NCI Protocol #: *N/a.*

DF/HCC Protocol #: 19-651

TITLE: Phase II study on the combination of ibrutinib and venetoclax in treatment naïve patients with Waldenström Macroglobulinemia

Coordinating Center: **Dana-Farber Cancer Institute**
450 Brookline Avenue
Boston, MA 02215 USA

Principal Investigator (PI): **Jorge J. Castillo, MD**
Dana-Farber Cancer Institute
Jorgej_castillo@dfci.harvard.edu

Other Investigators: **Steven P. Treon, MD, PhD**
Dana-Farber Cancer Institute
Steven_treon@dfci.harvard.edu

Project Manager:
Kirsten Meid
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215 USA
Kirsten_meid@dfci.harvard.edu

Agent(s): *Venetoclax & Ibrutinib*

IND #: *145237*
IND Sponsor: Jorge J. Castillo, MD

Protocol Type / Version # / Version Date: *Version #5 6.23.2022*

SCHEMA

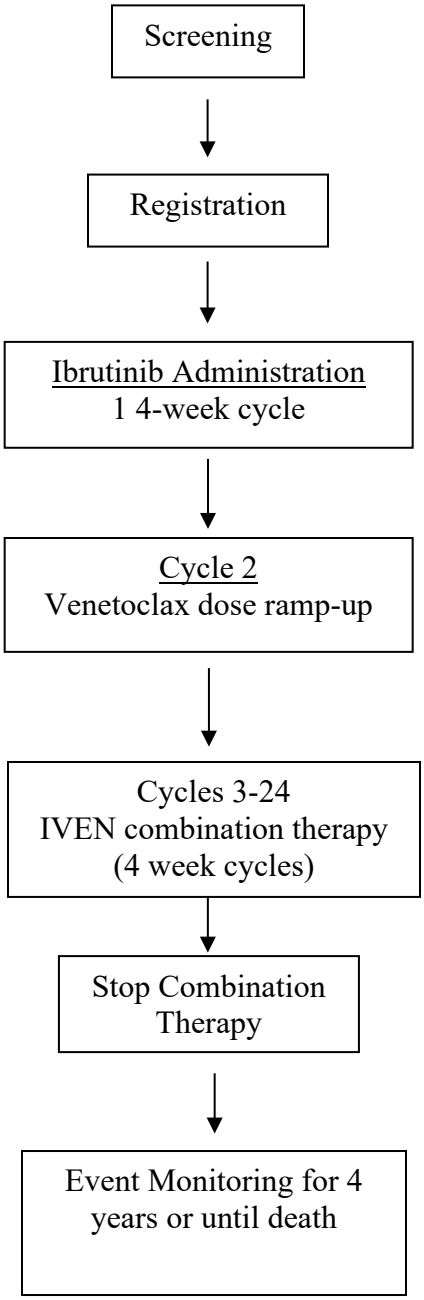

Screening
Registration
Ibrutinib Administration
1 4-week cycle
Cycle 2
Venetoclax dose ramp-up
Cycles 3-24
IVEN combination therapy
(4 week cycles)
Stop Combination Therapy
Event Monitoring for 4 years or until death

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a single-arm open-label Phase II study to evaluate the safety and efficacy of Ibrutinib combined with Venetoclax (IVEN) in symptomatic, treatment naive WM patients. Treatment will be administered daily to participants with WM, and participants will receive treatment for 24 28-day cycles. During the first cycle of therapy, participants will initiate Ibrutinib alone therapy, followed by dose escalation starting on Cycle 2 Day 1 to the target dose of Venetoclax with TLS prophylaxis. After a maximum of 24 cycles of therapy participants will discontinue ibrutinib and venetoclax and enter follow-up for 4 years or death.

A Screening visit will be conducted 30 days prior to Cycle 1, Day 1 of study drug administration. At the Screening visit, a medical history will be obtained, and a complete physical examination will be performed including vital signs and an ECOG performance status. A bone marrow aspirate and biopsy, and CT scanning of the chest, abdomen and pelvis will be done. Bone marrow and CT scans will not be repeated if collected within 90 days prior to Cycle 1 Day 1 visit. Clinical laboratory tests including a complete blood count plus differential, comprehensive chemistry panel (electrolytes, BUN, creatinine, albumin, total protein, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase), magnesium, beta-2-microglobulin, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies, Von Willebrand factor, ristocetin cofactor and FVIII level, HIV, HBsAg, HBsAb, HBcAb and HCV antibody. Serum pregnancy tests for women of childbearing potential will also be performed at the Screening visit. Cryoglobulins and cold agglutinins will be obtained if clinically indicated. Coagulation studies (PT, PTT, PT-INR) and tumor lysis laboratories (calcium, phosphorus, LDH, and uric acid) will also be performed at baseline. .

Participants who meet the eligibility requirements at the Screening visit will be enrolled in the study. To prevent the development of tumor lysis syndrome (TLS), dosing of venetoclax will not commence until the participants have completed 4 weeks of ibrutinib (Cycle 1). Participants will be evaluated for development of tumor lysis syndrome (TLS) on Days 1 and 2 of venetoclax dose escalation days during the lead-in phase (Cycle 2). TLS, however, is an extremely rare occurrence in patients with WM. To err in the side of safety, all patients will receive allopurinol 300 mg PO once daily starting 72 hours prior to first dose of venetoclax and continuing at least to the end of Cycle 2.

Patients will be evaluated for safety on the first day of each cycle (4 weeks ± 1 week) at cycle 2, and 3 and thereafter every 3 cycles (12 weeks ± 1 weeks) for the duration of therapy. Patients will also be evaluated for safety at each venetoclax dose escalation. Patients will be evaluated for response after completing 4 weeks of therapy. Response criteria updated at the Sixth International Workshop on Waldenström macroglobulinemia (Owen 2013) will be used to assess response, stable disease, and progressive disease. QOL questionnaire will be administered at Cycles 1, 4, 7, 13, 19, EOT, and every 6 months during follow-up.

The Sponsor-Investigator and other study investigators instructed all participants to undergo cardiac screenings, which included labwork, ECG, and Echocardiograms after 3 events of

ventricular arrhythmia, including 2 fatal, occurred on this study. Consultation with cardiology and cardiac stress tests were advised for some participants.

Study treatment for all participants was terminated by the Sponsor-Investigator in March of 2022 due to 4 events of ventricular arrhythmia. As of 4/1/22 all participants were notified and instructed to stop study treatment and accrual was permanently discontinued. Follow-up will continue for 4 years or until death, per protocol.

1.2 Primary Objectives

- To evaluate the rate of VGPR or better of the combination Ibrutinib + Venetoclax (IVEN) in participants with treatment naïve Waldenström macroglobulinemia within 24 cycles of therapy.

1.3 Secondary Objectives

- To evaluate the rate of CR with IVEN in participants with symptomatic, treatment naïve WM at 6, 12 and 24 cycles of therapy.
- To evaluate the best overall response to IVEN in participants with symptomatic, treatment naïve WM.
- To evaluate the rate of VGPR or better at 30 months post treatment initiation.
- To evaluate median time to response, median time to major response and median time to VGPR to IVEN in participants with symptomatic, treatment naïve WM.
- To evaluate the 24-, 36-, 48-, 60-month Progression Free Survival (PFS) of IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the overall survival for participants treated with IVEN
- To evaluate the time to next treatment with IVEN
- To evaluate the effect of IVEN in the bone marrow burden of disease in participants with symptomatic treatment naïve WM.
- To evaluate the impact of CXCR4 mutations on response to IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the safety profile of IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the impact of IVEN in the participants' QOL.

2. BACKGROUND

2.1 Study Disease(s)

The current state of Waldenström macroglobulinemia (WM)

WM is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of IgM-producing lymphoplasmacytic cells. Such malignant cells accumulate in the bone marrow, liver, spleen and lymph nodes. WM is diagnosed by the presence of lymphoplasmacytic cells in the bone marrow and an IgM monoclonal spike (M-spike) identified in a serum protein

electrophoresis (SPEP). The incidence of WM in the United States (US) is 3 per million persons per year accounting for 1500 new cases per year.

Recently, our group identified a recurrent mutation in the MYD88 gene (MYD88 L265P), which is seen in over 90% of cases with WM [1]. The occurrence of this mutation in WM has since been validated in several independent cohorts [2-5]. In contrast, the MYD88 L265P gene mutation was not detected in patients with IgM myeloma and was detected in less than 10% of patients with marginal zone lymphoma. The high specificity and sensitivity of the MYD88 L265P gene mutation has obvious diagnostic implications in patients in whom a diagnosis of WM is suspected but uncertain. The MYD88 L265P gene mutation has shown to support growth and survival of WM cells in several studies. A knockdown model of MYD88 showed decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of mutant *versus* wild-type MYD88 [6]. MYD88 acts as an adaptor molecule in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling [7]. Following stimulation of TLR or IL-1R, MYD88 is recruited to the activated receptor complex as a homodimer which complexes with IL-1R-associated kinase 4 (IRAK4) and subsequently activates IRAK1 and IRAK2 [8]. IRAK1 activation then leads to NF-κB activation via IκBα phosphorylation [9]. Recently, a study has shown that MYD88 L265P also activates the Bruton's Tyrosine Kinase (BTK) pathway [6]. In this pre-clinical study, the activation of BTK by MYD88 could be abrogated using BTK kinase inhibitors.

Another study from our group reported the occurrence of recurrent somatic CXCR4 gene mutations in approximately 30-40% of WM patients [10]. The somatic mutations occur in the C-terminal domain and are like those observed in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome. These mutations regulate signaling of CXCR4 by its ligand SDF-1a [11]. In WM patients, two classes of CXCR4 mutations occur: non-sense ($CXCR4^{WHIM/NS}$) and frameshift ($CXCR4^{WHIM/FS}$) mutations [10, 12]. Non-sense and frameshift mutations are equally divided among WM patients, and over 30 different types of CXCR4 mutations have been identified. Preclinical studies with the most common CXCR4 S338X mutation in WM have shown sustained signaling of AKT, ERK and BTK following SDF-1a binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells [13].

The B-cell lymphoma-2 (BCL-2) family of proteins is central to the regulation of apoptosis. Altered responses to normal apoptotic signals are one of the hallmarks of cancer and they are connected to defects in the apoptotic machinery in cancer cells. Apoptosis occurs via activation of two different pathways, the extrinsic pathway, triggered by the activation of the cell surface death receptors, and the intrinsic pathway, followed by the perturbation of mitochondrial membrane integrity. Studies have shown that the intrinsic pathway is tightly controlled by the interactions between the pro- and anti-apoptotic BCL-2 family proteins [14]. Twenty-five known members of the BCL-2 protein family can be grouped functionally according to their pro- and anti-apoptotic effects, as well as structurally according to the BCL-2 homology (BH) regions they contain. The six known anti-apoptotic family members, BCL-2, Bcl-x_L, Mcl-1, Bcl-w, Bcl-b and A1, contain four BH domains (BH1-4) and a transmembrane domain (TM). Pro-apoptotic proteins are subdivided into two classes: multi-domain members, such as Bax, Bak and Bok, which contain and share homology in the BH1, BH2, BH3 and BH4 domains and BH3-only proteins, including Bad, Bim, Puma, Bid, Bik, Noxa, Hrk and Bmf, which show homology only in the BH3 domain.

By gene expression analysis, we investigated differences in transcriptional regulation of CD19 and CD138 selected cells representing the B-cell and plasma cell compartments, respectively, versus similar healthy donor derived bone marrow cells. Samples from 30 untreated WM patients were compared to those of 10 healthy donors [15]. These studies demonstrated that Bcl-2 was overexpressed in both B-cell and plasma cell compartments in WM patients in comparison to healthy donors. By flow cytometric analysis, the overexpression of Bcl-2 protein has also been confirmed in a Spanish study on 60 cases meeting pathologic criteria for WM [16].

2.2 IND Agent Venetoclax

Venetoclax (also referred to as ABT-199, A-1195425.0, GDC-0199, RO5537382, Venclexta®, and Venclyxto®) is a novel, orally bioavailable, small-molecule B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity (inhibition constant [K_i] < 0.010 nM) to antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like B-cell lymphoma–extra-large (Bcl-X_L) and B-cell lymphoma- Walter and Eliza Hall Institute (Bcl-w) (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).

[redacted]

[redacted]

Currently, AbbVie is investigating venetoclax in oncology studies; additionally, Genentech/Roche is conducting oncology studies with venetoclax. [redacted]

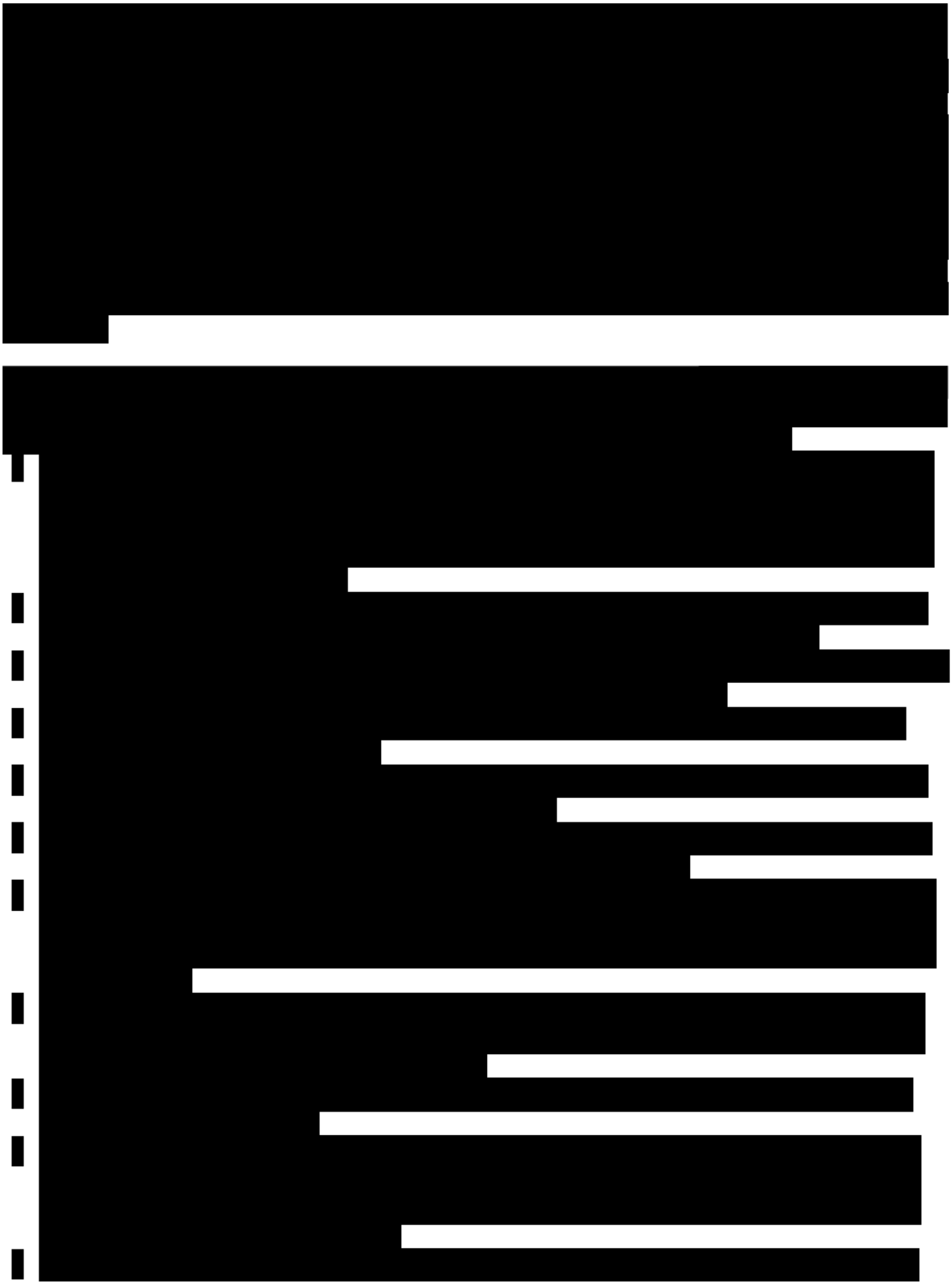
Venetoclax was first approved in the United States (US) on 11 April 2016 through accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) with deletion of the p13 locus on chromosome 17 (17p del) (as detected by a Food and Drug Administration [FDA]-approved test) who have received at least 1 prior therapy, as described in the US Package Insert (USPI). The accelerated approval is based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Subsequently, venetoclax was also approved in Argentina on 29 August 2016 and in Canada on 30 September 2016. On 05 December 2016, the European Commission (EC) issued a

conditional approval for Venclyxto® (venetoclax) for the treatment of CLL in the presence of 17p del or TP53 mutation in adult patients who are unsuitable or have failed a B-cell receptor pathway inhibitor and for the treatment of CLL in the absence of 17p del of TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor. On June 8, 2018, the Food and Drug Administration granted regular approval to venetoclax (VENCLEXTA, AbbVie Inc. and Genentech Inc.) for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

[redacted]

[redacted]

[redacted]



A phase II study evaluating venetoclax in patients with relapsed and/or refractory WM is underway at our institution. As of July 17, 2018, we have completed enrollment, and all patients have completed 6 months of therapy [17]. Our initial experience has been favorable with a safe adverse event profile. No evidence of clinical tumor lysis syndrome has been seen. In addition, out of the 30 evaluable patients, 26 (87%) have responded, including 5 patients (17%) who achieved a VGPR.

2.3 *Other Agent: Ibrutinib*

In 2015, the US FDA and the EMA approved the use of the oral BTK inhibitor ibrutinib for the treatment of patients with symptomatic WM.

The approval was based on the results of a phase II study in 63 patients with relapsed and/or refractory WM, in which ibrutinib induced an overall response rate (ORR) of 91% and a major response rate of 73%, as well as 2-year progression-free (PFS) and overall survival (OS) of 70% and 95%, respectively [18]. The VGPR rate was 16%. Despite these exceptional results, response rates are affected by the MYD88/CXCR4 mutational status. WM patients who carry MYD88 and CXCR4 mutations experience lower rates of ORR and major response rates than patients with MYD88 only disease (100% vs. 86% and 91% and 62%, respectively). WM patients who are wild type for MYD88 and CXCR4, the ORR and major response rates are lower than for the other two groups (72% and 29%, respectively). In a more recent study, the entire MYD88 gene was sequenced in wild type patients from the phase II study; 2 of the 7 patients were found to have non-L265P MYD88 mutations [19]. After removal of these patients from the double wild type group, the ORR and major response rates decreased to 60% and 0%, respectively.

More recently, a single-arm study evaluated ibrutinib in 31 patients with WM who were refractory to rituximab [20]. With a median follow-up of 34 months, ibrutinib therapy was associated with an ORR of 84% and a major response rate of 65%. VGPR rate was 29%. CXCR4 mutations were associated with more superficial responses to ibrutinib.

Ibrutinib was also evaluated in 30 previously untreated patients with symptomatic WM [21]. In this setting ibrutinib was well tolerated and was not associated with unexpected adverse events.

The overall and major response rates were 100% and 83%, respectively, and the 18-month PFS was 92%. CXCR4 mutations were associated with lower rates of VGPR.

2.4 Rationale

The clinical course of WM is variable and although patients might experience an overall survival (OS) measured in decades [22, 23], WM remains incurable with current therapeutic regimens. Hence, the disease course is characterized by continual relapses, each harder to treat than the previous one. Additionally, many of the disabling symptoms associated with the disease, such as hyperviscosity, fatigue, anemia or neuropathy, can be exacerbated by our therapy [24]. Hence, the careful evaluation of agents with novel mechanisms of action is needed to improve the quality of life (QOL), and response and survival rates in patients with WM.

Of note, no CR rates have been seen with single-agent ibrutinib therapy, and the rate of VGPR was 10-15% at 12 months. Therefore, investigating agents with increased activity that can induce deeper responses is warranted.

The combination of ibrutinib and venetoclax is being examined in patients with CLL and MCL and appears to be safe and well tolerated. In patients with CLL, after 8 weeks of ibrutinib monotherapy (420 mg/day), venetoclax was added initially at a dose of 10 mg/day with weekly escalations to 20 mg, 50 mg, 100 mg, 200 mg to a final dose of 400 mg/day [25]. In MCL, patients received 4 weeks of ibrutinib (560 mg/day), followed by introduction of venetoclax (weekly ramp-up to target 400 mg/day) [26].

Hypothesis:
The combination of ibrutinib and venetoclax (IVEN) is associated with a high rate of very good partial response in participants with symptomatic treatment naïve Waldenström Macroglobulinemia.

2.5 Correlative Studies Background

MYD88 L265P is a recently identified somatic mutation present in >90% of WM patients but in <5% of patients with other related processes such as CLL or MZL with plasmacytic differentiation or IgM myeloma [1]. Many groups have now validated the presence of this somatic mutation in WM patients. MYD88 L265P supports growth and survival of WM cells through both IRAK1 and IRAK4 [1] as well as by activation of Bruton tyrosine kinase (BTK) [6]. Based on these findings, we conducted a clinical trial using the BTK inhibitor ibrutinib in 63 patients with relapsed/refractory WM [18]. In this study, ibrutinib showed to be safe and effective. Median hemoglobin improved from 10.5 g/dl to 12.6 g/dl and IgM decreased from 3610 mg/dl to 1340 mg/dl. Bone marrow involvement decreased from 70% to 45% with a best ORR of 81% and a major response rate of 57%. The major response rate was 77% for patients with wild-type CXCR4 vs. 30% in those with WHIM-like CXCR4 mutations. Decreases in serum IgM as well as improvements in hemoglobin were greater in patients with wild-type CXCR4.

In recent studies, the MYD88 and CXCR4 mutational status are predictive of clinical status, response to therapy and survival outcomes [12, 27]. Activating MYD88 as well as nonsense and

frameshift WHIM-like CXCR4 somatic mutations are common in Waldenström macroglobulinemia. CXCR4 nonsense mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival. The MYD88 L265P mutational analysis by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing will be performed by the Bing Center for Waldenström Macroglobulinemia in Boston, MA.

Eligibility for the study includes known MYD88 mutation and will be based on testing at a CLIA certified laboratory. If the participant has had MYD88 mutation testing previously performed by a CLIA accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for eligibility determination.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate. Screening evaluations including consent, physical exam, and laboratory assessments will be done within 30 days prior to Cycle 1 Day 1. Bone marrow biopsy & aspirate, and CT C/A/P will be done within 90 days prior to Cycle 1 Day 1.

3.1.1 Clinicopathological diagnosis of Waldenström macroglobulinemia [28].

3.1.2 Known tumor expression of mutated MYD88 performed by a CLIA certified laboratory.

3.1.3 Symptomatic disease meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenström macroglobulinemia [29].

3.1.4 Participants with symptomatic hyperviscosity (e.g. nosebleeds, headaches, blurred vision) must undergo plasmapheresis prior to treatment initiation.

3.1.5 Age $\geq$ 18 years

3.1.6 ECOG performance status $\leq$2 (see Appendix A)

3.1.7 Measurable disease, defined as presence of serum immunoglobin M (IgM) with a minimum IgM level of >2 times the upper limit of normal of each institution is required

3.1.8 At the time of screening, participants must have acceptable organ and marrow function as defined below:

- Absolute neutrophil count ≥500/uL (no growth factor permitted)
- Platelets ≥50,000/uL (no platelet transfusions permitted)
- Hemoglobin ≥ 7 g/dL (transfusions permitted)
- Total bilirubin < 1.5 x institutional ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN
- Estimated GFR ≥30 mL/min

3.1.9 Females of childbearing potential (FCBP) must use one reliable form of contraception or have complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) while participating in the study; and 2) for at least 90 days after discontinuation from the study. FCBP must be referred to a qualified provider of contraceptive methods if needed. FCBP must have a negative serum pregnancy test at screening.

3.1.10 Men must agree to use a latex condom during treatment and for up to 90 days after the last dose of ibrutinib or venetoclax during sexual contact with a FCBP

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Participants who have one or more prior systemic therapies for WM.

3.2.2 Participants who are receiving any other investigational agents.

3.2.3 Participants with known CNS lymphoma.

3.2.4 Participants with known history of Human Immunodeficiency Virus (HIV), chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring active treatment. Note: Participants with serologic evidence of prior vaccination to HBV (i.e., HBs Ag-, and anti-HBs+ and anti-HBC-) and positive anti-HBc from IVIG may participate.

3.2.5 Concurrent administration of medications or foods that are moderate or strong inhibitors or inducers of CYP3A within 7 days prior to first dose of study drug.

3.2.6 Participants with chronic liver disease and hepatic impairment meeting Child-Pugh class C (Appendix B).

3.2.7 Concurrent administration of warfarin.

3.2.8 Concurrent systemic immunosuppressant therapy within 21 days of the first dose of study drug.

3.2.9 Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.

3.2.10 Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of the study drug.

3.2.11 Known bleeding disorders (e.g., congenital von Willebrand's disease or hemophilia)

3.2.12 History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

3.2.13 Major surgery within 4 weeks of first dose of study drug.

3.2.14 Malabsorption syndrome or other condition that precludes enteral route of administration.

3.2.15 Female participants who are pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days of last dose of study drug.

3.2.16 Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study drug

3.2.17 Participants with known history of alcohol or drug abuse.

3.2.18 Participants with inability to swallow pills.

3.2.19 On any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

3.2.20 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.21 Participants with a history of non-compliance to medical regimens.

3.2.22 Participants who are unwilling or unable to comply with the protocol.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.
An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.2 General Guidelines for Other Investigative Sites

N/a

4.3 Registration Process for Other Investigative Sites

N/a

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Treatment Regimen

Venetoclax and Ibrutinib will be administered daily, with 28 consecutive days defined as a treatment cycle. Ibrutinib will be administered for a maximum of 24 cycles. Venetoclax will be administered for a maximum of 23 cycles. Participants will be initiated on Ibrutinib on Cycle 1 Day 1, and Venetoclax dose escalation will begin on Cycle 2 Day 1 (+/- 2 days), starting at 100 mg PO QD for 1 week. Participants will then be escalated to 200 mg PO QD for 1 week and then to the target dose of 400 mg PO QD for the remainder of the study.

At the completion of 24 cycles of therapy, participants will stop all treatment and enter follow-up for four years or until death.

Treatment will be administered on an outpatient basis, except as specified below. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

Study treatment for all participants was terminated by the Sponsor-Investigator in March of 2022 due to 4 events of ventricular arrhythmia. As of 4/1/22 all participants were notified and instructed to stop study treatment and accrual was permanently discontinued.

Table 5-1

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ibrutinib	Not applicable	420mg	PO	QD	28 days (4 weeks)
Venetoclax	Allopurinol 300 mg QD beginning 72 hours prior to first administration and continuing through Cycle 2 for TLS prophylaxis; Oral hydration (2L per day) for 24 hours prior to	See Table 6-1.	PO	QD	

	dose escalation and the Day of and day after				
*Order of administration of Ibrutinib and Venetoclax does not matter. The medications should be taken at approximately the same time.					

5.2 Pre-Treatment Criteria

Cycle 1 Day 1 results do not need to meet eligibility parameters. Day 1 chemistry and hematology laboratories must be reviewed prior to treatment.

Participants must meet the following criteria on Day 1 of cycles with clinic visits (i.e. 1, 2, 3, 4, 7, 10, etc.). For venetoclax dose escalation days during Cycle 2, all below criteria must be met except for the neutrophil count (refer to section 6.2):

- No grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy)
- No grade 4 or unmanageable nonhematologic grade 3 toxicities
- Neutrophil count ≥500/ mm^3 (growth factor permitted)
- Platelet count ≥50,000/ mm^3 in the presence of bleeding (platelet transfusion permitted, including on day of treatment)
- Platelet count ≥25,000 mm^3 without bleeding (platelet transfusion permitted, including on day of treatment)

5.2.1 Cycle 1 Day 1

Participants will begin ibrutinib 420 mg PO QD on Cycle 1 Day 1 and continue it as a single agent for 4 weeks to mitigate the risk of tumor lysis syndrome (TLS). Participants will self-dose ibrutinib on an outpatient basis.

5.2.2 Cycle 2 Venetoclax dose escalation

Participants will return to clinic on Cycle 2 Day 1 to begin combination therapy with ibrutinib and venetoclax. Venetoclax will be administered at the DFCI, or a participating site, infusion room on the first day of treatment, and at the first dose of each escalation (C2D8 and C2D15), and participants will be monitored for tumor lysis syndrome.

5.3 Agent Administration

5.3.1 Venetoclax

All participants will begin venetoclax at 100 mg PO once daily on Cycle 2 Day 1 (+/- 2 days) for 7 days, followed by escalation to 200 mg PO once daily (Cycle 2 Day 8) for 7 days and then 400 mg PO once daily (Cycle 2 Day 15) for 14 days. If participants require dose adjustments or delays, Cycle 3 will not commence until the participant has taken venetoclax 400 mg for 7 consecutive days. Participants will continue venetoclax for a maximum of 23 cycles, or until unacceptable toxicity or disease progression. At the completion of 24 cycles of therapy participants will discontinue all protocol therapy and enter follow-up until next therapy or death.

Dose reductions due to toxicity will be permitted on information seen in Table 6-1.

The study drug venetoclax will be administered in the DFCI, or participating site, infusion room on the first dose of each dose escalation (C2D1, C2D8, C2D15, etc.) until a dose of 400 mg PO daily is reached. Otherwise, venetoclax will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. Participants will be instructed to take the study drug at approximately the same time each day. Participants will also be instructed on how to complete the diary. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken, and the patient should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit; this must be documented in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

One cycle of venetoclax is once daily, oral administration for 4 weeks ± 1 week. Venetoclax should be taken with a meal, preferably low-fat. Prescriptions for venetoclax will be written for daily administration for 1 cycle for participants in cycle 3 and will be written for daily administration for 12 weeks ± 1 week for participants being seen every 12 weeks starting on Cycle 4 Day 1. For cycle 2, a new prescription will be written for each dose escalation (i.e. 1 week of dosing for C2D1 at starting dose, 1 week of dosing for C2D8 at escalated dose, and 2 weeks of dosing for C2D15 at target dose). Participants who have difficulties reaching the maximum target dose during dose escalation may have additional prescriptions written during Cycle 2. Drug accountability will be done at each study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. A new prescription for either one cycle or three cycles, as detailed above, will be filled by the participant, and they will be given a new diary.

Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label.
Tumor Lysis Syndrome Prophylaxis *(Refer to Section 6.3 for Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS & refer to Appendix C for Definition of Laboratory and Clinical TLS))*

First Dose of Venetoclax

Tumor lysis syndrome prophylaxis must be initiated in all participants irrespective of their TLS risk category prior to the first dose of Venetoclax. TLS prophylaxis includes:

- An oral agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 72 hours prior to dosing. Treatment should be continued until at least Cycle 2 Day 28 based on the ongoing risk of TLS development. Participants allergic to allopurinol must use another uric acid reducer.
- Oral hydration consisting of fluid intake of 2 L per day starting at least 24 hours prior to

the start of treatment for all participants prior to first dose and continued for at least 24 hours after dosing and all the chemistries laboratory values remain within ULN. Oral hydration is recommended beyond 24 hours post-dose for participants who demonstrate any laboratory changes.

- Patients who are unable to maintain such oral hydration will receive IV hydration of 1 L in the outpatient setting on day 1 of venetoclax dosing in addition to oral hydration. In participants for whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be collected and sent to local laboratory within 72 hours prior to the first dose of venetoclax. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed by local laboratory STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8 hours post-dose (+/-30 minutes), and 24 hours (+/- 1 hour) after the first dose of venetoclax 100, 200 and 400 mg. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from pre-dose laboratory values are not required to be available prior to initiating venetoclax treatment. Participants must remain at the hospital, or clinic, until the 8-hour laboratory values have been reviewed by the investigator.
- Day 2 dose should not be taken until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator. Day 2 dose does not need to be administered in the clinic.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Cycle 2 Day 7 (day 7 of venetoclax dosing) in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see section 6.3 and Appendix D for recommendations on management. Additional laboratory assessments may be performed per investigator discretion.
- All 24-hour post-dose laboratory assessments (Chemistry and Hematology) may be taken within a +/- 1-hour window, if necessary.

First Dose of Venetoclax at Dose Escalation to 200 mg or 400 mg

All participants, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of Venetoclax:

- Continue administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 2 L/day starting at least 24 hours prior to each dose escalation and continued for at least 24 hours after the dose. In participants who are unable to maintain such oral hydration, IV hydration with 1 L of 0.9% normal saline will be given in the outpatient setting on the day of dose escalation. In participants for whom volume overload is considered a significant risk, hospitalization should be considered.
- For participants who receive their subsequent dose escalations in the outpatient clinic setting, Chemistry laboratory tests will be performed by the investigative site laboratory at 0 hours (pre-dose, within 4 hours before venetoclax administration), 8 hours post-dose (+/-30 minutes) and 24 hours post-dose (+/- 1 hour) administration. Hematology laboratory tests should be

performed at 0 hour (pre-dose, within 4 hours before venetoclax administration). These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. More frequent monitoring may be requested at the discretion of the investigator.

- Participants must remain at the hospital, or clinic, until the 8-hour laboratory values have been reviewed by the investigator.
- Day 2 dose should not be taken until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator. Day 2 dose does not need to be administered in the clinic.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued for 7 days in the outpatient setting. Additional laboratory assessments may be performed per investigator discretion.
- All 24-hour post-dose laboratory assessments (Chemistry and Hematology) may be taken within a +/- 1-hour window, if necessary.
- For participants who are hospitalized during subsequent dose escalations, Chemistry and Hematology laboratory tests will be collected and sent to local laboratories upon admission. Chemistry tests will be performed by local laboratory STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 (+/- 30 minutes) and 24 (+/- 1 hour) hours post dose. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
    - IV hydration should be started with a target of approximately 2 L per day, or as clinically appropriate, for participants who are hospitalized.
    - Hematology laboratory tests will be performed 24 hours post-dose.
    - The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the participant leaving the hospital or receiving any additional doses of the study drug.
    - Chemistry and Hematology laboratory tests for all participants treated in the outpatient setting must be collected within 72 hours prior to the first dose of each dose escalation, and results must be reviewed by the investigator prior to each escalation. For participants demonstrating any clinically significant laboratory abnormalities, additional prophylactic treatment should be administered prior to dosing (see section 6.3 for recommendations on management; Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]).

5.3.2 *Ibrutinib*

Ibrutinib 420 mg will be prescribed per the FDA package label, administered orally once daily. Ibrutinib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. The capsules should be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water. Participants will be reminded that dietary habits around the time of ibrutinib intake should be as consistent as possible throughout the study. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (see section 5.3).

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible within 6 hours, with a return to the normal schedule the following day. The participant should not take extra capsules to make up the missed dose. The participant will be instructed to document missed drug doses in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

One cycle of ibrutinib is once daily, oral administration for 4 weeks +/- 1 week. At each study visit, enough ibrutinib will be dispensed until the next cycle. For visits occurring monthly, one cycle of capsules in a bottle will be dispensed. For visits occurring every 12 weeks +/-1 weeks three cycles of capsules will be dispensed. Study drug may be shipped to participants through a traceable courier. Drug accountability will be done at each study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. Returned capsules must not be re-dispensed to any participant.

Dose reductions due to toxicity will be permitted on information seen in Section 6.

Participants will be treated with ibrutinib for up to 24 cycles or until progression, unacceptable toxicity, or decision to withdraw from the trial. Participants will then discontinue ibrutinib and enter follow-up for four years or until death.

5.4 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted. All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded. The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No anticancer agents other than the study medications should be given to participants. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Growth factors (i.e. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) can be administered prophylactically, except for eligibility, and may be prescribed at the discretion of the treating physician for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria.
- Transfusions of red blood cells can be administered to meet eligibility and for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria.

- Transfusions of platelets can be administered for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria. They may not be administered to meet eligibility.
- Warfarin or vitamin K antagonists should not be administered.
- Participants requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the participant is clinically stable and has no signs of bleeding. Participants should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.
- Use ibrutinib with caution in participants requiring other 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 participants 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 5.4.1). Participants with congenital bleeding diathesis have not been studied.
- Administration of moderate or strong CYP3A4 inhibitors and inducers should be avoided. Alternatives should be sought if possible. During the dose escalation phase, moderate or strong CYP3A4 inhibitors and inducers are prohibited. See table 5-2 below for ibrutinib and venetoclax dose modification guidelines during CYP3A treatment.
- Grapefruit and grapefruit juice affect CYP450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with systemic steroids (at dosages equivalent to prednisone >20 mg/day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

Table 5-2 Ibrutinib & Venetoclax Dose Modification Guidance for CYP3A Inhibitors/Inducers after Dose Escalation

Patient Population	Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]	Recommended Venetoclax Dose for the Duration of the Inhibitor Use
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg. No dose adjustment required.	No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.	Reduce the venetoclax dose by 50% during co-administration.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.	Reduce the venetoclax dose by at least 75% during co-administration. After discontinuation of CYP3A inhibitor, wait for 2-3 days before increasing venetoclax dose back to maintenance/target dose.
	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 below in table 5-3.

Table 5-3 Moderate and Strong Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5		Inducers of CYP3A4/5
Strong inhibitors:	**Moderate inhibitors:**	**Strong CYP3A inducers:**

Boceprevir Clarithromycin Cobicistat Conivaptan Danoprevir/ritonavir Elvitegravir/ritonavir Idelalisib Indinavir Itraconazole Ketoconazole Mibefradil Lopinavir/ritonavir Nefazodone Nelfinavir Ritonavir Paritaprevir/ritonavir combinations Posaconazle Squinavir Telaprevir Telithromycin Tipranavir/ritonavir Voriconazole	Amprenavir Aprepitant Atazanavir Cimetidine Ciprofloxacin Clotrimazole Crizotinib Cyclosporine Darunavir/ritonavir Diltiazem Erythromycin Fluconazole Fosamprenavir Imatinib Isavuconazole Tofisopam Verapamil	Avasimibe Carbamazepine Enzalutamine Mitotane Phenytoin Rifampin St. John's wort **<u>Moderate CYP3A inducers:</u>** Bosentan Efavirenz Etravirine Modafinil Nafcillin

Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm or http://medicine.iupui.edu/clinpharm/ddis/main-table/

Antiplatelet Agents and Anticoagulants

5.4.1 Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The mechanism for the bleeding events is not well understood. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), combination treatment may continue for 24 cycles, or until one of the following criteria applies:

- Dose delays of >28 days for either ibrutinib or venetoclax*
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

*Participants may be continued on protocol therapy at the discretion of the Principal Investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

Study treatment for all participants was terminated by the Sponsor-Investigator in March of 2022 due to 4 events of ventricular arrhythmia. As of 4/1/22 all participants were notified and instructed to stop study treatment and accrual was permanently discontinued.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6 Duration of Follow Up

Participants will be followed for a maximum of 6 years from Cycle 1 Day 1, with 4 years of follow-up or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed at a minimum until resolution or stabilization of the adverse event. Participants will be followed for progression free survival until documented disease progression or initiation of new therapy. After this, they will be followed for survival until the conclusion of the follow-up period.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure is the participant's status is updated in OnCore in accordance with DF/HCC policy REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment,

through the study and until 30 days after the last dose of study treatment. Participants continuing to experience toxicity at the off-treatment visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. If administration of Venetoclax or Ibrutinib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Section 6.1.

If dose reductions of Venetoclax are needed during the dose escalation period, dose escalation should continue on a weekly basis to reach the targeted dose of 400 mg PO daily (e.g. if a participant cannot tolerate the 400mg dose escalation, they should be reduced back to 200mg for 1 week, and then re-challenged at 400mg the following week, etc.). In this case, Cycle 2 could last for >4 weeks. Once at goal dose of 400 mg PO daily, dose reductions are permitted down to 100 mg PO daily before a patient is taken off study. However, patients will remain on study to assess for progression. If a participant requires a dose delay of > 28 days of either ibrutinib or venetoclax, then the participant must be discontinued from the study, unless permitted to resume after discussion with the Principal Investigator. If a participant requires permanent discontinuation of either ibrutinib or venetoclax, then the participant will be taken off study.

6.1 Dose Reduction Guidelines for Venetoclax & Ibrutinib

Table 6-1 Venetoclax Dose Modification Guidelines

Dose Level	Venetoclax Dose Level 1	Venetoclax Dose Level -1	Venetoclax Dose Level -2
Cycle 2 Day 1 Starting dose	100 mg QD	-	-
Cycle 2 Day 8 Escalation	200 mg QD	100 mg QD	-
Cycle 2 Day 15 Escalation, and all cycles thereafter	400 mg QD	200 mg QD	100 mg QD

Table 6-2 Ibrutinib Dose Modification Guidelines

Dose Level	Ibrutinib Dose and Schedule
Dose Level 1	420 mg QD
-1	280 mg QD
-2	140 mg QD

Table 6-3 Drug Modification/Discontinuation Actions for Venetoclax related (possibly, probably, definitely) events or pre-specified events per section 6.2 (i.e. nausea, vomiting, diarrhea, neutropenia, thrombocytopenia)

- 1st Hold: Venetoclax until recovery from criteria to hold; may restart at original dose level.
- 2nd Hold: Venetoclax until recovery from criteria to hold; restart at -1 dose level.

- 3rd Hold: Venetoclax until recovery from criteria to hold; restart at -2 dose level (if applicable, see table 6-1)
- 4th Hold: Discontinue Venetoclax

Table 6-4 Drug Modification/Discontinuation Actions for Ibrutinib related (possibly, probably, definitely) events or pre-specified events per section 6.2 (i.e. nausea, vomiting, diarrhea, neutropenia, thrombocytopenia)

- 1st Hold: Ibrutinib until recovery from criteria to hold; may restart at original dose level.
- 2nd Hold: Ibrutinib until recovery from criteria to hold; restart at -1 dose level.
- 3rd Hold: Ibrutinib until recovery from criteria to hold; restart at -2 dose level
- 4th Hold: Discontinue Ibrutinib

6.2 Venetoclax & Ibrutinib Dose Adjustments for AEs

Nausea	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 if persistent despite optimal antiemetic therapy. Resume per Table 6-3.	Hold until ≤ Grade 2 if persistent despite optimal antiemetic therapy. Resume per Table 6-4.
Grade 4	Hold until ≤ Grade 2. Resume per Table 6-3.	Hold until ≤ Grade 2. Resume per Table 6-4.
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 if persistent despite optimal antiemetic therapy. Resume per Table 6-3.	Hold until ≤ Grade 2 if persistent despite optimal antiemetic therapy. Resume per Table 6-4.
Grade 4	Hold until ≤ Grade 2. Resume per Table 6-3.	Hold until ≤ Grade 2. Resume per Table 6-4.
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 if persistent despite optimal antidiarrheal therapy. Resume per Table 6-3.	Hold until ≤ Grade 2if persistent despite optimal antidiarrheal therapy. Resume per Table 6-4.
Grade 4	Hold until ≤ Grade 2. Resume per Table 6-3.	Hold until ≤ Grade 2. Resume per Table 6-4.
Recommended management: Loperamide antidiarrheal therapy.		

Neutropenia	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose

Neutropenia	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
Grade 2	No change in dose	No change in dose
Grade 3	No change in dose. Hold until ≤Grade 2 if infection and/or fever present. Resume per Table 6-3.	No change in dose. Hold until ≤Grade 2 if infection and/or fever present. Resume per Table 6-4.
Grade 4	Hold if grade 4 >7 days until ≤ Grade 3. Resume per Table 6-3.	Hold if grade 4 >7 days until ≤ Grade 3. Resume per Table 6-4.
*Administer G-CSF or growth factors for neutropenia as indicated.		

Thrombocytopenia	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2 if bleeding present. No change in dose in the absence of bleeding. Resume per Table 6-3.	Hold until ≤ Grade 2 if bleeding present. No change in dose in the absence of bleeding. Resume per Table 6-4.
Grade 4	Hold until ≤ Grade 3. Resume per Table 6-3.	Hold until ≤ Grade 3. Resume per Table 6-4.
*Platelet transfusions for thrombocytopenia permitted.		

Non-Hematological Toxicities not otherwise specified*	**Management/Next Dose for *Venetoclax***	**Management/Next Dose for *Ibrutinib***
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume per Table 6-3.	Hold until ≤ Grade 2. Resume per Table 6-4.
Grade 4	Hold until ≤ Grade 2. Resume per Table 6-3.	Hold until ≤ Grade 2. Resume per Table 6-4.
* If the investigator determines that the toxicity is only attributable to either Venetoclax or Ibrutinib, but not both, dosing of the other medication may be continued.		

6.2.1 Ibrutinib Dose Modification for Hepatic Impaired Participants

Participants 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 6.2. Ibrutinib is metabolized in the liver and therefore participants 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 participants with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to Table 6.2.1 for dose modifications due to hepatic impairment.

Table 6.2.1. Dose Modification Guidance for Hepatic Impaired Participants

	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.

6.3 Venetoclax Dose Modifications for first dose of Venetoclax (100 mg) and first dose escalation (200 mg and 400 mg)

First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if laboratory values suggestive of laboratory tumor lysis syndrome are observed (see Table 6-5), the patient should be hospitalized for monitoring and the investigator notified. Use 0-4 hour pre-dose values for each escalation day for comparison for TLS determination. No additional venetoclax doses should be administered until resolution. Rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any participant hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of 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, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- If a diagnosis of laboratory or clinical TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to Table 6-5 below, for participants receiving the first dose of Venetoclax:

- For potassium increase ≥ 0.5 mmol/L from pre-dose baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT and refer to Appendix D for further management, unless determined to be not clinically indicated

by the investigator.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT, unless determined to be not clinically indicated by the investigator.

See Appendix D for additional recommendations on management of laboratory abnormalities not meeting the definition of laboratory TLS.

Table 6-5 Laboratory TLS

To meet the definition of laboratory TLS participants must experience two or more of the following criteria post-dose within a 24-hour span, and within seven days of initiating venetoclax therapy
or escalating the dose of venetoclax:
- Potassium > 6.0 mmol/liter
- Phosphorus > 4.5 mg/dL
- Corrected calcium < 7.0 mg/dL, or ionized calcium <1.12
- Uric acid > 8.0 mg/dL
- Increase in serum creatinine of 0.3 mg/dL

If TLS (laboratory or clinical) is diagnosed, hold venetoclax dosing until resolution to baseline and initiate supportive care per institutional guidelines. Upon resolution, resume dosing and consider additional monitoring and hospitalization for subsequent dose escalation.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Adverse events will be captured after study treatment initiation and through 30 days after the last dose of study treatment. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

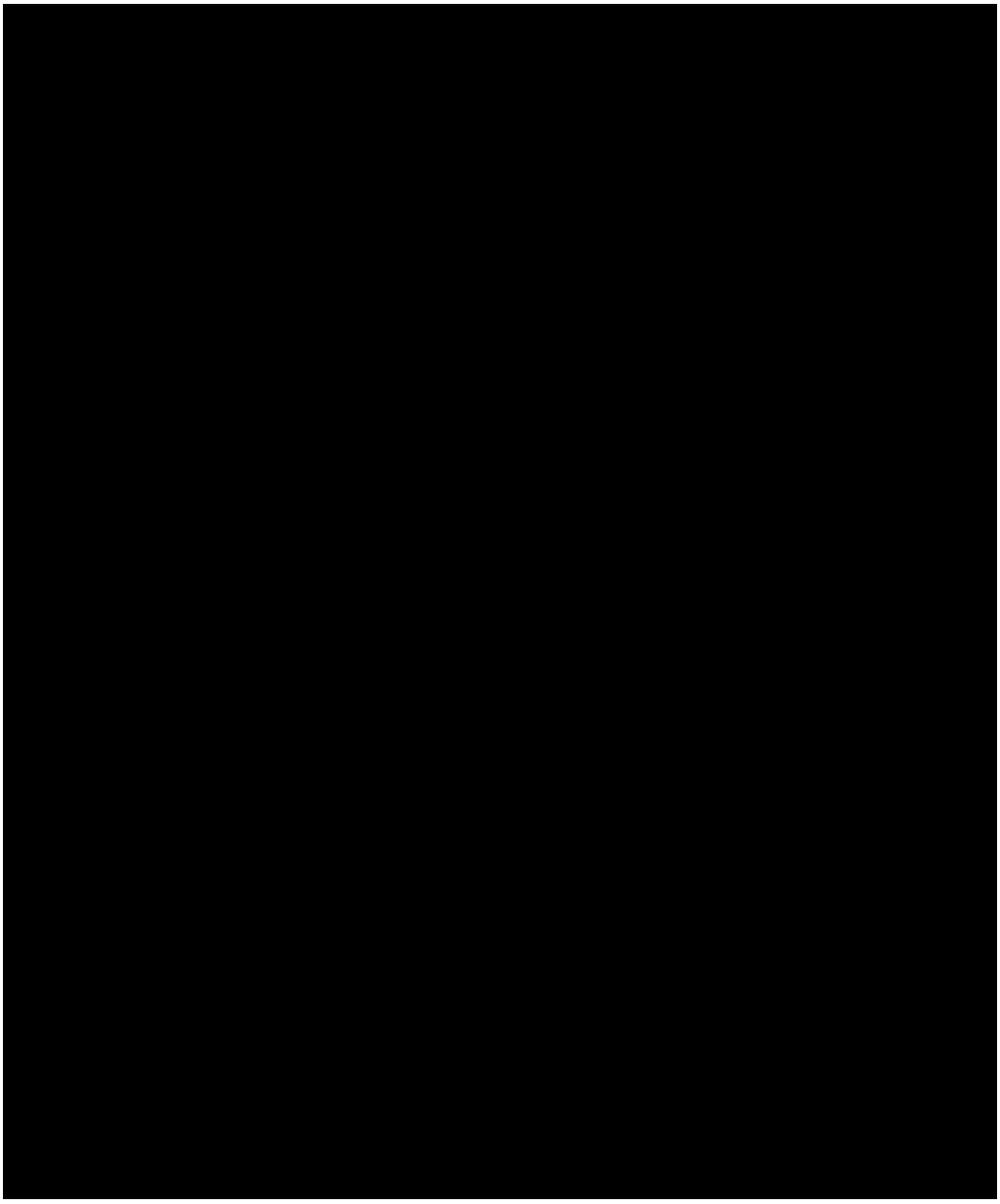
7.1 Expected Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for Venetoclax

Most subjects (93.8%) receiving venetoclax monotherapy reported at least 1 adverse event. The most common adverse events were neutropenia (32.7%), diarrhea (36.8%), nausea (35.8%), and fatigue (24.5%).



7.1.1.2 Adverse Event List(s) for Ibrutinib

Bleeding-related events

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

Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. See Section 5.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 5.4.1 for guidance on ibrutinib management with surgeries or procedures.

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).

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

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).

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

Infections
Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. 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.

Non-Melanoma Skin Cancer
Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Rash
Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. 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.

Lymphocytosis

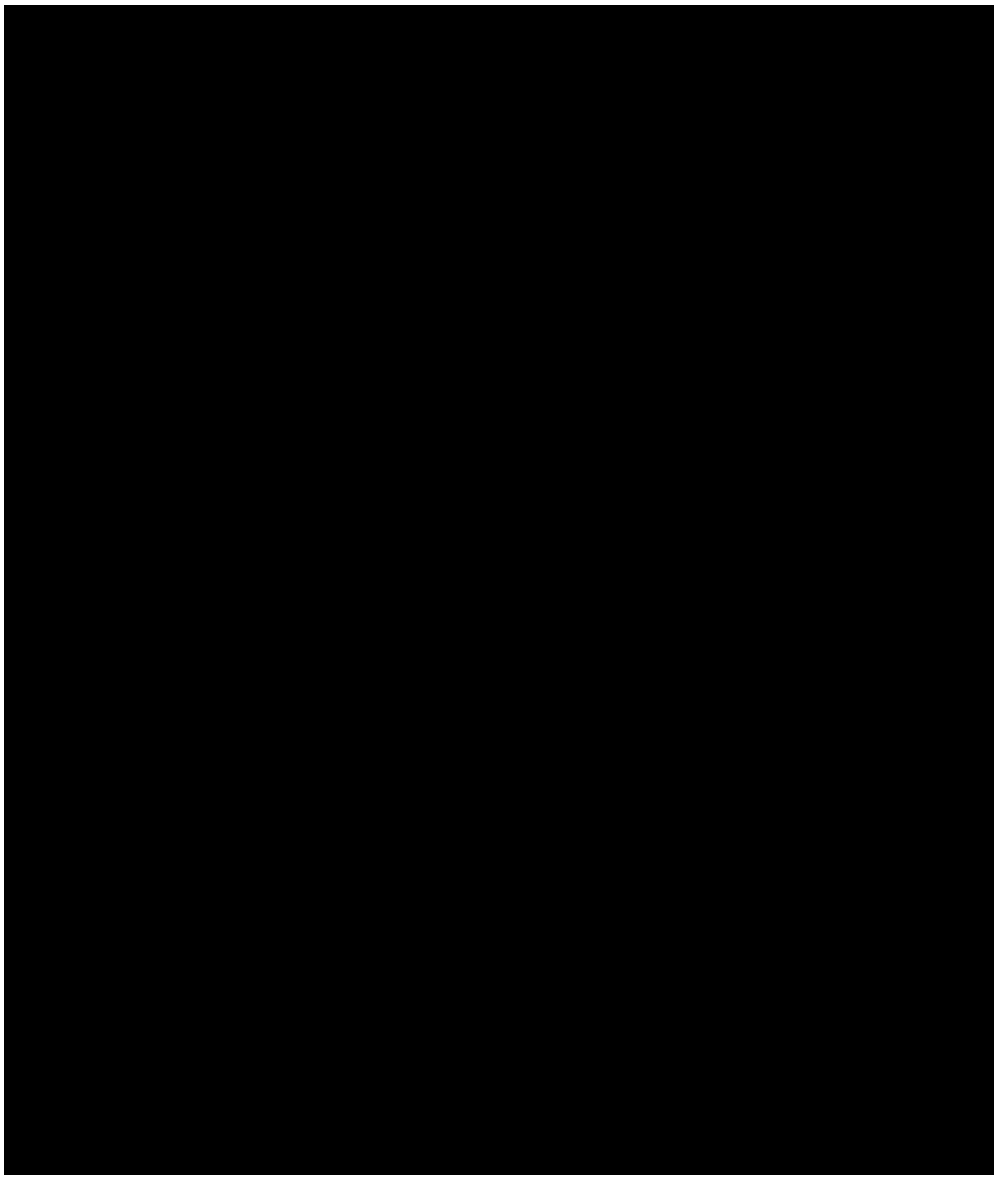
Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5,000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/small lymphocytic lymphoma (SLL) treated with ibrutinib as single agent. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. A large increase in the number of circulating lymphocytes (eg, >400,000/mcL) has been observed in some subjects.

Tumor Lysis Syndrome

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

Interstitial Lung Disease (ILD)

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



7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

N/a

7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Routine Adverse Event Reporting to 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 (A) all pregnancies and all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the pregnancy/event regardless of the relationship of the event to the AbbVie product; and (B) any pregnancies experienced by a partner of a Study subject receiving AbbVie product within one business day of becoming aware of such partner pregnancy; and (C) all non-serious adverse events of tumor lysis syndrome. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such pregnancy/event, if specifically requested by AbbVie..
    i. Serious AE (SAE) means any untoward medical occurrence that meets one of the following criteria:
        i. Results in death
        ii. Is life-threatening
        iii. Requires inpatient hospitalization for >24 hours or prolongation of hospitalization
        iv. Is a congenital anomaly
        v. Results in persistent or significant disability/incapacity
        vi. Other serious (Important Medical Events) Events that do not fit the other outcomes but may require medical or surgical intervention to prevent one of the other outcomes.
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 *PPDINDPharmacovigilance@abbvie.com*

7.8 Expedited Reporting to Pharmacyclics, LLC

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) and sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3372) to Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E) or designee, within 24 hours of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.
All SAEs that have not resolved by the end of the study, or that have not resolved upon

discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

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

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

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

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.
- Any pregnancy occurring in a female participant or female partner of a male participant must be reported from the time of first dose up until 90 days after the last dose of study drug. This should be reported on the Pregnancy Report Form Part 1. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

7.8.1 Adverse Events of Special Interest (AESI)

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

7.8.1.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

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

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 7.7.1 above.

7.8.2 Pregnancy

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

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

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

7.8.3 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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 *Venetoclax*

8.1.1 Description

Venetoclax (ABT-199) has the molecular formula C45H50ClN7O7S and a molecular weight of 868.44. ABT- 199 is a light yellow to dark yellow powder and is freely soluble in vinylpyrrolidone dimer; soluble in polyethylene glycol (PEG) 400; very slightly soluble in 1% (w/v) Cremophor RH40, and is practically insoluble in water. There are no optical isomers.

8.1.2 Form

Venetoclax (ABT-199) is provided as a yellow film-coated tablet in 50 and 100mg strength. 100mg tablets will be supplied for this study.

8.1.3 Storage and Stability

Venetoclax tablets will be supplied in blister cards or bottles and supplied by AbbVie. See label for storage conditions.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label.

8.1.4 Compatibility

N/a.

8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Venetoclax is provided by AbbVIE, Inc. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

8.1.7 **Preparation**

Venetoclax (ABT-199) is provided as a yellow film-coated tablet in 50 and 100mg strength. 100mg tablets will be supplied for this study in blister cards of 8 or 16, or in 120 count bottles which must not be opened and re- packaged. Additionally, the bottles cannot be opened for removal and destruction of excess pills to prevent a large overage quantity. It will be packaged in high density polyethylene (HDPE) plastic bottles to accommodate the study design. Each bottle or blister card will be labeled per regulatory requirements. Labels must remain affixed to the bottle or blister card.

8.1.8 **Administration**

Venetoclax (ABT-199) should be self-administered daily by the participant and should be taken at approximately 30 minutes after a meal, at approximately the same time each day. Venetoclax should be administered with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE due to CYP3A4 inhibition). The tablets should be swallowed intact. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the participant should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Dietary habits around the time of Venetoclax intake should be as consistent as possible throughout the study. If the pills are vomited this should be noted on the diary, but a replacement dose should not be taken that day. A study diary will be used to aid with study drug administration compliance. Except for cycle 2 which may be longer, one cycle of Venetoclax is once daily, oral administration for 4 weeks ± 1 week. At each study visit, enough Venetoclax will be dispensed until the next cycle. For cycle 2, a new prescription will be written for each dose escalation (i.e. 1 week of dosing for C2D1 at starting dose, 1 week of dosing for C2D8 at escalated dose, and 2 weeks of dosing for C2D15 at target dose). Participants who have difficulties reaching the maximum target dose during dose escalation may have additional prescriptions written during Cycle 2. For visits occurring monthly (every 4 weeks ± 1 week), one cycle of pills (5 weeks of venetoclax therapy) will be dispensed. For visits occurring every 12 weeks ± 2 weeks), three cycles of pills (14 weeks) will be dispensed.

8.1.9 **Ordering**

Venetoclax (ABT-199) is an investigational agent and will be supplied free-of-charge from AbbVIE, Inc.

The contact for ordering is:
iisoncologysupport@abbvie.com

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record

Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

Unused venetoclax tablets will be returned by the participant, collected and counted at each study visit, and will be returned to pharmacy for destruction. Unused supplies of venetoclax should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

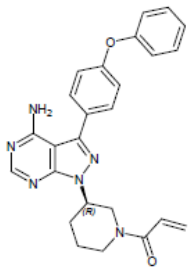
8.2 *Ibrutinib*

8.2.1 **Description**

Ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib exhibited 18% to 23% oral bioavailability in rats and 7% to 11% oral bioavailability in dogs. The mean terminal half-life of ibrutinib after oral administration ranged from 1.7 to 3.1 hours in mice, 1 to 4.7 hours in rats, and 3.3 to 6.4 hours in dogs. In healthy subjects and in patients with B-cell malignancies, ibrutinib is readily absorbed with a median time to maximum concentration (T_{max}) of 1 to 2 hours and half-life of 4 to 6 hours.There are no effects of mild and moderate renal impairment on drug clearance. . A hepatic impairment study was performed in non-cancer subjects administered a single dose of 140 mg ibrutinib under fasting conditions. Ibrutinib AUC_{last} increased 2.7-, 8.2- and 9.8-fold in subjects with mild (n = 6; Child-Pugh Class A), moderate (n = 10; Child-Pugh Class B) and severe (n = 8; Child-Pugh Class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0%, 3.8%, and 4.8% in subjects with mild, moderate, and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound,last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe impairment, respectively. The recommended doses for patients with mild and moderate liver impairment are 280 mg/day and 140 mg/day (Child-Pugh Class A and B, respectively). It is recommended not to administer ibrutinib to subjects with severe hepatic impairment (Child-Pugh Class C). In vitro studies have indicated that ibrutinib is metabolized extensively by cytochrome P450 (CYP) 3A4.

8.2.2 **Form**

The structure of ibrutinib is:



Ibrutinib is a white to off-white crystalline solid. Ibrutinib has a single chiral center and is the R-enantiomer. Ibrutinib product is manufactured for Pharmacyclics LLC by a contract manufacturer.

Ibrutinib PO Hard Gelatin Capsule is an oral formulation containing micronized ibrutinib and the following compendial excipients: microcrystalline cellulose (NF); croscarmellose sodium (NF); sodium lauryl sulfate (NF); may contain magnesium stearate (NF). The 140 mg strength contains 140 mg of the active ingredient, ibrutinib, adjusted for water content and purity in a size 0, gray, hard gelatin capsule. Capsules are packaged in 60-cc high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle is distributed by Pharmacyclics LLC. The number of capsules per bottle is indicated on the label.

8.2.3 **Storage and Stability**

Ibrutinib should be stored according to the package insert.

8.2.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 **Availability**

Ibrutinib is provided by Pharmacyclics, LLC. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations

8.2.6 **Preparation**

Ibrutinib capsules are packaged in 60-cc high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. 140mg capsules will be supplied for this study in 92 or 120 count bottles which must not be opened and re-packaged. Additionally, the bottles cannot be opened for removal and destruction of excess pills to prevent a large overage quantity. Each bottle will be labeled per regulatory requirements. Labels must remain affixed to the bottle.

8.2.7 **Administration**

Ibrutinib 420 mg will be prescribed per the FDA package label, administered orally once daily. Ibrutinib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. The capsules should be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water. Participants will be reminded that dietary habits around the time of ibrutinib intake should be as consistent as possible throughout the study. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (see section 5.3).

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible within 6 hours, with a return to the normal schedule the following day. The participant should not take

extra capsules to make up the missed dose. The participant will be instructed to document missed drug doses in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

One cycle of ibrutinib is once daily, oral administration for 4 weeks +/- 1 week. At each study visit, enough ibrutinib will be dispensed until the next cycle. For visits occurring monthly, one cycle of capsules in a bottle will be dispensed. For visits occurring every 12 weeks +/-1 weeks three cycles of capsules will be dispensed. Study drug may not be shipped to the participant without approval from Pharmacyclics, LLC and may not be dispensed to anyone other than the participant. Drug accountability will be done at each Day 1 study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. Returned capsules must not be re-dispensed to any participant.

8.2.8 **Ordering**

Ibrutinib will be provided free-of-charge. Ibrutinib will be supplied by Pharmacyclics LLC. Participating sites will order ibrutinib directly from Pharmacyclics LLC. Ibrutinib orders will be emailed to ist.ctep@pcyc.com.

8.2.9 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.10 **Destruction and Return**

Unused ibrutinib capsules will be returned by the participant, collected and counted at each study visit, and will be returned to pharmacy for destruction. Unused supplies of ibrutinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2.11 **Overdose**

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 Assessment of MYD88 L265P and CXCR4 WHIM genotyping.

Genomic and transcriptional studies

Serial whole exome (WES) and transcriptome studies will be performed using bone marrow aspirates (40 ml in 2 heparinized syringes and 2 purple tops) and peripheral blood (PB) samples (2 lavender tops) that will be collected from all study participants at baseline, cycles 7, 13, and EOT. This will include genotyping for MYD88 and CXCR4. Bone marrow (BM) and peripheral blood (PB) mononuclear cells will be isolated by density gradient centrifugation, and WM lymphoplasmacytic cells isolated from BM aspirates by $CD19^+$ selection using immunomagnetic MACS micro-beads (Miltenyi-Biotech, Auburn, CA). By previous studies, the purity of isolated B-cells ($CD19^+$) was over 90%, and median clonal B-cell population by light chain restriction was >95% by this method. CD19-depleted PBMC will be used as normal paired tissue. High molecular weight DNA will be isolated using Allprep DNA/RNA mini kit (Qiagen, Valencia, CA). Library construction and WES of paired-end clones will be performed by the Center for Cancer Genomic Discovery at the Dana-Farber Cancer Institute. Read sequences will be aligned to reference genome NCBI Build 37. High confidence somatic variants will be identified using CGAT version 1.3 with a somatic score of 0.1, giving an estimated one false somatic single nucleotide variant per 17.7 Mb of DNA. Copy number will be estimated by %GC normalized read depth, and acquired uniparental disomy (aUPD) identified as copy-neutral loss of heterozygosity. Allele imbalance will be determined by percentage of reads mapping to the minor allele at heterozygous SNPs averaged over 100 Kb. Transcriptome studies will be performed using Illumina HiSeq platform. Gene expression will be inferred from read counts, and correlated to genomic findings and response to therapy. Categorical comparisons will be analyzed using the Fisher's exact probability test, and the Mann-Whitney U-test to evaluate ordinal comparisons. Benjamini Hochberg correction will be used for multiple comparison testing with a p-value ≤ 0.05 deemed to be significant. Calculations will be performed with R (R Foundation for Statistical Computing, Vienna, Austria). Confirmatory and additional exploratory studies will also be performed on collected DNA and RNA that are relevant to WM pathobiology and treatment outcome.

The samples will be used until depletion.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 30 days prior to start of protocol therapy. Scans and bone marrow biopsy & aspirate must be done ≤90 days prior to the start of therapy.

	Screening	Treatment Phase								Off Treatment Assessment	Follow-Up Phase	EDC Timepoints
	≤ 30 days from study entry	Cycle 1 Ibrutinib Alone*	Cycle 2 Venetoclax Lead-in Period						Cycle 3	Cycles 4+ (every 12 weeks +/- 1weeks)	Within 4 weeks of completion or removal from study ± 2 weeks	Post Treatment; Every 12 ± 2 weeks for four years or death for maximum of 6 years from C1D1	
		Day 1	Day 1 (+/- 3 days)	Day 2	Day 8 (+/- 2 days)	Day 9	Day 15 (+/- 2 days)	Day 16	Day 1 (+/- 3 days)	Day 1			
Physical exam, weight, height[1]	X	X*	X						X	X[9]	X		Baseline
Medical History	X												Baseline
ECOG performance status (see Appendix A)	X	X*	X						X	X	X		Screening only
CT of the chest & abdomen / pelvis[2]	X									X[2]	X[2]	X (if applicable)	All required timepoints. If a CT is performed during any Cycle visit, it must be captured.
Bone marrow biopsy and aspiration, and peripheral blood research sampling[3]	X									X[3]	X[3]	X (if applicable)	All required timepoints. If a Bone marrow assessment is performed during any Cycle visit, it must be captured.
Serum immuno-electropheresis, Free light chains, & Response assessment	X	X	X						X	X	X	X(if applicable)[10]	All required timepoints
Serum IgM, IgA, IgG	X	X	X						X	X	X	X (if applicable)[10]	All required timepoints
Complete Blood Count plus differential[1, 4]	X	X	X	X	X	X	X	X	X	X	X	X (if applicable)[10]	All required timepoints
Coagulation profile: PT, PTT, PT-INR[5]	X												n/a
Chemistry including: Potassium, creatinine, bicarbonate, calcium, Electrolytes, Renal (BUN, Creatinine) and Hepatic function testing [ALT, AST, Alk phos, total Bilirubin], albumin, total protein,	X	X	X	X	X	X	X	X	X	X	X		Baseline
Tumor lysis labs: Potassium, Creatinine, Bicarbonate, Calcium, Phosphorus, LDH, uric acid**	X		X**	X**	X**	X**	X**	X**					Baseline, Cycle 2 Day 1, 2, 8, 9, 15, 16 & as needed during Cycle 2 only.
Beta-2 microglobulin, Von Willebrand screening Magnesium	X												Baseline
Pregnancy Test[6]	X												n/a

HBsAg, HBsAb, HBcAB, HCV Ab, HIV,	X												n/a
Cryoglobulins, Cold agglutinins	X												Baseline
Venetoclax in clinic administration[8]			X		X		X						All required timepoints
IND Agent Ibrutinib		As Described in Section 5.3											All cycles
IND Agent Venetoclax			As Described in Section 5.3										Cycle 2-24
QOL Questionnaire[8]		X	X							X[7]	X	X[7]	All required timepoints
Review patient diary			X						X	X			N/a
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X		During all visits
Survival status	X	X	X						X	X	X	X[11]	All required timepoints

* Physical exam, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 14 days of Screening. Height only needs to be collected at screening.

**TLS monitoring and management will depend on criteria in section 5.3.1 *Tumor Lysis Syndrome*. All Chemistry and TLS laboratories will be drawn on dose escalation days at 0 hour, 8 hours post dose, and 24 hours post dose until the target dose is reached. Hematology labs should be done at 0 hours and 24 hours post dose until the target dose is reached. At a minimum they will be drawn during Cycle 2 on Days 1, 2, 8, 9, 15, and 16.

[1]More frequent visits may be required at the discretion of the treating physician. Telehealth may be utilized at the discretion of the PI.

[2]**If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of C1D1 they will not be required at the screening visit.** Scans will be **repeated at cycles 7, 13, and EOT, and then every 12 months during follow-up for participants with extramedullary disease at baseline defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis.** Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease at baseline and at the discretion of the investigator.

[3]**If a bone marrow biopsy and aspiration were done within 90 days of C1D1, it will not be repeated.** Bone marrow biopsy and aspiration are **required at Cycles 7, 13, EOT, and then every 12 months during follow-up.** Bone marrow biopsy and aspiration may also be done at the investigator's discretion, and at any time to confirm a complete response if the participant has no detectable monoclonal protein. MYD88 and CXCR4 mutational status will be assessed at each bone marrow biopsy. 2 10 cc lavendar tops of peripheral blood should be collected at each bone marrow timepoint.

[4]For patients who demonstrate therapy-related hematological toxicity, more frequent CBC evaluations are strongly recommended.

[5]Coagulation profile. Prothrombin time (PT) will be performed at screening and repeated as clinically indicated. PT will be reported as well as the international normalized ratio (INR) and PTT.

[6]For women of childbearing potential only: Serum pregnancy test is required at screening.

[7]QOLs should be performed at C1, C4, C7, C13, C19, EOT, and every 6 months thereafter through follow-up.

[8] QOL can be collected via telephone or email

[9] Physical exam, and weight need to be collected at every other visit starting at Cycle 7 (i.e. C7D1, C13D1, C19D).

[10] Participants will undergo assessments during follow-up until time to progression or new therapy. After PD or new therapy initiation, participants will be followed for survival status only

[11] Participants who have experienced disease progression or started new therapy will be followed for survival status only every 6 months (+/- 2 weeks)

11. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be evaluated for response every 4 weeks ± 1 week for cycles 2, 3 and 4, and thereafter every 12 weeks ± 1 weeks for the remaining cycles, and within 4 weeks ± 2 weeks from when a participant is removed from trial or when treatment is completed. IgMs measured intra-cycle during Cycle 1 and 2 should not be used for response or nadir determination. Post-treatment, patients will continue to be followed-up every 12 weeks ± 2 weeks for 3 years. Participants will be assessed for efficacy by consensus panel criteria according to section 11.1.2 below adopted from the Sixth International Workshop on WM [30].

11.1 Antitumor Effect – Hematologic Tumors

11.1.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.1.2 Response Criteria Modified VIth IWWM (NCCN 2014)

Participants may undergo plasmapheresis when clinically indicated. Those who undergo plasmapheresis will be unevaluable for any response assessment for 28 days. If plasmapheresis occurs between screening and Cycle 1 Day 1, the screening serum IgM should be used for response determination.

Complete Response (CR): A complete response (CR) is defined as having resolution of WM related symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A complete response requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.

Very Good Partial Response (VGPR): is defined as ≥90% reduction in serum IgM levels, or normalization of serum IgM levels with persistent IgM monoclonal spike in SPEP or immunofixation.

Partial Response (PR): Partial response (PR) is defined as achieving a ≥50% reduction in serum IgM levels.

Minor Response (MR): A minor response (MR) is defined 25-49% reduction in serum IgM levels.

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM level occurs with an absolute increase of at least 500 mg/dL from the lowest attained response value, or progression of clinically significant disease related symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event. For participants on active therapy who are on an ibrutinib drug hold for > 7 days, serum IgM levels will be considered unevaluable for response assessment. Patient must be on ibrutinib for >2 consecutive weeks to be considered eligible for serum IgM response assessment. An increase of 1 cm in any axis for adenopathy, or 2 cm in the craniocaudal axis of the spleen will be considered evidence of progression of extramedullary disease. Development of Bing Neel syndrome, or other extramedullary disease manifestations, as well as disease transformation will be considered as progressive events.

Stable Disease (SD): Stable disease is defined as having <25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

Overall Response Rate (ORR): Includes patients who achieved MR, PR, VGPR and CR.

11.1.1 Time-to-event definition

- Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death). Median, 2-year and 4-year landmark PFS analysis will be determined.
- Overall survival (OS) is defined as the duration of time from start of treatment to time of death or last follow-up. Median, 2-year and 4-year landmark OS analysis will be determined.
- The duration of response (DOR) for a given participant will be defined as the number of days from the day the criteria are met for ORR to the date that PD or death are objectively documented. If a participant is still responding, then the participant's data will be censored at the last study visit at which a tumor assessment was performed.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review the protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

- N/a

12.4 Collaborative Agreements Language

N/a.

13. STATISTICAL CONSIDERATIONS

This is a single-arm open-label Phase II study to evaluate the safety and efficacy of Ibrutinib combined with Venetoclax (IVEN) in symptomatic, treatment naïve WM patients.

Study treatment for all participants was terminated by the Sponsor-Investigator in March of 2022 due to 4 events of ventricular arrhythmia. As of 4/1/22 all participants were notified and instructed to stop study treatment and accrual was permanently discontinued.

13.1 Study Design/Endpoints

The primary endpoint of the current study is:

- To evaluate the rate of VGPR or better of the combination Ibrutinib + Venetoclax (IVEN) in participants with symptomatic, treatment naïve WM, within 24 months of therapy.

13.2 Sample Size, Accrual Rate and Study Duration

Following a Fleming's one step approach, and assuming a null (H0) VGPR or better rate of 25% (based on previous experience on single-agent ibrutinib efficacy in previously untreated patients with WM), and an alternative (H1) VGPR rate of 45%, a total of 50 evaluable patients need to be accrued to show the proposed difference with an alpha (2-sided type I error) of 0.03 and a power (1-beta or type II error) of 87%. Assuming 10% drop out or unevaluable rate, up to 55 participants will be enrolled. If 19 or more participants obtain a VGPR then the combination of ibrutinib and venetoclax warrants further evaluation. If fewer than 19 participants obtain a VGPR, the combination should not continue further evaluation.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	6	=	8
Not Hispanic or Latino	10	+	32	=	42
Ethnic Category: Total of all participants	12 (A1)	+	38 (B1)	=	50 (C1)
Racial Category					
American Indian or Alaskan Native		+		=	
Asian		+	1	=	1
Black or African American	1	+	1	=	2
Native Hawaiian or other Pacific Islander		+		=	
White	11	+	36	=	42
Racial Category: Total of all participants	12 (A2)	+	38 (B2)	=	50(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

13.3 Stratification Factors

N/a.

13.4 Interim Monitoring Plan

N/a.

13.5 Analysis of Primary Endpoint

Continuous variables will be presented as medians and interquartile ranges. Categorical variables will be presented as numbers and proportions. Responses will be defined based on the criteria established by the 6th International Workshop on WM. The outcome of interest will be achievement of VGPR or better at 24 months from treatment initiation. For this study, a VGPR rate of 25% or less will be considered H0, and a VGPR of at least 45% for patients on IVEN will be considered H1. Participants who have completed at least 4 weeks (1 cycle) of n therapy are evaluable. Participants who are evaluable and discontinue protocol therapy for any reason prior to Cycle 2 Day 1 will be considered to be non-responders.

13.6 Analysis of Secondary Endpoints

The secondary endpoints are:

- To evaluate the rates of CR with IVEN in participants with symptomatic treatment naïve WM at 6, 12 and 24 cycles of therapy.
- To evaluate the best overall response to IVEN in participants with symptomatic, treatment naïve WM.
- To evaluate the rate of VGPR at 30 months post treatment initiation. To evaluate median time to response, median time to major response and median time to VGPR to IVEN in participants with symptomatic, treatment naïve WM.
- To evaluate the 24-, 36-, 48-, 60-month Progression Free Survival (PFS) of IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the overall survival of participants treated with IVEN
- To evaluate the time to next treatment with IVEN
- To evaluate the effect of IVEN in the bone marrow burden of disease in participants with symptomatic treatment naïve WM.
- To evaluate the impact of CXCR4 mutations on response to IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the safety profile of IVEN in participants with symptomatic treatment naïve WM.
- To evaluate the impact of IVEN in the participants' QOL.

Continuous variables will be presented as medians and interquartile ranges. Categorical variables will be presented as numbers and proportions Responses will be defined based on the criteria established by the 6th International Workshop on WM. Secondary outcomes will include the rate of VGPR at 30 months from treatment initiation, and the rate of progression-free survival (PFS) at 24, 36, 48 and 60 months from initiation of study treatment. Overall survival will also be evaluated as a secondary endpoint.

PFS analysis will be performed using the Kaplan-Meier methodology, and participants will be censored at the time of last relevant assessment if they have not demonstrated the event of interest by the end of the study. Interim analyses for safety and efficacy will be performed when 15 patients had completed 6 and 12 months of study treatment.

In recent studies, the MYD88 and CXCR4 mutational status are predictive of clinical status, response to therapy and survival outcomes (Cao 2013, Treon 2013, Treon 2014). Activating MYD88 as well as nonsense and frameshift WHIM-like CXCR4 somatic mutations are common in Waldenström macroglobulinemia. CXCR4 nonsense mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival. The MYD88 L265P mutational analysis by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing will be performed by the Bing Center for Waldenström Macroglobulinemia in Boston, MA.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants who receive at least one dose of any test material during the study will be included in the safety analysis.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All participants who have completed at least 4 weeks of protocol therapy will be included in the evaluation of primary efficacy endpoint. Each participant should be assigned a response category based on the response criteria in Section 11.1.2.

14. PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

14.1 Protocol Amendments

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

REFERENCES

1. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2012. 367(9): 826-33.
2. Jimenez C, Sebastian E, Chillon MC, et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenstrom's macroglobulinemia. *Leukemia*. 2013. 27(8): 1722-8.
3. Mori N, Ohwashi M, Yoshinaga K, et al. L265P mutation of the MYD88 gene is frequent in Waldenstrom's macroglobulinemia and its absence in myeloma. *PLoS One*. 2013. 8(11): e80088.
4. Poulain S, Roumier C, Decambron A, et al. MYD88 L265P mutation in Waldenstrom macroglobulinemia. *Blood*. 2013. 121(22): 4504-11.
5. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. *Blood*. 2013. 121(13): 2522-8.
6. Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. *Blood*. 2013. 122(7): 1222-32.
7. Watters TM, Kenny EF, O'Neill LA. Structure, function and regulation of the Toll/IL-1 receptor adaptor proteins. *Immunol Cell Biol*. 2007. 85(6): 411-9.
8. Lin SC, Lo YC, Wu H. Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL-1R signalling. *Nature*. 2010. 465(7300): 885-90.
9. Kawagoe T, Sato S, Matsushita K, et al. Sequential control of Toll-like receptor-dependent responses by IRAK1 and IRAK2. *Nat Immunol*. 2008. 9(6): 684-91.
10. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood*. 2014. 123(11): 1637-46.
11. Busillo JM and Benovic JL. Regulation of CXCR4 signaling. *Biochim Biophys Acta*. 2007. 1768(4): 952-63.
12. Treon SP, Cao Y, Xu L, et al. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. *Blood*. 2014. 123(18): 2791-6.
13. Roccaro AM, Sacco A, Jimenez C, et al. C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. *Blood*. 2014. 123(26): 4120-31.
14. Bajwa N, Liao C, Nikolovska-Coleska Z. Inhibitors of the anti-apoptotic Bcl-2 proteins: a patent review. *Expert Opin Ther Pat*. 2012. 22(1): 37-55.

15. Hatjiharissi E, Mitsiades CS, Bryan CT, et al. Comprehensive Molecular Characterization of Malignant and Microenvironmental Cells in Waldenstrom's Macroglobulinemia by Gene Expression Profiling. *ASH Annual Meeting Abstracts*. 2007. 110(11): 3174-.
16. San Miguel JF, Vidriales MB, Ocio E, et al. Immunophenotypic analysis of Waldenstrom's macroglobulinemia. *Semin Oncol*. 2003. 30(2): 187-95.
17. Castillo JJ, Gustine J, Meid K, et al. PROSPECTIVE PHASE II STUDY OF VENETOCLAX (VEN) IN PATIENTS (PTS) WITH PREVIOUSLY TREATED WALDENSTROM MACROGLOBULINEMIA (WM). *EHA abstract*. 2018: S854.
18. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med*. 2015. 372(15): 1430-40.
19. Treon SP, Xu L, Hunter Z. MYD88 Mutations and Response to Ibrutinib in Waldenstrom's Macroglobulinemia. *N Engl J Med*. 2015. 373(6): 584-6.
20. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol*. 2017. 18(2): 241-250.
21. Treon SP, Gustine J, Meid K, et al. Ibrutinib Monotherapy in Symptomatic, Treatment-Naive Patients With Waldenstrom Macroglobulinemia. *J Clin Oncol*. 2018: JCO2018786426.
22. Castillo JJ, Olszewski AJ, Cronin AM, Hunter ZR, Treon SP. Survival trends in Waldenstrom macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database. *Blood*. 2014. 123(25): 3999-4000.
23. Castillo JJ, Olszewski AJ, Kanan S, et al. Overall survival and competing risks of death in patients with Waldenstrom macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. *Br J Haematol*. 2015. 169(1): 81-9.
24. Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood*. 2015. 126(6): 721-32.
25. Hillmen P, Rawstron A, Munir T, et al. THE INITIAL REPORT OF THE BLOODWISE TAP CLARITY STUDY COMBINING IBRUTINIB AND VENETOCLAX IN RELAPSED, REFRACTORY CLL SHOWS ACCEPTABLE SAFETY AND PROMISING EARLY INDICATIONS OF EFFICACY. *Haematologica*. 2017. 102(s2): S570.
26. Tam CSL, Roberts AW, Anderson MA, et al. Combination ibrutinib (Ibr) and venetoclax (Ven) for the treatment of mantle cell lymphoma (MCL): Primary endpoint assessment of the phase 2 AIM study. *J Clin Oncol*. 2017. 35(15_suppl): 7520-7520.
27. Cao Y, Hunter ZR, Liu X, et al. CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P) -directed survival signalling in Waldenstrom macroglobulinaemia cells. *Br J Haematol*. 2015. 168(5): 701-7.
28. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003. 30(2): 110-5.
29. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003. 30(2): 116-20.

30. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol*. 2013. 160(2): 171-6.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B. CHILD-PUGH SCORE FOR SUBJECTS WITH LIVER IMPAIRMENT

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

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

Source:

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

APPENDIX C. DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Classification of Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid > 8.0 mg/dl (475.8μmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dl (1.5mmol/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 definited as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injurt 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.

APPENDIX D: MANAGEMENT RECOMMENDATIONS FOR LABORATORY ABNORMALITIES FOR VENETOCLAX FIRST DOSE AND ESCALATION

The following table includes recommendations for the management of laboratory abnormalities in the setting of venetoclax first dose and dose escalation. If laboratory TLS is suspected or confirmed, venetoclax should be stopped until resolution and treatment should be administered per institutional guidelines. Otherwise, additional monitoring will be at the discretion of the investigator and venetoclax may be continued.

Abnormality	**Dose Modification and Management recommendation**
Laboratory Events	
Hyperkalemia (Including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL]) *Hospitalization at discretion of investigator ****If sample is hemolyzed, sample should be re-taken before any intervention is instituted**	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-2 hours 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 but less than (6 mmol/L) 6 mEq/L and/or asymptomatic *Hospitalization at discretion of investigator ****If sample is hemolyzed, sample should be re-taken before any intervention is instituted**	• Consider performing ECG. • Consider Kayexalate 60 g (or Resonium A 60 g). • Consider furosemide 20 mg IV × 1. • If there is ECG/telemetry evidence of life-threatening arrhythmia, the patient should be sent to ED and managed accordingly • Recheck potassium, phosphorus, uric acid, calcium and creatinine STAT within 1-2 hours of intervention. • If potassium < ULN on recheck and no evidence of tumor lysis, resume per protocol. • If potassium > ULN but less than 6 mmol/L 1-2 hours later and no evidence of tumor lysis, treat as potassium > ULN but less than 6 mmol/L. • If potassium >6 mmol/L, the patient should be sent to ED for further management
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g.,	• Perform STAT EKG • The patient should be sent to ED for further

muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea) *Hospitalization Indicated ****If sample is hemolyzed, sample should be re-taken before any intervention is instituted**	management
Hyperuricemia	
Uric acid ≥ 8.0 but <10 mg/dL (476 µmol/L) *Hospitalization at discretion of investigator	• IVF and recheck • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-2 hours 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 *Hospitalization Indicated	• The patient should be sent to ED for further management
Hypocalcemia	
Corrected Calcium ≤ 7.0 mg/dL (1.75 mmol/L) **AND** Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) *Hospitalization Indicated	• The patient should be sent to ED for further management
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase *Hospitalization at discretion of investigator	• Consider administering a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. If phosphorus <5.0 mg/dL 1-2 hours later and no evidence of tumor lysis, resume per protocol. • Send to ED per clinician judgement
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids.

*Hospitalization at discretion of investigator	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT. Resume per protocol testing if no further ≥25% increase. • Send to ED per clinician judgement