reviewed by the Sponsor-Investigator every 6 months and the Fred Hutchinson Cancer Research Center (FHCRC) Protocol Data Monitoring Committee (PDMC) annually. In addition, the study will be monitored by the Research Trials Office according to the Fred Hutchinson Cancer Research Center monitoring plan.

12.13 Product quality complaint handling

All initial PQCs must be reported to Janssen Scientific Affairs by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to Janssen Scientific Affairs 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.

12.14 Required Records and Materials

Original signed informed consent form will be retained with the study records. A copy will be sent to the clinical chart and to the patient.

Data will be collected on patient characteristics, disease characteristics, protocol therapy, response to treatment, adverse events and follow-up for relapse and

survival. Copies of the patient's medical record including history and physical exams, documentation of protocol therapy, labs, scans, x-rays, hospitalizations, operative reports, pathology reports etc. are required. Case report forms will be completed by the study staff.

13.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all patients entering the study.

14.0 REFERENCES:

1. Bernstein SH, Burack WR. The incidence, natural history, biology, and treatment of transformed lymphomas. Hematology Am Soc Hematol Educ Program 2009; 532-541.
2. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 1984; 311: 1471-1475.
3. Al-Tourah AJ, Gill KK, Chhanabhai M et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol 2008; 26: 5165-5169.
4. Lossos IS, Gascoyne RD. Transformation of follicular lymphoma. Best Pract Res Clin Haematol 2011; 24: 147-163.
5. Wong E, Dickinson M. Transformation in follicular lymphoma: biology, prognosis, and therapeutic options. Curr Oncol Rep 2012; 14: 424-432.
6. Eide MB, Lauritzsen GF, Kvalheim G et al. High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study. Br J Haematol 2011; 152: 600-610.
7. Sabloff M, Atkins HL, Bence-Bruckler I et al. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and nontransformed follicular lymphoma. Biol Blood Marrow Transplant 2007; 13: 956-964.
8. Villa D, Crump M, Panzarella T et al. Autologous and allogeneic stem-cell transplantation for transformed follicular lymphoma: a report of the Canadian blood and marrow transplant group. J Clin Oncol 2013; 31: 1164-1171.
9. Williams CD, Harrison CN, Lister TA et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. J Clin Oncol 2001; 19: 727-735.
10. Fisher RI, Kaminski MS, Wahl RL et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005; 23: 7565-7573.
11. Advani RH, Buggy JJ, Sharman JP et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013; 31: 88-94.
12. Irish JM, Czerwinski DK, Nolan GP, Levy R. Altered B-cell receptor signaling kinetics distinguish human follicular lymphoma B cells from tumor-infiltrating nonmalignant B cells. Blood 2006; 108: 3135-3142.
13. Ansell SM. Two targets for the price of one. Blood 2013; 122: 2529-2531.
14. de Rooij MF, Kuil A, Geest CR et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012; 119: 2590-2594.
15. Wang ML, Rule S, Martin P et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013; 369: 507-516.
16. Wilson WH, et al. The Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity in the ABC Subtype of Relapsed/Refractory De Novo Diffuse Large B-Cell Lymphoma (DLBCL): Interim Results of a Multicenter, Open-Label, Phase 2 Study ASH Annual Meeting 2012.
17. Ponader S, Chen SS, Buggy JJ et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. Blood 2012; 119: 1182-1189.

18. Byrd JC, Furman RR, Coutre SE et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013; 369: 32-42.
19. Barrington SF, Qian W, Somer EJ et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. Eur J Nucl Med Mol Imaging 2010; 37: 1824-1833.
20. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32: 3059-3068.

Appendix A: Ann Arbor staging system for lymphomas

Principal stages

The principal stage is determined by location of the tumor:

Stage I indicates that the cancer is located in a single region, usually one lymph node and the surrounding area. Stage I often will not have outward symptoms.

Stage II indicates that the cancer is located in two separate regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to one side of the diaphragm - that is, both are above the diaphragm, or both are below the diaphragm.

Stage III indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen.

Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs.

These letters can be appended to some stages:

A or B: the absence of constitutional (B-type) symptoms is denoted by adding an "A" to the stage; the presence is denoted by adding a "B" to the stage.

E: is used if the disease is "extranodal" (not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.

X: is used if the largest deposit is >10 cm large ("bulky disease").

S: is used if the disease has spread to the spleen.

Appendix B: ECOG Performance Status

0 – Asymptomatic (Fully active, able to carry on all predisease activities without restriction)

1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)

2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)

3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)

4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

5 – Death

Appendix C: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. This list may not be all inclusive. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A		**Inducers of CYP3A**
STRONG		Carbamazepine
INDINAVIR		Efavirenz
NELFINAVIR		Nevirapine
RITONAVIR		Barbiturates
CLARITHROMYCIN		Glucocorticoids
ITRACONAZOLE		Modafinil
KETOCONAZOLE		Oxcarbarzepine
NEFAZODONE		Phenobarbital
SAQUINAVIR		Phenytoin
SUBOXONE		Pioglitazone
TELITHROMYCIN		Rifabutin
		Rifampin
MODERATE	**WEAK**	St. John's Wort
aprepitant	cimetidine	Troglitazone
erythromycin		
diltiazem		
fluconazole		
grapefruit juice		
Seville orange juice		
verapamil		
ALL OTHER INHIBITORS		
amiodarone		
NOT azithromycin		
chloramphenicol		
boceprevir		
ciprofloxacin		
delaviridine		
diethyl-dithiocarbamate		
fluvoxamine		
gestodene		
imatinib		
mibefradil		
mifepristone		
norfloxacin		
norfluoxetine		
star fruit		
telaprevir		
troleandomycin		
voriconazole		

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix D: The Lugano Response Classification [20]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Lymph nodes and extralymphatic sites	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
	allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: 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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved 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

Response and Site	PET-CT–Based Response	CT-Based Response
		be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement