TITLE:	Ibrutinib and Venetoclax in Relapsed and Refractory Follicular Lymphoma
PROTOCOL NUMBER:	**2016-0014**
STUDY DRUGS:	Ibrutinib, Venetoclax
INVESTIGATOR:	Study Chair Chaitra Ujjani, MD Seattle Cancer Care Alliance [redacted] Principal Investigator Kieron Dunleavy, MD Medstar Georgetown University Hospital Lombardi Comprehensive Cancer Center [redacted]
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SYNOPSIS

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<tr><td>Protocol Number:</td><td>2016-0014</td></tr>
<tr><td>Study Phase:</td><td>1b/2</td></tr>
<tr><td>Study Duration:</td><td>24 months</td></tr>
<tr><td>Objectives:</td><td>Phase I study:
<u>Primary Objective:</u> To determine the recommended phase II doses of ibrutinib and venetoclax when combined in relapsed and refractory follicular lymphoma
<u>Secondary Objective:</u> To determine the pharmacokinetics of ibrutinib and venetoclax when dosed in combination in relapsed and refractory follicular lymphoma
Phase II study:
<u>Primary Objective:</u> To determine the efficacy of ibrutinib and venetoclax when combined in relapsed and refractory follicular lymphoma
<u>Secondary Objective:</u> To determine the safety and tolerability of ibrutinib and venetoclax when combined in relapsed and refractory follicular lymphoma</td></tr>
<tr><td>Study Design:</td><td>This is a phase I/II study in which patients will be enrolled in a standard 3+3 design. Once the maximum tolerated dose is determined, there will be a 17-patient phase II study using Simon’s Minimax 2-stage design.</td></tr>
<tr><td>Inclusion Criteria:

Refer to Section 4.0 for the complete and detailed list of inclusion/exclusion criteria.</td><td>• Relapsed or refractory, histologically confirmed grade 1-3a follicular lymphoma which requires therapy
• Must have received at least one prior systemic therapy
• All risk by FLIPI 0-5 factors
• No prior BTK inhibitor or BCL-2 inhibitor
• ECOG performance status of ≤ 2

<u>Required Initial Lab Values</u>
ANC ≥ 1000/uL*
Hemoglobin ≥8.0 g/dL*
Platelet count ≥ 50,000/uL*
AST and ALT ≤ 2.5 x ULN*
Total bilirubin ≤ 1.5 x ULN*,**
CrCl ≥ 50 mL/min***
PT/INR and PTT (aPTT) <1.5 x ULN

*Unless attributable to disease, See Section 3
**Unless attributable to Gilbert’s syndrome
***Use of Cockcroft-Gault actual weight</td></tr>
<tr><td>Exclusion Criteria:</td><td>• Chemotherapy, monoclonal antibody, or small molecule inhibitor ≤ 21 days prior to first administration of study treatment</td></tr>
</table>

	• Concurrent systemic immunosuppressant therapy ≤ 4 weeks of the first dose of study drug (e.g. cyclosporine A, tacrolimus, etc. or chronic administration of > 20 mg day of prednisone or equivalent) • Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects at risk for tumor lysis syndrome • Infection requiring systemic treatment that was completed ≤14 days • Significant unresolved toxicities from prior anti-cancer therapy • Known bleeding disorders (e.g. von Willebrand's disease) or hemophilia. • History of stroke or intracranial hemorrhage within 6 months • Known history of HIV • Active hepatitis C or hepatitis B infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. • Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C (See Appendix X) • Major surgery within 4 weeks of first dose of study drug. • Concomitant use of warfarin or other Vitamin K antagonists. • Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (See Appendix VI) • Lactating or pregnant. • Current or history of graft versus host disease

<table>
<tr><td>Study Treatment:</td><td>
Phase I study:
Three patients will be enrolled at Dose Level 0 (DL0): Ibrutinib 420 mg daily and Venetoclax 400 mg daily. Each cycle is 28-days. Patients will be monitored for dose limiting toxicity (DLT) during Cycle 1. Patients will receive the combination until progression or unacceptable toxicity. Patients will be followed throughout the duration of therapy through progression until next line of therapy.
<table>
<tr><th colspan="3">Dose Levels</th></tr>
<tr><td>Dose Level</td><td>Ibrutinib</td><td>Venetoclax</td></tr>
<tr><td>0</td><td>420 mg</td><td>400 mg</td></tr>
<tr><td>1</td><td>560 mg</td><td>400 mg</td></tr>
<tr><td>2</td><td>560 mg</td><td>600 mg</td></tr>
</table>
Phase II study:
Patients will be enrolled at the recommended phase II dose. Duration of therapy will depend on depth of response. Patients who achieve a complete remission may discontinue therapy after 24 cycles. These patients must undergo a PET-CT during Cycle 24 to confirm they are still in a complete remission prior to discontinuation. Patients who achieve a partial response will continue therapy until progression or unacceptable toxicity. Patients will be followed throughout the duration of therapy through progression until next line of therapy. Patients who achieve a complete remission and discontinue therapy after 24 cycles will be monitored closely with serial imaging and may be reinitiated on treatment within one year of discontinuation for either progression of disease or at the discretion of the treating physician.
</td></tr>
<tr><td>Participating Centers:</td><td>MedStar Georgetown University Hospital
Hackensack University Medical Center
Seattle Cancer Care Alliance</td></tr>
</table>

ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate transaminase
AUC	Area under the curve
BCR	B-cell receptor
BTK	Bruton-tyrosine kinase
CDUS	Clinical data update system

CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	Peak concentration
CR	Complete response
CRF	Case report form
CTCAE	NCI Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FCBP	Female of childbearing potential
FL	Follicular lymphoma
GCP	Good Clinical Practice
GELF	Groupe d'Etude des Lymphomes Folliculares
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	human immunodeficiency virus
IAC	Interim Analysis Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVF	Intravenous fluids
IVRS	Interactive voice response system
IWRS	Interactive web response system
LC-MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma

MRU	Medical Resource Utilization
MTD	Maximal tolerated dose
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PQC	Product Quality Complaint
PR	Partial response
PRO	patient-reported outcome(s)
QD	Daily
SAE	Serious adverse event
SD	Stable disease
SJS	Stevens-Johnson Syndrome
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
Tmax	Time to reach maximum concentration
Vd	Volume of distribution
Vss	Volume of distribution at steady state
USP	United States Pharmacopeia

1. BACKGROUND

1.1. Follicular Lymphoma

1.1.1 Disease Biology

The most common of the indolent non-Hodgkin lymphomas (NHL), follicular lymphoma, represents 25% of all NHLs in the United States. The median age at diagnosis is 60 years, and the majority of patients present with advanced-stage disease. While the pathogenesis of follicular lymphoma is not completely established, the hallmark chromosomal abnormality found in > 90% of patients is the t(14;18) translocation. This rearrangement of the BCL-2 oncogene results in overexpression of the anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein, which contributes to lengthy tumor cell survival.

The pathogenesis of the follicular lymphoma is an intricate, multistep process. The t(14;18) translocation is attributed to as the first genetic hit necessary for the development of the disease. As many healthy individuals are also found to have this translocation, Bcl-2 is not the sole culprit for malignant transformation. The B-cell receptor (BCR) is a critical factor in the development of the disease, as its active tonic signaling leads to recruitment of the spleen tyrosine kinase and activation of multiple downstream pathways including Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3-kinase (PI3K), ultimately resulting in malignant lymphocyte maturation, proliferation and survival.

1.1.2 Treatment Options

Follicular lymphoma is characterized by a variable clinical course. Asymptomatic patients can be closely monitored for years without treatment, while symptomatic patients require more immediate therapy. Indications for treatment are defined by the GELF (Groupe d'Etude des Lymphomes Follicularies) criteria: single lesion > 7cm, three nodal sites > 3 cm, splenomegaly, cytopenias, effusions, and threat of or evidence of organ compression. [1]

Whereas symptomatic patients with limited stage follicular lymphoma have several options including single-agent rituximab, radiation, and chemoimmunotherapy depending on their performance status and comorbidities, chemoimmunotherapy is currently the standard of care for those with advance-stage disease. Either BR (bendamustine and rituximab) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) are reasonable options for induction. [2,3]

Despite high response rates to chemoimmunotherapy, patients inevitably relapse, and further treatment options are necessary. Approved options include chemoimmunotherapy with the same or alternative chemoimmunotherapy regimen. Responses in the second-line setting, however, are not as high or durable. Aside from chemoimmunotherapy, approved options include radioimmunotherapy, which is cumbersome in the fact that it requires the incorporation of an experienced nuclear medicine team. [4] Furthermore, the patient must fulfill certain criteria in terms of complete blood count levels and limited prior exposure to radiation. Idelalisib, a potent inhibitor of the delta isoform of PI3K, was approved for patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. [5] The indication in follicular lymphoma was based on the results of a phase II trial in patients with rituximab-refractory indolent NHL. Of the 72 patients with follicular lymphoma, the ORR was 56% and only 10 patients achieved a CR. The median progression-free survival (PFS) was 11 months and the median duration of response was 12.5 months. Given these suboptimal responses for patients with relapsed disease, further treatment options are necessary.

1.2. Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of BTK. Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of

the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved in over 80 countries, including the United States (US) and European Union (EU) for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia (WM), patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and adult patients with cGVHD after failure of 1 or more lines of systemic therapy.

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the BCR, which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways. [6]

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development. [7] Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells. [8]

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

For the most up to date and 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 Investigator's Brochure.

1.3. Summary of Nonclinical Data with Ibrutinib

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

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK. [10] In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 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 (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression. [13]

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.2. Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. In vivo safety pharmacology assessments performed in a cardiovascular study in telemetry-monitored dogs showed PR interval prolongation, lowered heart rate and shortening of QT interval corrected for heart rate (QTc). Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current IB.

1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.4. Summary of Clinical Data with Ibrutinib

For the most comprehensive clinical information regarding ibrutinib, refer to the current IB.

1.4.1 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) of 1 to 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by CYP 3A4 mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. About 8% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCL) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of ibrutinib has not been evaluated in patients with hepatic impairment.

For the most comprehensive pharmacokinetics (PK) and product metabolism, please refer to the current version of the IB.

1.4.2 Summary of Clinical Efficacy with Ibrutinib in Follicular Lymphoma

The ORR with ibrutinib in follicular lymphoma in 40 heavily pretreated patients was 30% and median PFS of 9.9 months. [10] Efficacy was also noted in patients with marginal zone lymphoma. [11] Many of the responses with ibrutinib are partial, however, and drug resistance can develop. Therefore, efforts have been made to improve upon its efficacy, such as combination with chemotherapy. In a phase Ib study of ibrutinib and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in treatment naïve patients with B-cell NHL, the ORR was 100% (CR 73%) and 1-year PFS was 90%. [12] The regimen was well-tolerated with the most common adverse events being neutropenia, nausea, and thrombocytopenia. Ibrutinib is also being studied in combination with other targeted therapies. The Alliance for Clinical Trials in Oncology is conducting a phase I trial of rituximab,

lenalidomide, and ibrutinib in patients with previously untreated follicular lymphoma (NCT01829568). Preliminary (unpublished) data indicate activity and the lack of dose limiting toxicities with this combination.

1.5. Summary of Clinical Safety with Ibrutinib

Integrated safety data for a total of 1,971 subjects with hematologic malignancies from 17 combination therapy studies that have completed primary analysis or final analysis included in the CSR as of 12 November 2019 are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), cytarabine, azacytidine, dexamethasone, durvalumab, lenalidomide with cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone +/- rituximab (EPOCH-R), nivolumab and obinutuzumab. The median duration of ibrutinib exposure for subjects with hematologic malignancies receiving ibrutinib as combination therapy was 5.8 months and the mean was 11.0 months.

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=1,971):

Most frequently reported TEAEs ≥ 10% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 2% [a]	Most frequently reported Serious TEAEs ≥ 1% [b]
Neutropenia	Neutropenia	Neutropenia
Diarrhea	Diarrhea	Diarrhea
Nausea	Platelet count decreased	Thrombocytopenia
Thrombocytopenia	Thrombocytopenia	
Fatigue	Fatigue	Anemia
Anemia	Anemia	Pyrexia
Pyrexia	Neutrophil count decreased	Pneumonia
Hypokalemia	Rash maculo-papular	Febrile neutropenia
Upper respiratory tract infection	Pneumonia	Atrial fibrillation
	Febrile neutropenia	Cellulitis
Constipation	Hypokalemia	Urinary tract infection

Vomiting	Atrial fibrillation	Sepsis
Headache	Hypertension	Lung infection
Cough	Hyponatremia	Acute kidney injury
Muscle spasms	Lymphocyte count decreased	
Pneumonia	White blood cell count decreased	Dyspnoea
Oedema peripheral	Urinary tract infection	Dehydration
Arthralgia	Hyperglycemia	
Decreased appetite		
Abdominal pain	Leukocytosis	
Back pain	Leukopenia	
Platelet count decreased	Lymphocyte count decreased	
Neutrophil count decreased	Syncope	
Lymphocyte count increased		
White blood cell count decreased		
Hypertension		
Urinary tract infection		
Contusion		
Myalgia		
Rash maculo-papular		
Dyspnea		
Insomnia		

Peripheral sensory neuropathy
Stomatitis
Dizziness
Pain in extremity
Infusion related reaction
Blood creatinine increased
Febrile neutropenia

[a] *Source is Table 8 of IB (v13)* [b] *Source is Table 9 of IB (v13)*

For more detailed information refer to the current version of the IB. See Appendix I for most recent Reference Safety Information with Ibrutinib.

1.5.1. Risks with Ibrutinib

1.5.1.1. Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section X. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs or and symptoms of bleeding. See Section 7.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 7.4 for guidance on ibrutinib management with surgeries or procedures. Subjects with congenital bleeding diathesis have not been studied.

1.5.1.2. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension acute infections, and a previous history of cardiac arrhythmia.

Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6.2)

1.5.1.3. Cytopenias

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

1.5.1.4. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 6.2).

1.5.1.5. Infections

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

1.5.1.6. Non-melanoma Skin Cancer

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

1.5.1.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be

observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.5.1.8. Tumor Lysis Syndrome

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

1.5.1.9. Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate. **1.5.1.10 Interstitial lung disease**

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6).

1.5.1.11 Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Long-term safety

The long-term safety data over 5 years from 1,178 subjects (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n=646, and relapsed/refractory MCL n=370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of subjects receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of subjects receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2 – 3), 9% (year 3- 4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

1.6. Venetoclax

1.6.1. Bcl-2 Function in the Antiapoptotic Pathway

Programmed cell death (apoptosis) is responsible for removal of aged and damaged cells from a healthy multicellular organism, and the balance between cell survival and cell death, as maintained by apoptosis, is critical for normal development and homeostasis of multicellular organisms. Distinct from the signaling pathways downstream of the B-cell receptor (i.e. BTK, PI3K), the Bcl-2 family of proteins is a crucial mediator of B-cell survival. Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway, and were first identified in FL. In contrast to other known oncogenes, Bcl-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of proapoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat, and deregulated oncogenes.

Resistance to apoptosis is one hallmark of neoplasms. [13] Drug-induced restoration of the apoptotic pathway can therefore be a viable treatment strategy for cancer. Selective killing of the tumor cells may be achieved because, unlike normal cells, tumor cells are under continuous stress and therefore reliant on aberrant apoptotic signaling to stay alive. [14] Overexpression of antiapoptotic Bcl-2 family members is associated with tumor initiation, disease progression, and drug resistance, and thus Bcl-2 family members are compelling targets for antitumor therapy. Apoptosis also plays an essential role in the immune system, where the elimination of self-reactive cells is important in the selection of both T cells and B cells during the development of an immune response. Failure of the immune system to eliminate self-reactive lymphocytes is believed to be one of the leading causes of autoimmune disease. [15] The anti-apoptotic protein Bcl-2 has been demonstrated to regulate apoptosis in lymphoid tissues, and is a key factor in immune response resolution and in the elimination of autoreactive lymphocytes.

Venetoclax is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL (Ki – 48 nM) and Bcl-w (Ki – 245 nM). Overexpression of antiapoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy. In vitro, venetoclax demonstrated broad cell killing activity against a panel of lymphoma and leukemia cells including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), and acute myeloid leukemias (AMLs). Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than non-mutated cell lines.

Venetoclax inhibits subcutaneous xenograft growth of human tumor cell lines derived from ALL, NHL, and AML, and is highly efficacious using various doses and regimens. The drug is also active in models of disseminated ALL and AML. Venetoclax enhanced the activity of a broad variety of chemotherapeutic agents (e.g., R-CHOP, bendamustine, rituximab, and bortezomib) in other human hematological xenograft models. Leukemia and lymphoma cell lines bearing the t(14;18) chromosome translocation are significantly more sensitive to venetoclax

than nonmutated lines. Venetoclax also demonstrated potent killing of MM cell lines and primary tumor samples bearing the t(11;14) translocation, which tend to express high levels of Bcl-2 relative to Mcl-1.

1.6.2. Summary of Non-clinical Data with Venetoclax

1.6.2.1. Pharmacology

The pharmacokinetic profile of venetoclax was evaluated in multiple animal species. In mouse, rat, monkey and dog, the venetoclax pharmacokinetic profile was characterized by low plasma clearance and low volumes of distribution. Half-lives ranged from 2.2 hours in monkey to 12 hours in dog. Food had a marked effect on the oral bioavailability in dog.

1.6.2.2. Toxicology

On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related antiapoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia, signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-XL sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a dose limiting toxicity (DLT) clinically.

In vitro studies have shown that venetoclax is metabolized primarily by CYP3A4; thus, co-administration of venetoclax with drugs that inhibit CYP3A4 (such as ketoconazole) is predicted to cause a significant increase in the exposure of venetoclax and will be undertaken with caution.

For more detailed and comprehensive information regarding venetoclax, refer to the current version of the Investigator's Brochure.

1.6.2.3. Carcinogenesis, Mutagenesis, Impairment of Fertility

The nonclinical toxicology of venetoclax has been evaluated in repeated-dose studies in mice and dogs with up to 4 weeks of once daily oral dosing (and with 4-week recovery periods) and in dogs with 2 weeks of dosing (18-week recovery period); safety pharmacology studies (cardiovascular, neurofunctional, and pulmonary); and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays). The primary toxicities associated with venetoclax administration included effects on the hematologic system (lymphocytes and red blood cell parameters) in mice and dogs and on the male dog reproductive system. There was no evidence of genotoxicity of venetoclax.

Male dog reproductive effects consisted of markedly reduced numbers of spermatogonia in the testes at all venetoclax dose levels after 4 weeks of dosing, with progression to severe decreases in the numbers of all germ cells in testes during the 4-week recovery period. Male mice did not have testicular changes associated with venetoclax administration. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax

pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis. [16] In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies.

1.7. Summary of Clinical Data with Venetoclax

1.7.1 Pharmacokinetics and Product Metabolism

Venetoclax has high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes. Volumes of distribution at steady state (Vss) were low to moderate in all species, with values increasing from 0.30 L/kg in dog to 1.1 L/kg in rat. Plasma clearance values were low in all species, decreasing from a high of 0.27 L/hr•kg in monkey to a low of 0.02 L/hr•kg in dog.

Formulation-dependent bioavailability was noted following oral administration in all species. The initial pharmacokinetic studies using a 10% dimethyl sulfoxide (DMSO) in PEG-400 solution formulation provided baseline bioavailability values ranging from a low of 8.6% in monkey to highs of 26.8% in mouse and 27.8% in dog. Plasma concentrations obtained from fed dogs were 30% to 50% higher than those obtained from fasted animals.

In vivo, venetoclax was metabolized by CYP3A4.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current version of the Investigator's Brochure.

1.7.2 Clinical Efficacy with Venetoclax in Lymphoma

As a single agent, Venetoclax achieved an ORR of 48% in a phase I study of patients with multiply relapsed/refractory NHL (n=40). [17] Responses were noted in DLBCL, mantle cell lymphoma, Waldenstrom's and follicular lymphoma. A greater percentage of responses occurred at the higher dose of 600 mg. Two dose limiting toxicities (Grade 3 febrile neutropenia, Grade 4 neutropenia) occurred at this dose. Dosing modifications including a lead-in period and step-wise dose escalation were developed to help prevent the occurrence of tumor lysis syndrome. Grade 3 laboratory TLS occurred after the initial dose in one patient with bulky mantle cell lymphoma (>10 cm) and one with DLBCL. Common toxicities included nausea and diarrhea. Venetoclax is currently being studied in combination with BR (bendamustine and rituximab) in a phase I study of relapsed/refractory NHL (NCT01594229) and will be studied in an upcoming 3-arm phase II study of BR+ Venetoclax, BR, and R+ Venetoclax (NCT02187861) in relapsed/refractory follicular lymphoma.

1.8. Summary of Clinical Safety with Venetoclax

As of 03 February 2014, a total of 153 subjects have been enrolled in Study M12-175 and had data available for the study (95 in Arm A and 58 in Arm B). Most common adverse events in CLL/SLL subjects were diarrhea (38.9%), neutropenia (37.9%), nausea (34.7%), upper respiratory tract infection (30.5%), fatigue (27.4%), and cough (20.0%). The most common adverse events in NHL subjects were nausea (32.8%), diarrhea (24.1%), and fatigue and upper respiratory tract infection (20.7% each). The most common adverse events reported for all subjects in the study were nausea (34.0%), diarrhea (33.3%), neutropenia (29.4%), upper respiratory tract infection (26.8%), and fatigue (24.8%). The most common events grade 3 or above reported in CLL/SLL subjects were neutropenia (34.7%) and anemia (10.5%), and in NHL subjects were anemia (15.5%) and neutropenia (10.3%). Overall, the most common adverse events Grade 3 and above reported in all subjects were neutropenia (25.5%) and anemia (12.4%).

1.8.1. Risks with Venetoclax

1.8.1.1. Tumor Lysis Syndrome

As a result of on-target effects, the potential for tumor lysis syndrome (TLS) was identified early in the program.

Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is characterized as highest when initiating venetoclax dosing, especially with a higher initial dose of venetoclax, as well as being greater in subjects with a large tumor burden. The available data suggest that in non-CLL subjects the risk of TLS is low. It is being closely monitored among subjects with AML, NHL and MM. There have two cases of TLS in NHL, one patient with DLBCL and one patient with mantle cell lymphoma.

1.8.1.2. Neutropenia

Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in combination studies. Even though neutropenia and febrile neutropenia adverse events of grade 3 or higher are observed, serious events of neutropenia and febrile neutropenia that are related to venetoclax administration or lead to discontinuations are few across the entire venetoclax oncology program. The assessment of neutropenia in the study population of subjects with hematological malignancies is confounded by various factors that could affect bone marrow reserves, including older age, multiple prior therapies, disease infiltrating the bone marrow, and the use of growth factor prior to entering the studies.

1.8.1.3. Diarrhea

Approximately one-third of CLL/SLL and one-fourth of NHL subjects receiving venetoclax reported diarrhea, primarily low-grade in nature. Other frequently reported gastrointestinal event was nausea.

1.8.1.4. Food Effect

Preliminary pharmacokinetic data indicate that compared with fasting conditions, food increased venetoclax bioavailability by 3- to 4-fold. It is recommended that all venetoclax doses be administered within 30 minutes after the completion of breakfast or the subject's first meal of the day during a regular treatment cycle. All ongoing venetoclax studies follow this recommendation.

1.8.1.5. Infections

Approximately one-fourth of NHL subjects receiving venetoclax reported upper-respiratory infections. Serious infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies. The most common infection adverse events include upper respiratory, lower respiratory tract infections, and urinary tract infections.

1.8.1.6. Other Hematological Effects

Anemia has been reported in the oncology studies with slightly higher frequency when venetoclax was combined with other chemotherapeutic agents; however most of the events were not serious and were confounded by disease factors in the hematological cancer population.

Thrombocytopenia adverse events, including grade 3 events and higher, have been reported in the oncology studies, with slightly higher frequency in studies in which venetoclax is combined with other chemotherapeutic agents. However, most of the events were not serious and assessment of these events is confounded by the subjects' underlying disease state and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several subjects.

Hemoglobin/hematocrit values and red blood cell counts and indices as well as platelet counts should be monitored for all subjects.

Lymphopenia has been observed in preclinical studies. No serious opportunistic infections attributed to venetoclax dosing have been reported in the clinical program.

1.8.1.7. Other Malignancies

To date, a total of 10 serious second primary malignancies, excluding non-melanoma skin cancers, have been reported across the oncology program; all are confounded by age, multiple prior therapies, and other host characteristics. No pattern was observed in the occurrence of second primary cancers, and none were considered to be related to venetoclax.

1.8.1.8. Reproductive System Effects

There is potential for decreased spermatogenesis. Non-reversible depletion of testicular germ cells has been observed in dogs at all doses tested after 4 weeks of dosing.

In the oncology studies, male subjects should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

1.9. Study Rationale

In vitro studies of ibrutinib and venetoclax have noted significant cytotoxicity and synergy in mantle cell lymphoma and chronic lymphocytic leukemia cell lines. [18] Data have demonstrated synergy between the two agents in various other B-cell NHL cell lines. [19] We theorize that the combination of ibrutinib and venetoclax will provide dual, yet unique, targeted inhibition for patients with follicular lymphoma, resulting in both significant efficacy and less nonspecific toxicity.

1.10. Correlative Science Background

As targeted therapies become more ubiquitously used in the treatment of follicular lymphoma, accurate predictive biomarkers are crucial for the management of patients. The focus of the correlative science portion of this study is to identify potential mechanisms of resistance to the combination of ibrutinib and venetoclax, in order improve treatment selection for patients with relapsed and refractory follicular lymphoma.

1.10.1 Mutations of Resistance

Although active in indolent B-cell malignancies, cases of primary and secondary resistance to ibrutinib have emerged. To better understand the mutations of secondary resistance in CLL, whole exome sequencing was performed on peripheral blood samples from patients prior to starting therapy and at the time of progression. [20] Of the 6 patients who relapsed after achieving a durable response with ibrutinib, 5 had developed new cysteine-to-serine mutations in BTK at position 481 (C481S). This mutation disrupted covalent binding and allowed for reversible binding of BTK by ibrutinib, resulting in 25-fold less potent BTK inhibition and acquired resistance. Two patients had developed new mutations of PLCγ2: arginine to tryptophan at 665 (R665W), leucine to phenylalanine at 845 (L845F), and serine to tyrosine at 707 (S707Y). As PLCγ2 is downstream of BTK, these gain-of-function mutations lead to autonomous BCR signaling, independent of BTK, and disease progression. A limited data set suggests BTKC481S is also a culprit of secondary resistance to ibrutinib in mantle cell lymphoma. [21] Preclinical studies in ibrutinib-resistant diffuse large B-cell lymphoma (DLBCL) cell lines possessing either BTKC481or PLCγ2 R665W have demonstrated the ability to be re-sensitized to ibrutinib with co-administration of BCL-2 inhibitors, resulting in inhibition of cell growth, cell adhesion, and migration. [19] These data suggest that some B-cell NHL may utilize alternative survival pathways, including BCL-2, which can be exploited through other

targeted therapies. There are currently no mutational data regarding ibrutinib sensitivity or resistance available in FL. [10] Mutations associated with resistance to BCL-2 inhibitors in FL have not yet been established either. Based on the above-mentioned observations, we believe next generation sequencing (NGS) to be a potentially effective tool for the identification of key predictors of response and resistance to the doublet regimen. Genetic profiles will be obtained from pretreatment tumor samples for NGS in order to help recognize potentially clinically significant mutations or alterations of the genome.

1.10.2. BCL-2 Family Proteins

Theorized mechanisms of resistance to BCL-2 inhibition include upregulation of the antiapoptotic members of the BCL-2 family, such as BCL-XL, MCL1, and BCL-W. In vitro studies of the first generation BCL-2 inhibitor, ABT-737, have demonstrated drug resistance via upregulation of BCL-XL and BCL2A1 in CLL lymph node models. [22] In a different CLL lymph node model, made resistant to venetoclax through stimulation with CD40 and IL4, upregulation of BCL-XL was also noted. [23] In follicular lymphoma cell lines, higher levels of the proapoptotic BIM were associated with increased sensitivity to BCL-2 inhibition; whereas cells with acquired resistance after continuous exposure to venetoclax were found to have increased levels of MCL-1. [24] Co-administration of venetoclax and either BCL-XL or MCL-1 inhibitors resulted in synergistic cell death in resistant cell lines, supporting the direct correlation of these anti-apoptotic proteins and venetoclax resistance. [25] Additional alterations in venetoclax-resistant B-cell lymphoma cell lines (follicular, mantle cell, DLBCL) included change in level of BCL-2 expression and decrease in pro-apoptotic proteins (BAX, BIM, NOXA).

Preclinical studies of venetoclax and ibrutinib in DLBCL cell lines have shown that higher levels of BCL-2 expression were associated with greater sensitivity to single-agent venetoclax than lower levels. [19] In addition, single-agent ibrutinib increased BCL-2 expression and sensitivity to venetoclax. Pretreatment samples from patients who responded to ibrutinib had lower BCL-2 expression; whereas a high BCL-2 mutation rate was observed in patients who responded poorly to ibrutinib. Concurrent administration of ibrutinib and venetoclax resulted in complete tumor growth inhibition in a DLBCL (activated B-cell subtype) murine model. There are currently no data available from follicular lymphoma clinical trials evaluating the correlation between BCL-2 family members and sensitivity to venetoclax. Similarly, the clinical implications of the pro- and antiapoptotic members of the BCL-2 family have not been evaluated in patients receiving concurrent venetoclax and ibrutinib. Levels of expression of various BCL-2 family member proteins will be assessed on tumor samples prior to treatment, bone marrow biopsy samples after achieving a complete response, and tumor samples at progression in order to understand the implications of these proteins in terms of response to therapy, development of resistance, and the ability to overcome resistance.

1.10.3. Tumor Cell Cultures and Drug Sensitivity

The survival and proliferative activity of FL is thought to be highly dependent on the micro-environment within involved lymph nodes and in the bone marrow, where tumor cells are intimately associated with a variety of stromal cells within the so-called follicular lymphocyte niche. [26] Thus, although established FL cell lines have proven useful for modeling the role of various mutations on the sensitivity and resistance profile of the disease to therapeutic agents, these models, by their nature, ignore the contribution of tumor-stromal cell interactions. To address this concern, several co-culture models have been used in recent years that seek to model these interactions between tumor cell lines, or cells derived from patient bone marrow or lymph nodes, and a variety of fresh or immortalized bone-marrow stromal cells, mesenchymal cells, and dendritic cells. [27-30] These models have been used to probe the interactions between the tumor and stromal cells and how they influence the behavior of each other, but they have also been used to test drug sensitivity. This study will evaluate the feasibility of using patient-derived follicular lymphoma cells isolated from bone marrow aspirates to be grown in simple and co-culture systems in order to evaluate sensitivity to venetoclax and ibrutinib.

2. STUDY OBJECTIVES

2.1. Phase I Study

2.1.1. Primary Objective

- To determine the recommended phase II doses of ibrutinib and venetoclax for combination in relapsed and refractory follicular lymphoma

2.1.2. Secondary Objective

- To determine the pharmacokinetics of ibrutinib and venetoclax when dosed in combination in relapsed and refractory follicular lymphoma

2.2. Phase II Study

2.2.1. Primary Objective

- To determine the efficacy of ibrutinib and venetoclax when combined in relapsed and refractory follicular lymphoma

2.2.2. Secondary Objective

- To determine the safety and tolerability of ibrutinib and venetoclax when combined in relapsed and refractory follicular lymphoma

2.3 Exploratory Objectives

- To evaluate mutations of resistance via next-generation sequencing to the regimen when administered in combination in relapsed and refractory follicular lymphoma
- To evaluate for an association between BCL-2 and other family member protein levels of expression and efficacy of the regimen

- To evaluate the feasibility of developing tumor cell cultures from bone marrow aspirates with lymphomatous involvement in order to better characterize activity of the combination

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

1. Relapsed or refractory, histologically confirmed follicular lymphoma, grade I, II, or IIIa which requires therapy defined by at least one of the following:

   o Constitutional symptoms

   o Cytopenias

   o High tumor burden (single mass > 7 cm, three masses > 3 cm, symptomatic splenomegaly, organ compression or compromise, ascites, pleural effusion)

   o Any other clinical indication for treatment per investigator discretion. For example, patients with masses that do not fulfill the above stated dimensions but require therapy as determined by treating physician are eligible.

2. Must have received at least one prior systemic therapy
3. All risk by FLIPI 0-5 factors (Appendix I)
4. Measurable disease

   Measurable disease must be present either on physical examination or imaging studies; non-measurable disease alone is not acceptable. Any tumor mass > 1.5 cm is acceptable.

   Lesions that are considered non-measurable include the following:

   - Bone lesions (lesions if present should be noted)
   - Ascites
   - Pleural/pericardial effusion
   - Lymphangitis cutis/pulmonis
   - Bone marrow (involvement by lymphoma should be noted)

5. Adequate hematologic function independent of transfusion and growth factor support for at least 3 weeks prior to screening unless attributable to disease. Defined as:
   - ANC $\geq$1000 cells/mm^3 (1.0 x 10^9/L).
     ANC > 500 cells/mm^3 is permissible if due to disease.
   - Platelet count $\geq$50,000 cells/mm^3 (50 x 10^9/L) unless attributable to disease.
     Platelet count $\geq$ 20,000 cells/mm^3 is permissible if due to disease.
   - Hemoglobin $\geq$8.0 g/dL.
6. Adequate hepatic and renal function defined as:

- Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN)

  Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 5 is permissible if due to disease.
- Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

  Bilirubin ≤3 x ULN is permissible if due to disease.
- Estimated Creatinine Clearance ≥50 ml/min (Cockcroft-Gault based on actual weight)

7. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.
8. Men and women ≥ 18 years of age.
9. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. (Appendix II)
10. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
11. Male and female subjects who agree to use highly effective methods of birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 30 days after the last dose of study drug

3.2. Exclusion Criteria

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

1. Chemotherapy, monoclonal antibody, or small molecule kinase inhibitor ≤21 days prior to first administration of study treatment
2. Prior exposure to a BTK or BCL-2 inhibitor.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib or venetoclax.
4. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects at risk for tumor lysis syndrome.
5. History of other malignancies, except:
   - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   - Adequately treated carcinoma in situ without evidence of disease.

6. Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration [>14 days] of > 20 mg/day of prednisone) within 28 days of the first dose of study drug.
7. Undergone an allogeneic stem cell transplant within the past 1 year.
8. Current or history of graft versus host disease
9. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
10. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
11. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
12. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
13. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
14. Known HIV infection
15. Active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
    - Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, hepatitis C antibody, must have a negative polymerase chain reaction (PCR) result for the respective disease before enrollment. Those who are PCR positive will be excluded.
16. Any uncontrolled active systemic infection.
17. Major surgery within 4 weeks of first dose of study drug.
18. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
19. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
20. Unable to swallow capsules or tablets or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
21. Concomitant use of warfarin or other Vitamin K antagonists.
22. Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (See Appendix VI)
23. High-grade transformation confirmed by biopsy.
24. Malabsorption syndrome or other condition precluding enteral route of administration.
25. Known CNS involvement by lymphoma

26. Erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome
27. Lactating or pregnant.
28. Unwilling or unable to participate in all required study evaluations and procedures.
29. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
30. Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the Child Pugh classification (class B or C)) (see Appendix X)

3.3 Inclusion of Women and Minorities

- Both men and women of all races and ethnic groups are eligible for this trial.
  - Inclusion of Women and Minorities:
  - It is the intent of Lombardi Comprehensive Cancer Center to enroll patients regardless of gender or race. Both men and women of all races and ethnic groups are eligible for this study. In the development of this protocol, the possibility of inherent gender or racial/ethnic differences in treatment response has been considered.

4. REQUIRED DATA

4.1. Screening Phase

To be completed within 14 DAYS before Cycle 1 Day 1:

- All blood work

To be completed within 28 DAYS before Cycle 1 Day 1

- Any radiologic study (e.g., PET, CT, or MRI) that is utilized for tumor measurement
- History and physical

4.2. Schedule of Events

Table 1: Schedule of Events

All scheduled visits during Cycle 1 can occur +/- 1 day.
All scheduled visits during Cycles 2-12 can occur +/- 3 days if necessary.
For patients who continue on therapy after Cycle 12, scheduled visits and associated testing will occur every 2 cycles (instead of every cycle) with even numbered cycles only (i.e. Cycle 14, 16, etc.) All scheduled visits for patients receiving treatment after Cycle 12 can occur +/- 7 days if necessary.

As the bone marrow biopsy and aspirate are not needed to determine eligibility for trial enrollment, this test has been removed from the screening phase of the study. The bone marrow procedures must be performed after the patient has been provided an official identification subject number, but before the administration of the first dose of study drugs on Cycle 1 Day 1. The bone marrow biopsy at enrollment may be waived per investigator discretion. If a patient achieves a complete response by imaging, a bone marrow biopsy should be performed to confirm a complete response.

	Prior to Cycle 1 Day	Cycle 1 D1, 8, 15, 22	Cycle 2-12 Day1	Even Numbered Cycles after C12	At time of restaging*	Follow-up**
TESTS & OBSERVATIONS						
History and progress notes	X	X	A	X	X	X
Medication History	X	X	A	X	X	
Physical examination	X	X	A	X	X	X
Pulse, blood pressure	X	X	A	X	X	X
Height	X					
Weight/body surface area	X	X	A			
Performance status	X	X	A	X	X	X
Tumor measurements	X	B	B	B	B	B
Solicited baseline abnormalities/ adverse events assessment	X	X	X			
LABORATORY STUDIES						
CBC, differential, platelets	X	X	A	X	X	X
CMP, CrCl (estimated)	X	X	A	X	X	X
Uric acid, LDH, Mg, Phos, Ca	X	X	A	C	C	C
β2-microglobulin	X					
Serum or urine βHCG‡	X		A			
HBsAg, HBsAb, HB core Ab	X					
HCV antibody, HIV	X					
PT/INR, PTT	X					
EKG	X	C	C	C	C	C
Pharmacokinetics		X				
CORRELATIVE STUDIES						
Caris Life Sciences MI Tumor Seek	D					E

BCL-2 Protein Assessment	D					E
Tumor cell cultures	D					
STAGING						
PET-CT	X				X	F
CT/MRI (neck/chest/abd/pelvis)	X					X
Bone marrow aspirate & biopsy	G				H	
Histologic review	X					I

* Restage during week 12 (cycle 3), week 24 (cycle 6), and during week 52 (cycle 13).

** After week 52 of cycle 13, follow up every 6 months for 2 years, then every 12 months until disease progression or for a maximum of 10 years from study entry. If the patient ends treatment for any reason other than disease progression, follow up every 6 months until disease progression or for a maximum of 10 years from study entry. If disease progresses, follow up annually for a maximum of 10 years from study entry.

In the phase II portion of the study, patients who achieve a complete remission and electively discontinue therapy after 24 cycles will have a more frequent follow up schedule of every 3 months for a 1 year after discontinuation. Follow up consists of physical exam, labs, and imaging. After 1 year, they then resume follow up every 6 months for 2 years, then every 12 months until disease progression or for a maximum of 10 years from study entry. Patients may resume therapy for progression of disease or at the discretion of the investigator within one year of discontinuing therapy. If the patient resumes therapy within this time frame, study assessments should be performed as per Cycle 2 and beyond with the original restaging schedule. Patients will continue therapy until progression of disease or unacceptable toxicity.

‡ For women of childbearing potential.

A May be performed within 48 hours of Day 1

B If accessible to physical examination, record measurements.

C PRN

D To be performed on bone marrow sample after patient determined eligible and enrolled in study, but prior to administration of study drugs on Cycle 1 Day 1. If bone marrow not sufficiently involved with lymphoma, patient should be referred for a biopsy for the correlative studies or recent biopsy of another affected area may be submitted. Lack of marrow involvement does not impact patient eligibility. (Section 10).

E At the time of progression or relapse

F In the phase II portion of the study, patients who achieve a complete remission may discontinue therapy after 24 cycles. These patients must undergo a PET-CT during Cycle 24 to confirm they are in a complete remission prior to discontinuation.

G The bone marrow biopsy must be performed prior to administration of study drugs on Cycle 1 Day 1. The results are not needed for treatment unless the only indication for treatment is lymphomatous involvement of the bone marrow. Obtain 10 cc of aspirate (5 cc in EDTA tube, 5 cc in yellow citrate tube) and three centimeters of core. One centimeter of core and 5 cc of aspirate in an EDTA tube will be submitted to pathology for standard assessment for lymphomatous involvement. One centimeter of core and 5 cc aspirate in yellow tube will be submitted to HTSR. One centimeter of core will be submitted to Caris Life Sciences. See Appendix XII regarding sample submission. The bone marrow biopsy may be waived at investigator discretion.

H If initially positive, repeat only in patients who are in CR by all other criteria. If marrow is negative on one restaging biopsy, no subsequent bone marrow exam need be performed unless lymphoma has progressed clinically at another site. If bone marrow is still positive on restaging biopsy, it should be repeated at yearly intervals until determined to be negative. If not performed at enrollment, patients should undergo a bone marrow biopsy if imaging indicates a CR.

I At time of progression or relapse, a biopsy of suspected area of involvement is recommended.

5. STUDY DESIGN

5.1. Overview of Study Design

This is a phase I/II study in which patients will be enrolled in a standard 3+3 design. Once the maximum tolerated dose (MTD) is determined amongst patients with relapsed or refractory grade 1-3a follicular lymphoma, there will be a 17-patient phase II study.

5.2. Treatment Plan

5.2.1 Phase I Study Treatment Plan

Patients will be treated with combination therapy of ibrutinib and venetoclax according to their assigned dose level cohort. Dose escalation is described in Table 2 and the paragraph below.

Each cycle is 28-days. Patients will be monitored for dose limiting toxicity (DLT) weekly during Cycle 1. Patients will receive the combination until progression or unacceptable toxicity. Patients will be followed during therapy through progression until next line of therapy. Questions regarding treatment should be directed to the Study Chair.

Table 2: Dose Level Cohorts

Dose Levels		
Dose Level	**Ibrutinib**	**Venetoclax**
0	420 mg	400 mg
1	560 mg	400 mg
2	560 mg	600 mg

*Dose Level 0 is the starting level dose

The MTD finding procedure starts at DL0. Three patients will initially be entered at this dose level.

- If 0/3 DLT is observed, dose escalation will continue to the next upper dose level.
- If ≥ 2/3 DLTs are observed, then the dose finding procedure will be terminated.
- If 1/3 DLT is observed, then 3 additional patients will be enrolled in the same dose level. If no DLT is observed from the additional 3 patients, then dose escalation will continue to the next upper dose level. If any DLT is observed from the 3 additional patients, then the

previously lower dose will be chosen as the MTD and the dose finding procedure will be terminated.

Dose escalation will be continued as per Table 2 until a dose with no more than 1/6 DLTs is found and is chosen as the MTD. Once the MTD is determined, there will be a 17-patient phase II study at this dose level.

The original design of this study included a Dose Level 3 of Ibrutinib 560 mg and Venetoclax 800 mg. After examining the pharmacokinetic data at Dose Level 2, which showed a significantly increased systemic plasma exposure to ibrutinib, it was determined not to proceed with Dose Level 3. One patient had initiated therapy at Dose Level 3 before the decision was made for closure.

5.2.2 Phase II Study Treatment Plan

Patients will be enrolled at the recommended phase II dose. Duration of therapy will depend on depth of response. Patients who achieve a complete remission may discontinue therapy after 24 cycles. These patients must undergo a PET-CT during Cycle 24 to confirm they are still in a complete remission prior to discontinuation. Patients who achieve a partial response will continue therapy until progression or unacceptable toxicity. Patients will be followed throughout the duration of therapy through progression until next line of therapy. Patients who achieve a complete remission and discontinue therapy after 24 cycles will be monitored closely per Table 1 and may be reinitiated on treatment within one year of discontinuation for either progression of disease or at the discretion of the treating physician.

Ibrutinib (capsules) and venetoclax (tablets) should be administered orally once daily at the same time. The capsules and tablets are to be taken at the same time each day with 8 ounces (approximately 240 mL) of water. The capsules and tablets should be swallowed intact and subjects should not attempt to open capsules or tablets or dissolve them in water. The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. All subjects must be trained to self-administer therapy orally 30 minutes after the completion of breakfast or the subject's first meal of the day. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Subject should not take extra capsules or tablets to make up the missed dose.

At study entry, patients will receive a Medication Calendar, and will be instructed on how to use the Medication Calendar. Study drugs will be dispensed to subjects in bottles at each visit. At monthly visits, the patient will bring the Medication Calendar to the clinic. All bottles of study medication (full, partial, and empty) should be brought to the clinic to compare with the Medication Calendar. The Medication Calendar for the previous month will be reviewed, and new Medication Calendar will be given to the patient (APPENDIX V). Unused study drugs

dispensed during previous visits must be returned to the site. Returned capsules and tablets must not be re-dispensed to anyone.

5.3. Prophylaxis and Management of Tumor Lysis Syndrome

5.3.1. Prophylaxis for Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents. Risk is highest for those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, and dehydration. Patients with bulky disease, defined as any lymph node ≥ 8 cm on the screening CT scan, and/or lymphocytosis due to circulating lymphoma cells, are considered at higher risk of TLS and must be hospitalized for more intensive monitoring during the initial dose of study drugs. Patients who do not present with bulky disease are not considered at higher risk for TLS and do not require hospitalization, but may be hospitalized per discussion with the investigator and Medical Monitor.

All patients must receive prophylaxis for TLS prior to the initiation of the first dose of the study drugs. Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2-3L/day starting 24-48 hours days prior to start of the study drugs and continued for at least 24 hours after the first does (for patients for whom volume overload is considered a significant risk, hospitalization should be considered).

- Administration of an agent to reduce uric acid, such as allopurinol 300 mg/day, orally beginning 72 hours prior to the first study drugs dose. Rasburicase IV should be administered (unless medically contraindicated) for those patients with elevated uric acid levels prior to treatment which is, defined as a value above the local laboratory ULN or 476 μmol/L. Agents should be given until normalization of serum uric acid and other laboratory evidence of TLS (e.g. elevated serum LDH levels).

- Laboratory results should be reviewed, and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of study drugs or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.

- Patients at higher risk of TLS will be hospitalized for initial study drugs dose.

- For patients at particularly high risk for TLS, as judged by the investigator, consideration may be given to starting at a lower dose of study drugs and increasing study drugs dose in a stepwise fashion in discussion with the Medical Monitor.

On the day of initial visit with administration of study drugs, serial vital sign assessments will be performed, and serum chemistry and hematology samples will be drawn prior to the dose of

study drugs and at 8 and 24 hours following the dose. The serum chemistry and hematology samples will be immediately sent to the laboratory and the investigator or designee must promptly review the results. Laboratory results from pre-dose samples must be reviewed prior to study drugs administration unless laboratory results from within the prior 24 hours have already been reviewed and do not require intervention. Laboratory values obtained prior to the dose of study drugs are to be used to determine whether a patient developed a change related to TLS. Laboratory results from the 24-hour post-dose assessments must be reviewed prior to receiving the dose of study drugs for that day.

Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix VII. Definitions of Laboratory and Clinical Evidence of Tumor Lysis Syndrome are listed in Appendix VIII. In addition:

- The next day's dose of venetoclax should be held. If electrolyte changes are resolved within 24-48 hours of the last dose, venetoclax should be resumed at the same dose.
- For any electrolyte changes requiring more than 48 hours to resolve, venetoclax should be resumed at a dose of 100 mg less than the last dose.
- For any events of clinical TLS, venetoclax should be resumed at a dose of 100 mg less than the last dose following resolution of the TLS.

5.3.2. Hospitalization

Patients at higher risk for TLS (any lymph node ≥ 8 cm and/or circulating lymphoma cells) must be hospitalized for the initial dose of study drugs. Hospitalization should also be considered for patients with creatinine clearance <80 mL/min, in discussion with the study chair, Dr. Ujjani. Hospitalization will begin the evening prior to the first dose of study drugs and continue for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn, and IV hydration should be started with a target of 150-200 cc/hr or as clinically appropriate. Laboratory results should be reviewed, and electrolyte values should not demonstrate clinically significant abnormalities prior to the first dose of study drugs, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. A nephrologist (or acute dialysis service) must be consulted/contracted on hospital admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Serial vital sign assessments will be performed, and TLS laboratory samples will be drawn prior to the first dose of study drugs at 8, 12, and 24 hours post-dose, additionally, hematology samples will be drawn at 8 and 24 hours post-dose. These samples are to be immediately sent to the laboratory and the investigator or designee must promptly review the results. Laboratory values obtained prior to the dose of study drugs are to be used to determine whether a patient

developed a change related to TLS. Patients are still considered eligible to initiate therapy on Cycle 1 Day 1 if their hematologic parameters have dropped below eligibility requirements due to aggressive intravenous hydration. Laboratory results from the 24-hour post-dose sample must be reviewed prior to receiving the dose of study drugs for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix VII. Reintroduction of venetoclax in these patients should be performed as described in Section 5.3.1.

5.4. Pharmacokinetics

5.4.1. Objective

Steady-state plasma concentrations of ibrutinib, PCI-45227, and venetoclax after therapy administration will be determined on all patients enrolled during Phase I portion of the study on Cycle 1 Day 1.

5.4.2. Methods

Blood specimens for ibrutinib

Pharmacokinetic venous blood samples for ibrutinib (3 mL) will be collected pre- and post-administration (Section 5.4.3) in a green top tube. Blood specimens will be processed promptly, and plasma separated, frozen and stored. Plasma will be split into 2 cryovials (0.5 mL each). The tubes will be ultimately transported to Frontage Laboratories, Inc. See Appendix X for further details.

Frontage Laboratories, Inc.,
ATTENTION: [redacted]
Sample Coordinator
700 Pennsylvania Drive
Exton, PA 19341
[redacted]

Blood specimens for venetoclax

The blood samples for venetoclax will be collected in 3 mL evacuated potassium EDTA (K2 EDTA)-containing collection tubes pre- and post-administration (Section 5.4.3). Sufficient blood will be collected to provide approximately 1 mL plasma from each sample. Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath or cryoblock until centrifuged. The blood samples for venetoclax will be centrifuged at approximately 1100 – 1600 × g for 10 – 15 minutes using a refrigerated centrifuge (2° to 8°C) to separate the plasma within 1 hour of collection. The plasma samples will be transferred using plastic pipettes into screw-capped polypropylene tubes (Greiner # 122263-2DG) labeled with the drug name (Venetoclax), type of sample (plasma), the protocol number, the subject number, the study period and/or study day, and the planned

time of sampling relative to dosing. The plasma samples will be placed in a freezer within 2 hours of collection and maintained and at –20°C or colder until transferred to AbbVie.

Abbvie, Inc.
Attn: Sample Receiving
Dept. R43F, Bldg. AP13A, Room 2310
c/o: AbbVie Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL USA 60085
[redacted]

Measurement of plasma concentrations
Plasma concentrations of ibrutinib, PCI-45227, and venetoclax will be determined using validated liquid chromatography followed by tandem mass spectrometry (HPLC-MS/MS) methods.

Pharmacokinetic parameter estimation
The plasma concentration-time profiles will be analyzed using non-compartmental analysis. The following pharmacokinetic parameters will be calculated, whenever possible: area under the plasma concentration-time curve from time 0 to 24 hours (AUC(0-24)), area under the plasma concentration-time curve from time 0 to infinity (AUC(0-inf)), peak concentration (Cmax), time to reach the maximum concentration (Tmax), elimination half-life (T1/2), accumulation factor R to the PK parameters (e.g., Cmax and AUC), and metabolite-to-parent AUC ratio. Additional parameters including CL/F and Vd/F for ibrutinib may be calculated as appropriate.

5.4.3. Schedule

Table 3: Pharmacokinetic Sampling Schedule

Cycle	Day	Predose[b]	Time after ibrutinib and venetoclax dosing[a]			
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h (± 1 h)
1	1	X	X	X	X	X
1	2	X				
1	15	X	X	X	X	X

a. Record actual time of sample collection.
a. Ibrutinib will be dosed at the same time as venetoclax.
b. Samples for ibrutinib and venetoclax on Cycle 1 Day 15 should be collected approximately 24 (± 2 h) hours after previous study dose and before administration of study drugs

Refer to the instructions on collecting and processing PK samples (Section 5.4.2.). On the day of the sampling visit, the clinical staff will instruct the subject to not take ibrutinib and venetoclax before arrival at the clinic. Study drug intake will be observed and recorded by clinic staff. The actual time (versus requested time) that each PK sample is drawn must be recorded in the using a 24-hour format.

6. MODIFICATIONS AND MANAGEMENT OF TOXICITY

6.1. 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 or venetoclax. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day) of ibrutinib. In a separate study 1 healthy subject who received a dose of 1,680 mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). Refer to the IB for additional details about this case. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 13.3 for further information regarding special reporting situations as a result of overdose.

6.2. Dose Modification for Adverse Reactions

The dose of study drugs should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities occur:

- Grade $\geq$ 3 non-hematologic toxicity
- Grade 4 hematologic toxicity, except grade 4 neutropenia $\leq$ 7 days
- Grade 3 thrombocytopenia (<50,000/µL) in the presence of clinically significant bleeding
- Grade $\geq$ 3 neutropenia with infection or fever
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation. (See section 7.2.4)

If the dose of ibrutinib or venetoclax is reduced, at the investigator's discretion, the dose of ibrutinib or venetoclax may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

In patients with persistent and/or problematic Grade 1/2 non-hematologic adverse events such as fatigue, diarrhea, or nausea, the dose of study drugs can be reduced by one dose level at the discretion of the study investigator. The dose of study drugs may be re-escalated after 2 cycles of a dose reduction at discretion of the study investigator. If there is a recurrence of the prior toxicity, the patient will return to and remain on the lower dose. Dose changes must be recorded in the Dose Administration eCRF.

Table 4. Ibrutinib and Venetoclax Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drugs until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drugs until recovery to Grade ≤1 or baseline; Ibrutinib should be reduced by 140 mg per day and Venetoclax should be reduced by 100 mg
Third	Withhold study drugs until recovery to Grade ≤1 or baseline; Ibrutinib should be reduced by 140 mg per day and Venetoclax should be reduced by 100 mg
Fourth	Discontinue study drug

****See Section 7 regarding permissible concomitant medications, include growth factor support and CYP3A inhibitors.**

6.2.1.1. Leukocytosis/Leukostasis

A high number of circulating malignant cells (>400,000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib may be temporarily held, and investigator should be contacted. Venetoclax should be continued in the setting of leukocytosis/leukostasis.

6.2.1.2. Dose Modification for Subjects with Hepatic Impairment

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section **Error! Reference source not found.**. Ibrutinib is metabolized in the liver. In the population PK analysis (1,202 subjects), 179 subjects (14.9%) had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. In a hepatic impairment study, data showed an increase in ibrutinib exposure. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily. For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140mg daily. Monitor subjects for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment Subjects with clinically significant chronic hepatic impairment at the time of

Screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to Table 3 for dose modifications due to hepatic impairment.

Table 5. Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.

** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

7. CONCOMITANT MEDICATIONS/PROCEDURES

7.1. 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 red blood cell growth factors (erythropoietin) is permitted while on therapy per institutional policy and in accordance with the ASCO guidelines. [31] Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

If clinically indicated, antimicrobial prophylaxis can be considered. Consider drug-drug interactions before initiating an agent. (Appendix V) Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects, therefore Bactrim

(trimethoprim sulfamethoxazole) can be considered for Pneumocystis prophylaxis, with close clinical monitoring.

After consultation with the investigator the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

7.2. Medications to be used with caution

7.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and strong CYP3A inhibitors should be avoided. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 6.

Table 6. Ibrutinib Dose Modification Guidance for Co-Administration with CYP3A Inhibitors

Patient Population	Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole 200mg twice daily Posaconazole suspension 100mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

a. Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (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).

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib.

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

A list of common CYP3A inhibitors and inducers is provided in Appendix VI. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Venetoclax should be administered using caution with weak CYP3A4 inducers and inhibitors. If a moderate CYP3A inhibitor must be used, venetoclax should be dose reduced by at least 50%. Venetoclax can be resumed at the normal dose 3 days after discontinuance of the moderate CYP3A inhibitor.

This website is continually revised and should be checked frequently for updates. For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

7.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib or Venetoclax

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib or venetoclax. If a P-gp inhibitor must be used with venetoclax, venetoclax should be dose reduced by at least 50%.

7.2.3. QT Prolonging Agents

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

7.2.4. Antiplatelet Agents and Anticoagulants

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

7.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

Due to drug-drug interactions, strong CYP3A inhibitors and inducers should not be administered with venetoclax or ibrutinib. (See Appendix V).

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment.

7.4. Guidelines for Ibrutinib and Venetoclax Management with Surgeries or Procedure

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

- **Minor Surgical Procedures**

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

- **Major Surgical Procedures**

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

8. DEFINITION OF DOSE LIMITING TOXICITY

Assessment of DLT will be defined as any non-hematologic or hematologic toxicity listed below that occurs during the first cycle of treatment. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Patients will be included in the DLT assessment as long as they have received at least 85% of planned doses of each drug or have experienced a DLT any time after the 1st dose. For each patient who did not receive ≥85% of therapy, another patient will be enrolled at that dose level.

8.1. Non-hematologic toxicity

Non-hematologic toxicity will be defined as any of the following:

- Any Grade 3 or 4 non-hematologic toxicity except
  - Grade 3 fever without neutropenia
  - Grade 3 fatigue
  - Anorexia
  - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring prolonged hospitalization
- Failure of any Grade 3 or 4 fever without neutropenia, fatigue, anorexia, nausea, vomiting, or diarrhea to resolve or recover to baseline level after delaying the next dose by more than 2 weeks
- Any treatment-related death

8.2. Hematologic Toxicity

All subjects, regardless of baseline hematologic status (i.e. neutrophil and platelet counts), will be included in the DLT assessment. Hematologic toxicity will be defined as any of the following:

- Any Grade 4 hematologic toxicity, except for Grade 4 neutropenia $\leq$ 5 days
- Grade 4 neutropenia > 5 days
- Grade 3 or 4 neutropenia complicated by fever $\geq$ 38.5°C or infection
- Grade 4 thrombocytopenia (must be repeated same day by a separate peripheral blood draw to confirm toxicity), that is considered a treatment emergent adverse event
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 2 thrombocytopenia with clinically significant bleeding felt to be drug related
- Grade 4 anemia unexplained by underlying disease

9. DRUG FORMULATION, AVAILABILITY, AND PREPARATION

9.1. Ibrutinib

Availability

Ibrutinib is supplied as hard gelatin capsules containing micronized ibrutinib and the following excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and may contain magnesium stearate. Capsules are available 140 mg strength size 0, gray, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 120 capsules.

Storage and Stability

Ibrutinib Hard Gelatin Capsules should be stored at 15 – 25°C. Shelf life surveillance of the intact bottles is ongoing.

Administration

Ibrutinib is taken orally, around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact.

The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (see Appendix V).

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

9.2. Venetoclax

Availability

The venetoclax tablets will be packaged in high-density polyethylene (HDPE) plastic bottles or blister packs to accommodate the study design. Each container will be labeled per local

regulatory requirements. Venetoclax is available in tablets of 100 mg consisting of light yellow to dark yellow powder.

Storage and Stability

The clinical supply should be stored at 15° to 25°C (59° to 77°F).

Administration

The tablets are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The tablets should be swallowed intact and subjects should not attempt to open tablets or dissolve them in water. All subjects will be trained to self-administer venetoclax orally QD 30 minutes after the completion of breakfast or the subject's first meal of the day.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

10. CORRELATIVE SCIENCE COMPANION STUDY

10.1. Next-Generation Sequencing

Next generation sequencing via the MI TumorSeek™ will be performed on bone marrow aspirate samples from eligible patients, prior to initiation of targeted therapy. MI TumorSeek™ is a 596 gene Next-Generation Sequencing Cancer Service available through Caris Life Sciences. Patients will undergo a bone marrow core biopsy and aspirate prior to initiation of therapy. One 1-cm core biopsy will be submitted to Caris Life Sciences in 50 mL of 10 % neutral buffered formalin overnight. If the patient is found to have greater than 20% involvement with FL in their bone marrow sample by standard hematopathology review, MI TumorSeek™ analysis will be performed on the submitted sample through Caris Life Sciences. If the patient lacks greater than 20% lymphomatous involvement of their bone marrow, they will be recommended to undergo a biopsy of an affected lymph node or other disease-involved area as determined by pretreatment staging PET-CT. The MI TumorSeek™ assay will be repeated on new tissue samples from patients who initially achieve a partial or complete remission and subsequently progress. Special focus will be placed on BTK and BCL-2, including variants of unknown significance, as well as PI3K, as idelalisib is an FDA approved PI3Kδ inhibitor the patient may have received previously or will subsequently receive.

10.2. BCL-2 Family Proteins

Levels of expression of various BCL-2 family member proteins will be assessed on tumor samples from patients prior to treatment, on bone marrow biopsy samples after achieving a complete response, and tumor samples at progression. Assessments will be performed on bone marrow biopsy core samples of patients with lymphomatous involvement. One centimeter of the core biopsy will be submitted to the Lombardi Comprehensive Cancer Center

Histopathology and Tissue Shared Resource (HTSR) for processing. The presence of tumor will be assessed by H&E. Sections will be stained by the HTSR for BCL-2 family proteins including BCL-2, MCL-1, BIM, and BCL-XL. The stained slides will be subsequently transported to the Department of Pathology for H-score assessment of individual BCL-2 family member proteins. Samples will be reviewed independently by two hematopathologists (Metin Ozdemirli, MD; Bhaskar Kallakury, MD). If the bone marrow is not involved, the patient may be recommended to undergo a biopsy of an affected lymph node or other disease-involved area as determined by pretreatment staging PET-CT. Alternatively, if tissue is already available from a recent biopsy of an affected area, it may be submitted. These patients will only undergo a follow up biopsy if they experience a progression on study.

10.3. Tumor Cell Cultures

The cell culture studies will be conducted in the laboratory of Dr. Michael Johnson, who has recently established similar primary co-culture models with other B-cell malignancies. Bone marrow aspirates will be assessed for tumor cell content as described above and processed by ficoll-gradient centrifugation. Five milliliters of aspirate will be collected in a yellow citrate tube. Depending on tumor cell percentage, the cells may be enriched by depletion of CD3, CD14, and CD16 positive cells with magnetic beads or used directly after assessment of viability and cell number. A variety of co-culture systems will be tested initially including culture with the follicular dendritic cell-like cell line HK, the immortalized mesenchymal stromal cell line HS-5, and primary bone marrow-derived mesenchymal stromal cells. [28-30] The tumor cells will be plated in IDEM, or α-MEM supplemented with 10%FBS on mono-layers of un-modified or irradiated co-culture cells plated in wells. Tumor cell viability and proliferation will be assessed at various periods after culture by EdU-Click-IT-Alexa Fluor labeling assay and colorimetric vital dye assay. Drug sensitivity assays will be done in a similar fashion by treating wells of co-cultured cells with various concentrations of venetoclax and ibrutinib alone and in combination for 24 hours followed by staining the cells with CD19 to mark the tumor cells and Calcine AM to assess viability, followed by quantification using a custom MetaMorph macro.

11. SUBJECT COMPLETION AND WITHDRAWAL

11.1. Completion

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and the sponsor. The investigator will provide a final report to the IEC/IRB following conclusion of the study. The investigator must retain any records related to the study according to local requirements. The end-of-study is defined as the date of the last subject's last visit.

11.2. Withdrawal from Study Treatment

Each subject has the right to withdraw from the study at any time. In addition, the investigator will discontinue a subject from the study at any time if the investigator considers it necessary for any reason including:

- The investigator believes it is in the best interest of the subject;
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug;
- The subject requires radiotherapy, cancer-related surgery as a result of tumor progression, or alternate anti-neoplastic agents during the study period;
- Noncompliance with the protocol;
- Unacceptable adverse event(s), or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

If, at any time the constraints of this protocol are detrimental to the patient's health and/or patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair
- Document the reason(s) for discontinuation of therapy in the study record.
- Follow the patient for relapse, progression, survival, and secondary malignancies or new primaries.

12. STATISTICAL METHODS AND ANALYSIS

This is a phase I/II study in which patients will be enrolled in a standard 3+3 design. Once the maximum tolerated dose is determined, there will be a 17-patient phase II study.

12.1. Phase I study

The maximum tolerated dose (MTD) finding procedure uses the traditional 3+3 cohort method, starting from dose level 0. A dose level will be chosen as the MTD if it has 6 patients, and number of observed DLT is 0 or 1. The MTD is also known as the recommended phase II dose.

Three patients will be enrolled at Dose Level 0 (DL0). Patients will be assessed for DLTs during Cycle 1.

Three patients will initially be entered at DL0.

- If 0/3 DLT is observed, dose escalation will continue to the next upper dose level.
- If ≥ 2/3 DLTs are observed, then the dose finding procedure will be terminated.
- If 1/3 DLT is observed, then 3 additional patients will be enrolled in the same dose level.

  If no DLT is observed from the additional 3 patients, then dose escalation will continue to

the next upper dose level. If any DLT is observed from the 3 additional patients, then the previously lower dose will be chosen as the MTD and the dose finding procedure will be terminated.

Dose escalation will be continued as per Table 2 until a dose with no more than 1/6 DLTs is found and is chosen as the MTD.

12.2. Phase II Study

Once the MTD, also the known as the recommended phase II doses are determined, the phase II portion of the study will open to potentially 17 patients with relapsed or refractory follicular lymphoma at this dose level. A Simon's Minimax 2-stage design will be used to test the null hypothesis that the response rate is at most 30% against an alternative response rate of 60% (a desirable rate). This design assumes that current individual therapies for this group of patients would have response rate about 30% and it is hoped that the Ibrutinib and Venetoclax would improve the response rate to 60% or more. In Stage 1, 10 patients will be enrolled. The study will proceed to Stage 2 if there are 3 or more responders, otherwise the study will be stopped for futility. In Stage 2, an additional 7 patients will be enrolled for a total of 17 patients and we would accept Ibrutinib and Venetoclax for further studies if there are at least 9 responders out of 17 patients. This design would have 80% statistical power for detecting the advantage in response rate for Ibrutinib and Venetoclax at a statistical significance level of 5% (one-sided). If the combination of Ibrutinib and Venetoclax is actually not effective, there is a 0.04 probability of concluding that it is (targeted value is 0.05). If the combination is actually effective, there is a 0.199 probability of concluding that is not (the targeted value is 0.2).

The 17 patients for the phase II portion will include the FL patients who are treated at the MTD level in phase I and who satisfy the phase II enrollment criteria.

Descriptive statistics (mean, median, n, min, max, std, etc.) will be used to summarize patients' demographics as well as prognostic information. Complete response rate and overall response rate will be estimated for each dose level as per the revised Lugano Response Criteria for Non-Hodgkin Lymphoma with their 90% exact Binomial confidence intervals (Appendix VI). [24] Progression-free survival (defined as time between enrollment and disease progression or death) and overall survival (defined as time between enrollment and death) with their 95% confidence intervals will be estimated by Kaplan-Meier method for the whole number of patients in this study and at the MTD.

12.3. Toxicity Evaluation

Ineligible patients will be replaced by new eligible patients during both phases of the study and will be excluded in the data analysis. Ineligible patients are defined as patients who were initially believed to be eligible, but with full screening have been found to be ineligible. Toxicity (attribute and grade) will be summarized for each dose level as per the NCI Common

Terminology Criteria for Adverse Events (CTCAE Version 4.03) for all patients who receive at least one dose of study treatment.

12.4. Target Accrual and Study Duration

The real sample size of this study is variable. The minimum required sample size is 6, but this number may change based on the number of DLTs experienced by patients during the phase I portion of the study. The maximum samples size will be 35 patients (= 3 dose levels x 6 patients + 17 patients for expansion). The patient accrual will be closed as soon as the MTD is found and the phase II expansion is completed. We will have conference calls every 2 weeks with all sites with patients enrolled to discuss toxicity in individual cases. The safety data of all patients will be reviewed during the biweekly conference calls, and the stopping rule for the 3+3 cohort scheme will be applied.

The estimated accrual rate is about 2 patients per month. As a result, it will take about 13 months to find and expand the MTD. However, observation of PFS will require longer follow-up. A maximum of 10 years of follow-up is required for all patients. Once the targeted number of patients has been accrued to this study, a notice suspending accrual will be issued to the Group via email broadcast announcing permanent termination of patient accrual within 14 days.

12.5. Correlative Science Statistical Considerations

12.5.1. Mutations of Resistance

The frequency table will be used to summarize patients' clinical outcome status (partial or complete remission and progression). Fisher's Exact test will be used to assess the relationship between the clinical outcomes and the occurrence of new mutations or alterations in the genome.

12.5.2. BCL-2 Family Proteins

Descriptive statistics (including mean, median, std, min, max) will be used to summarize the H-score assessment of individual BCL-2 family member proteins. The H-score will then be categorized, and Fisher's Exact test will be used to explore its relationship with varying expression of BCL-2 family member proteins.

12.5.3. Tumor Cell Cultures

Evaluate for possible correlations between in vitro sensitivity, patient response, the pattern of BCL-2 family member expression, and the spectrum of gene mutations identified by NGS.

13. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

13.1. Definitions

13.1.1. Adverse Events

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

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

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

Adverse events may include, but are not limited to:

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

The following are NOT considered AEs:

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

- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures

13.1.2. Serious Adverse Events

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 subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the IND Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.

- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).

- Is a congenital anomaly/birth defect.

- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, however, the event will be considered expected for the purpose of determining expedited reporting requirements to regulatory authorities. If the cause of death is unknown at the time of reporting, "unexplained death" should be recorded on the eCRF. If the cause of death

later becomes available "unexplained death" should be replaced by the established cause of death.

For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, but the event will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

13.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be used for grading the severity (intensity) of adverse events. The CTCAE version 4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE version 4.03, 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 subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

13.1.4. 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:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Related: The AE is clearly related to use of the investigational product.

13.2. Unexpected Adverse Events

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.

13.3. Special Reporting Situations

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

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

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

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

13.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

13.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

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

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

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

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

13.4.3. 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.

Pharmacyclics

All Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), and Special Reporting Situations (SRSs) (initial and follow-up information) should be reported to the Pharmacyclics Drug Safety team. All notifications should be sent via email (preferred method) or fax to the following inbox: [redacted]

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 reported to Pharmacyclics Drug Safety, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics Drug Safety, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

AbbVie

Adverse Events; Pregnancy. In addition to compliance with all FDA reporting requirements pursuant to 21 C.F.R. § 312, the Principal Investigator shall:

a) Report to Abbvie all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition, report all non-serious adverse events of tumor lysis syndrome for studies involving ABT-199.

b) Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and

c) Notify AbbVie upon any subject receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be [redacted]

13.4.4. Other Malignancies

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

13.4.5. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 15 days of awareness.

Major hemorrhage is defined as any of the following:

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

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

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

Tumor lysis syndrome

Tumor lysis syndrome is an important identified risk for Venetoclax, especially in CLL indications. For active surveillance and continual characterization of the safety concern, both non-serious and serious events of TLS are requested to AbbVie.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be [redacted].

13.5. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email ([redacted]) or fax [redacted]) to Pharmacyclics Drug Safety within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

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

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

14. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

14.1. Regulatory and Ethical Compliance

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an Institutional Review Board (IRB). The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guideline governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP. Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

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

14.2. Enrollment

Enrollment must occur prior to the initiation of therapy. Enrollment to the optional correlative science companion studies will be performed at the time enrollment occurs to the treatment study. Enrollment to both the treatment study and the correlative studies will not be completed if eligibility requirements are not met for both trials. The multicenter clinical trial project

manager must be contacted by the site regarding each potential patient (email: [redacted]). Eligibility will be confirmed by Lombardi CCC quality assurance office (email: [redacted]).

14.3. Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedure and the subject received a signed copy.

14.4. Case Report Forms and Record Maintenance

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the RAVE system. All data entered into eCRF will be supported by source determination.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

14.5. Publication of Study Results

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

14.6. Study Discontinuation

Per the IST Contract, the Investigator reserves the right to terminate the study at any time. Should this be necessary, both the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

14.7 Data and Safety Monitoring

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator-initiated study Phase I/II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high-risk study which requires real-time monitoring by the PI and study team and review every 4 months by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution-based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must

be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

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APPENDIX I REFERENCE SAFETY INFORMATION FOR IBRUTINIB

Table 21: Serious Adverse Reactions for Ibrutinib Considered Expected for Safety Reporting Purposes (RSI Study Pool)

System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=3597)		Synonymous Medical Terms by Preferred Term[b]
		Frequency n (%)	Frequency Category[a]	
Blood and lymphatic system disorders	Febrile neutropenia	122 (3.4%)	Common	N/A
	Leukocytosis	3 (0.1%)	Uncommon	White blood cell count increased
	Neutropenia	33 (0.9%)	Uncommon	N/A
	Neutrophil count decreased	8 (0.2%)	Uncommon	N/A
	Thrombocytopenia	26 (0.7%)	Uncommon	Platelet production decreased
	Platelet count decreased	4 (0.1%)	Uncommon	N/A
Cardiac disorders	Atrial fibrillation	75 (2.1%)	Common	N/A
	Ventricular tachycardia	2 (0.1%)	Uncommon	N/A
Gastrointestinal disorders	Diarrhoea	48 (1.3%)	Common	Frequent bowel movements
	Nausea	10 (0.3%)	Uncommon	N/A
	Stomatitis	9 (0.3%)	Uncommon	Aphthous ulcer
	Vomiting	13 (0.4%)	Uncommon	N/A
General disorders and administration site conditions	Oedema peripheral	3 (0.1%)	Uncommon	N/A
	Pyrexia	50 (1.4%)	Common	Hyperthermia, Body temperature increased
Infections and infestations	Atypical pneumonia	2 (0.1%)	Uncommon	N/A
	Bacteraemia	3 (0.1%)	Uncommon	N/A
	Bacterial sepsis	3 (0.1%)	Uncommon	N/A
	Bronchopulmonary aspergillosis	7 (0.2%)	Uncommon	N/A
	Cellulitis	15 (0.4%)	Uncommon	Skin bacterial infection, Soft tissue infection
	Enterococcal sepsis	2 (0.1%)	Uncommon	N/A
	Erysipelas	2 (0.1%)	Uncommon	N/A
	Lung abscess	2 (0.1%)	Uncommon	N/A
	Lung infection	26 (0.7%)	Uncommon	Lower respiratory tract infection, Respiratory tract infection
	Neutropenic sepsis	5 (0.1%)	Uncommon	N/A
	Pneumocystis jirovecii pneumonia	10 (0.3%)	Uncommon	N/A
	Pneumonia	150 (4.2%)	Common	N/A
	Pneumonia bacterial	8 (0.2%)	Uncommon	N/A

Table 21: Serious Adverse Reactions for Ibrutinib Considered Expected for Safety Reporting Purposes (RSI Study Pool)				
System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=3597)		Synonymous Medical Terms by Preferred Term[b]
	Pneumonia fungal	2 (0.1%)	Uncommon	N/A
	Pneumonia haemophilus	3 (0.1%)	Uncommon	N/A
	Pneumonia klebsiella	3 (0.1%)	Uncommon	N/A
	Pneumonia pseudomonal	2 (0.1%)	Uncommon	N/A
	Pneumonia viral	2 (0.1%)	Uncommon	N/A
	Pseudomonal sepsis	2 (0.1%)	Uncommon	N/A
	Pulmonary tuberculosis	2 (0.1%)	Uncommon	N/A
	Sepsis	26 (0.7%)	Uncommon	N/A
	Septic shock	12 (0.3%)	Uncommon	N/A
	Skin infection	2 (0.1%)	Uncommon	N/A
	Staphylococcal sepsis	2 (0.1%)	Uncommon	Staphylococcal bacteraemia
	Streptococcal bacteraemia	2 (0.1%)	Uncommon	Streptococcal sepsis
	Upper respiratory tract infection	8 (0.2%)	Uncommon	N/A
	Urinary tract infection	19 (0.5%)	Uncommon	N/A
	Urosepsis	3 (0.1%)	Uncommon	N/A
Injury, poisoning and procedural complications	Subdural haematoma	12 (0.3%)	Uncommon	Subdural haemorrhage
	Hematoma	2 (0.1%)	Uncommon	N/A
Metabolism and nutrition disorders	Tumour lysis syndrome	10 (0.3%)	Uncommon	N/A
Musculoskeletal and connective tissue disorders	Arthralgia	4 (0.1%)	Uncommon	N/A
	Myalgia	7 (0.2%)	Uncommon	Musculoskeletal pain, Musculoskeletal discomfort
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Basal cell carcinoma	3 (0.1%)	Uncommon	N/A
Nervous system disorders	Cerebrovascular accident	4 (0.1%)	Uncommon	N/A
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	10 (0.3%)	Uncommon	Alveolitis, Hypersensitivity pneumonitis, Diffuse alveolar damage
	Pneumonitis	7 (0.2%)	Uncommon	N/A
	Epistaxis	2 (0.1%)	Uncommon	N/A
Skin and subcutaneous tissue disorders	Rash	2 (0.1%)	Uncommon	N/A
	Rash maculo-papular	6 (0.2%)	Uncommon	N/A

Table 21: Serious Adverse Reactions for Ibrutinib Considered Expected for Safety Reporting Purposes (RSI Study Pool)

System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=3597)		Synonymous Medical Terms by Preferred Term[b]
Vascular disorders	Hypertension	5 (0.1%)	Uncommon	Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Systolic hypertension, Diastolic hypertension

N/A: not applicable; SAR: serious adverse reaction.

n: number of subjects who experienced a SAR assessed as related.

PTs are coded according to MedDRA version 22.0

[a] Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), based on percentages rounded to 1 decimal place.

[b] These events would not be subject to expedited reporting.

APPENDIX II FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

Follicular Lymphoma International Prognostic Index (FLIPI)
(abstracted from Solal-Céligny et al. Blood. 2004; 104(5):1258-65) [9]

Risk Group	Number of Risk Factors*
Low Risk	0-1
Intermediate Risk	2
High Risk	≥ 3

*** Risk Factors include:**

- Age > 60
- Ann Arbor Stage III-IV
- Number of nodal sites > 4
- Serum LDH > upper limit of normal
- Hemoglobin < 12 g/dL

Follicular Lymphoma International Prognostic Index 2 (FLIPI2)
(abstracted from Federico et al. JCO. 2009) [11]

Risk Group	Number of Risk Factors*
Low Risk	0
Intermediate Risk	1-2
High Risk	3-5

*** Risk Factors include:**

- Age > 60
- Bone marrow involvement
- Longest diameter of the largest involved node > 6 cm
- β2-microglobulin > upper limit of normal
- Hemoglobin < 12 g/dL

APPENDIX III ECOG PERFORMANCE SCALE

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX IV COCKCROFT- GAULT FORMULA FOR ESTIMATED CREATININE CLEARANCE

For Serum Creatinine Concentration (SrCr) in mg/dL[a]

$$\text{CrCl(mL/min)} \quad \frac{(140 - \text{age})\ (\text{weight})^{b}}{(72)\ (\text{SrCr})}$$

FOR FEMALES, USE 85% OF CALCULATED CR_{CL} VALUE.

a Age in years and weight in kilograms
b Use actual weight

APPENDIX V MEDICATION CALENDAR

PATIENT MEDICATION DIARY

Today's date _____ **Agents: Ibrutinib and Venetoclax**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **ibrutinib and venetoclax**.
2. You will take ibrutinib and venetoclax drugs every day.
3. Record the date, the number of capsules and tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. If you miss a dose of ibrutinib and/or venetoclax, you should take it as soon as you remember, as long as it is on the same day. You should not take two doses of the same drug on the same day.
6. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken of Ibrutinib	# of tablets taken of Venetoclax	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					

17					
Day	**Date**	**Time of daily dose**	**# of capsules taken of Ibrutinib**	**# of tablets taken of Venetoclax**	**Comments**
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's dose cohort _____
4. Total number of capsules and tablets taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature

_____

APPENDIX VI DRUGS TO BE AVOIDED OR USED WITH CAUTION

PROHIBITED MEDICATIONS

Warfarin (Coumadin)
Biologic agents
Anticancer therapy
Other investigational agents
Steroid therapy for anti-neoplastic intent

CYP3A Strong Inhibitors
Atazanavir
Clarithromycin
Itraconazole
Fluvoxamine
Nefazodone
Nelfinavir
Ritonavir
Saquinavir
Telithromycin
Voriconazole
Ketoconazole
Boceprevir
Cobicistat
Conivaptan
Indinavir
Lopinavir
Mibefradil
Posaconazole
Telaprevir
Troleandomycin

CYP3A Moderate Inhibitors
Fluconazole
Aprepitant
Erythromycin
Diltiazem
Verapamil
Amprenavir
Atazanavir
Ciprofloxacin
Crizotinib
Darunavir
Dronedarone
Fosamprenavir
Imatinib
Grapefruit juice
Seville orange juice

CYP3A Strong Inducers
Avasimibe
Carbamazepine
Mitotane
Modafinil
Phenobarbital
Phenytoin
Rifabutin
Rifampin
St. John's Wort

CYP3A Moderate Inducers
Bosentan
Efavirenz
Etravirine
Modafinil
Nafcillin
Oxcarbazepine
Troglitazone

MEDICATIONS TO USE WITH CAUTION

CYP3A Weak Inducers
Armodafinil
Clobazam
Pioglitazone
Glucocorticoids such as prednisone
Rufinamide
Nevirapine
Pioglitazone
Vemurafenib

CYP3A Weak inhibitors
Alprazolam
Amlodipine
Atorvastatin
Cimetidine
Ranitidine
Amiodarone
Bicalutamide
Cilostazol
Cyclosporine
Fluvoxamine
Fluoxetine
Ginkgo
Goldenseal
Isoniazid
Nilotinib
Oral contraceptives
Pazopanib
Ranitidine
Ranolazine
Suboxone
Tipranavir
Ticagrelor
Zileuton

Note that this is not an exhaustive list. Further information can be found at the following websites:
http://medicine.iupui.edu/clinpharm/ddis/main-table/

and

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

APPENDIX VII LUGANO REVISED RESPONSE CRITERIA FOR NON-HODGKIN LYMPHOMA [32]

Site	PET-CT- Based Response	CT-Based Response
Complete Response	**Complete metabolic response**	**Complete radiologic response** (all of the following):
Lymph nodes & extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5-point scale	Target nodes/nodal masses must regress ≤ 1.5cm in longest transverse diameter of a lesion (LDi); no extralymphatic sites of disease
Non-measured lesion	NA	Absent
Organ enlargement	NA	Regress to normal
New Lesions	None	None
Bone Marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, and flow cytometry IHC negative
Partial Response	**Partial metabolic response**	**Partial remission** (all of the following):
Lymph nodes & extralymphatic sites	Score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. No new or progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings indicate residual disease.	≥50% decrease in SPD of up to 6 target measurable node & extranodal sites. When a lesion is too small to measure on CT, assign 5x5mm as the default value; when no longer visible, 0x0 mm. For a node >5x5mm, but smaller than normal, use actual measure for calculation.
Non-measured lesion	NA	Absent/normal, regressed but no increase
Organ enlargement	NA	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 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.	NA

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular

to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions; NA, Not applicable

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
Non-measured lesion	NA	No increase consistent with progression
Organ enlargement	NA	No increase consistent with progression
New lesions	None	None
Bone Marrow	No change from baseline	NA
Progressive Disease	**Progressive metabolic disease**	**One of the following:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or nadir with evidence of new or enlarging FDG avid nodes.	PPD progression: An individual node/lesion must be: • LDi > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • Increase in LDi or SDi from nadir - 0.5 cm for lesions ≤ 2 cm - 1.0 cm for lesions > 2 cm
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	• In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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 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

***PET 5-point scale**
1-No uptake above background
2-Uptake ≤ mediastinum
3-Uptake > mediastinum but ≤ liver
4-Uptake moderately > liver
5-Uptake markedly higher than liver and/or new lesions
X-New areas of uptake unlikely to be related to lymphoma

APPENDIX VIII RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES AND PREVENTION OF TUMOR LYSIS SYNDROME

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional study drugs doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g. D5 ½ normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS; e.g. fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorous, uric acid, calcium and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention
- The management recommendations below focus on the minimum initial response required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be as per institutional protocols.

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

Hyperkalemia (including rapidly rising potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 to 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	Consider rasburicase (dose based on local guidelines and/or institutional standards). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	Administer rasburicase (dose based on local guidelines and/or institutional standards). When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Notify nephrology (or other acute dialysis service). Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.

Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. Telemetry. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	Start or increase rate of IV fluids. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

APPENDIX IX DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter) in adults or > 6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium > 6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4- albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury from Levin at al.

Note: In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54

APPENDIX X CHILDS PUGH CLASSIFICATION

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

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

Source:

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

APPENDIX XI IBRUTINIB PK SAMPLE COLLECTION

Collect the PK blood samples according to the time points described in the protocol.

USE 1 x 2-mL GREEN TOP SODIUM HEPARIN TUBE FOR EACH PK COLLECTION.

1. Allow tube to fill COMPLETELY, as far as the vacuum will allow.
2. Mix the tube immediately upon completion to avoid clotting by inverting gently 5 times. DO NOT SHAKE.
3. Place the blood samples on melting ice until centrifugation
4. Place the sample in a refrigerated centrifuge (0-4°C).

NOTE: When necessary use a refrigerated centrifuge bucket in cases where a refrigerated centrifuge is not available. Maintain cold temperature during the plasma preparation process.

5. Centrifuge tube within 60 minutes of collection at 4°C for 15 minutes at 2500 rpm.
6. Transfer plasma with pipette equally into two 2-mL cryovials (approximately 0.5 mL of plasma in each tube).
7. Enter the Subject ID number on the sample labels.
8. Store plasma samples in a freezer at -80°C or below, within approximately 60 minutes of blood collection.
9. Ship samples FROZEN in batches (after collection from each subject is completed) to Frontage Laboratories, Inc.

NOTE: Every effort should be made to collect the full 2 mL blood sample at each time point. In the event that less than 1 mL of blood is collected, the sample will be processed as described above except that the plasma will not be divided into two tubes. All deviations will be recorded on the PK worksheet. This single plasma sample should be frozen, stored and shipped with the primary set of samples.

All PK Timepoints

TEST	COLLECT	PREPARE	CONTAINER	SHIP TEMP
PK	1 x 2ml Green Sodium Heparin 	Centrifuge & Transfer Plasma	2 x 2ml cryovials 	Frozen to

PK Sample Shipping Instructions

PK SPECIMENS to be batch shipped (FROZEN) after collection from each subject. Please include:

- One primary set of samples for each subject
- One back-up set of samples for each subject (unless only single plasma sample available)

Samples should be shipped on dry ice Monday through Wednesday only.

As much as possible, a complete set of primary samples (all timepoints) for a subject should be batched and shipped together in the same shipment.

Ship the back-up set after the confirmation of receipt of the primary set by Frontage Laboratories, Inc.

Do NOT ship back-up aliquots of plasma in the same shipment as the primary samples from the same subject.

Contact FEDEX customer service to determine the latest pickup time for your site and the scheduling deadline.
Record the FEDEX Tracking number from the top of each airbill for your records and tracking purposes.

Note: A Shipping Notification fax should be send prior to shipping.
Electronic packaging slip must be sent to [redacted]

SHIPPING ADDRESS

[redacted]
Sample Coordinator
Frontage Laboratories, Inc.
700 Pennsylvania Drive
Exton, PA 19341
[redacted]

APPENDIX XII CORRELATIVE STUDY SAMPLE SUBMISSION

A. PATIENTS ENROLLED AT MEDSTAR GEORGETOWN UNIVERSITY HOSPITAL

Georgetown HTSR contacts:

[redacted]

[redacted]

Checklist for procedure:

1) One bone marrow biopsy kit
2) Caris Life Sciences Fresh Tissue Shipper Kit (Will include a formalin container)
3) 1 EDTA tube
4) 1 Yellow-top (ACD) tube
5) Two standard pathology formalin containers

Correlative samples to be collected per protocol from Bone Marrow Biopsy (See Table 1):

1) Collect 10 cc of bone marrow aspirate in heparinized syringe
    a. Place 5 cc of aspirate in yellow-top tube
    b. Place 5 cc of aspirate in EDTA tube
2) Three 1-cm cores of bone marrow should be obtained. A core sample should be placed in both of the standard formalin containers and in the one from the Caris Life Sciences Fresh Tissue Shipper Kit.

Local Pathology:

The EDTA tube and 1 cm core in standard formalin container should be sent to local pathology department for standard assessment to evaluate for presence and extent of lymphomatous involvement. **Please send the bone marrow biopsy pathology report to the multicenter trials project manager as soon as available.**

Caris Lab:

The core sample in the Caris Life Sciences Fresh Tissue Shipper Kit should be shipped directly to Caris. Fill out forms included in kit.

If the patient lacks greater than 20% lymphomatous involvement of their bone marrow, they will be recommended to undergo a biopsy of an affected lymph node or other disease-involved area. This sample will need to be submitted to Caris Life Sciences. Please use the Caris Life Sciences Block Shipper kit to submit the sample. If the patient has recently undergone a biopsy of another affected area, this sample may be submitted instead after approval by Dr. Ujjani.

Georgetown HTSR: The yellow-top tube and other 1 cm core which was placed in the standard formalin container should be given to HTSR at Georgetown. The yellow-top tube should be sent at room temperature. It does not need to be spun or otherwise prepared.
Prior to shipment, each specimen container must be labeled with

- subject ID
- site/institution
- collection date
- specimen type

When possible, samples should be collected Mon- Thurs to avoid weekend or holiday-related delays. Notify HTSR of specimen submission at least 1 business day prior to the date samples will submitted.

B. PATIENTS ENROLLED AT NON-GEORGETOWN SITES

Checklist for procedure:

1) One bone marrow biopsy kit
2) Caris Life Sciences Fresh Tissue Shipper Kit (Will include a formalin container)
3) 1 EDTA tube
4) 1 Yellow-top (ACD) tube
5) Two standard pathology formalin containers
6) Pre-labeled histology cassettes with Telfa paper inside for biopsy collection

Correlative samples to be collected per protocol from Bone Marrow Biopsy (See Table 1):

1) Collect 10 cc of bone marrow aspirate in heparinized syringe
    a. Place 5 cc of aspirate in yellow-top tube
    b. Place **5 cc** of aspirate in EDTA tube
2) Three 1-centimeter bone marrow cores should be obtained
    a. One core should be placed into one of the standard formalin containers
    b. One core should be placed in between the two sheets of Tefla paper inside the histology cassette. The cassette should be closed and placed into the other standard formalin container.
    c. One core should be placed in the formalin container from the Caris Life Sciences Fresh Tissue Shipper Kit.

Local Pathology:

The EDTA tube and 1 cm core in standard formalin container (**without** the histology cassette) should be sent to local pathology department for standard assessment to evaluate for presence and extent of lymphomatous involvement. **Please send the bone marrow biopsy pathology report to the multicenter trials project manager as soon as available.**

Caris Lab:

The core samples in the Caris Life Sciences Fresh Tissue Shipper Kit should be shipped directly to Caris. Fill out forms included in kit.

If the patient lacks greater than 20% lymphomatous involvement of their bone marrow, they will be recommended to undergo a biopsy of an affected lymph node or other disease-involved area. This sample will need to be submitted to Caris Life Sciences. Please use the Caris Life Sciences Block Shipper kit to submit the sample. If the patient has recently undergone a biopsy of another affected area, this sample may be submitted after approval by Dr. Ujjani.

Georgetown HTSR:

The yellow-top tube and other 1 cm core which was placed into the **histology cassette** in the standard formalin container should be shipped to the HTSR at Georgetown. The yellow-top tube should be sent at room temperature. It does not need to be spun or otherwise prepared. The core biopsy should be kept in formalin and should NOT be paraffin embedded prior to shipping.

Prior to shipment, each specimen container must be labeled with

- subject ID
- site/institution
- collection date
- specimen type

When possible, samples should be shipped **Mon- Thurs** to avoid weekend or holiday-related delays. **FedEx Priority Overnight shipment is strongly recommended**.

Notify HTSR of specimen shipment **at least 1 business day prior to** the date samples will be shipped and include the tracking number.

Georgetown HTSR Shipping Address:

c/[redacted]
LR-10C Pre-Clinical Science Bldg
3900 Reservoir Road NW
Washington, DC 20007
Phone[redacted]
Email: [redacted]

HTSR Contacts: *** Include all contacts on shipment notification emails. ***

[redacted]