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Phase II Study of Bendamustine and Rituximab plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age

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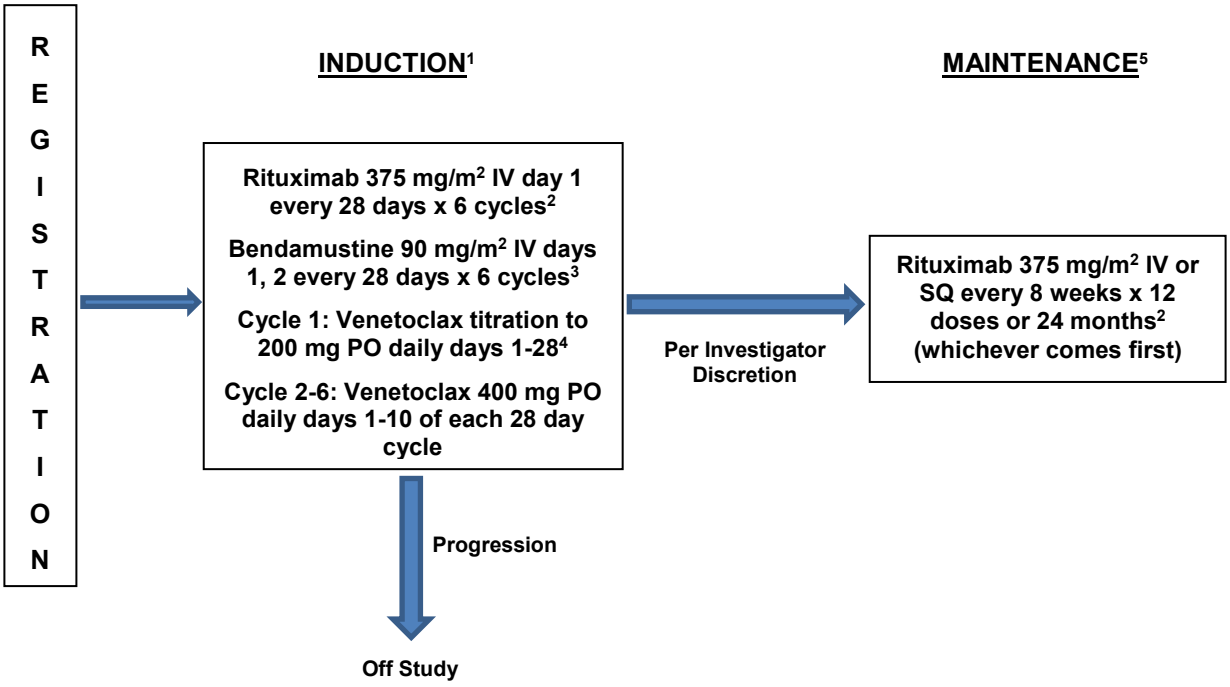
Brief Protocol Synopsis

See Protocol Document Sections for complete details

Study Schema

Mantle Cell Lymphoma (MCL)



Accrual goal: 33 patients

Cycle length: 28 days (4 weeks)

[1] Interim safety analysis planned after 19 patients are enrolled for review of tumor lysis syndrome (TLS) events. Section 12.2.1 for details.

[2] If the first two cycles of intravenous (IV) rituximab (or two consecutive cycles) are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units subcutaneous (SQ) rituximab/hyaluronic acid on Day 1 of Cycles 3-6 (or after 2 consecutive cycles are well tolerated). See Section 5.2.3 for details.

[3] Per investigator discretion, bendamustine may be started at 70 mg/m^2 in patients over the age of 75 years with comorbid conditions or patients over the age of 80 years without comorbid conditions. See Section 5.2.2 for details.

[4] Cycle 1: Goal venetoclax dose will be 400 mg but careful titration and escalation of dose will need to be done during Cycle 1 to mitigate the risk of TLS. See Section 5.3 and Section 5.4 for details.

[5] After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

NOTE: At the time of restaging (or if a scan is done earlier for another reason) and disease progression is noted, patients will come off study.

List of Abbreviations

5-HT_3	5-Hydroxytryptamine 3 Serotonin Receptor
5PS	5 Point Scale
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
anti-HBc or HBcAB	Hepatitis B Core Antibody
AST	Aspartate Aminotransferase
BCL1	B-Cell Lymphoma 1
BCL2	B-Cell Lymphoma 2
BR	Bendamustine Rituximab
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Celsius
CBC	Complete Blood Count
CBPF	Central Biorepository Pathology Facility
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CMV	Cytomegalovirus
CNS	Central Nervous System
CI	Confidence Interval
CR	Complete Response or Complete Remission
CrCl	Creatinine Clearance
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapeutic Evaluation Program
dL	Deciliter
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
ECOG-ACRIN	Eastern Cooperative Oncology Group-American College of Radiology Imaging Network
eCRF	electronic Case Report Form
eDC	Electronic Data Capture
EDTA	Ethylenediamine Tetraacetic Acid
F	Fahrenheit
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed Paraffin-Embedded

FISH	Fluorescence In Situ Hybridization
FR	Fludarabine and Rituximab
g	gram
GCP	Good Clinical Practice
GCSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCO_3	Bicarbonate
Hct	Hematocrit
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIPPA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hr	Hour
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LDH	Lactate Dehydrogenase
LDi	Longest Transverse Diameter of a Lesion
m	Meter
m^2	Meter Squared
mcg	Microgram
MCL	Mantle Cell Lymphoma
mg	Milligram
min	Minute
MIPI	MCL International Prognostic Index
mL	Milliliter
mm	Millimeter
mm^3	Cubic Millimeter
mmol	Millimole
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
n	number

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
NHL	Non-Hodgkin Lymphoma
OBI	On Body Injector
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase-Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PJP	*Pneumocystis Jiroveci* Pneumonia
PO	*per os*; By Mouth (orally)
PPD	Cross Product of the LDi and Perpendicular Diameter
PR	Partial Response or Partial Remission
PS	Performance Status
R-BAC	Rituximab-Bendamustine Cytarabine
RCHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
RPM	Revolutions Per Minute
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SDi	Shortest Axis Perpendicular to the LDi
SPD	Sum of the Product of the Perpendicular Diameters of Multiple Lesions
SQ	Subcutaneous
SRM	Study Reference Manual
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
µmol	Micromole
US	United States
vs	versus
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential
wt	Weight

1. Introduction- Background and Rationale

1.1 Mantle Cell Lymphoma – Disease Overview

Mantle cell lymphoma (MCL) is a subtype of Non-Hodgkin Lymphoma (NHL) which is considered incurable with conventional therapy. With an incidence of approximately 70,000 cases diagnosed in the United States (US) per year, the disease is rare. It typically occurs in patients over the age of 60 and 2/3rd of the cases are male.[1]

There are three variants of MCL that have different clinical and treatment implications. First is considered the typical form of MCL, occurring in 60-75% of cases. This form typically presents with symptomatic disease with lymphadenopathy and occasionally cytopenias. The second is an indolent form typically presenting with an elevated white blood cell (WBC) count and circulating lymphoma cells as well as splenomegaly. This indolent form is characterized by an often-slow course and observation alone is recommended if asymptomatic.[2] The final form is a blastic variety which is typically quite aggressive, often presenting with marked lymphadenopathy and B-symptoms including fevers, chills, sweats, and/or weight loss. Other than observation in the indolent variety, there is no treatment differences between the variants of MCL.

1.2 Induction Therapy in MCL

Initial treatment in MCL includes a combination of chemotherapy and immunotherapy. For patients who can tolerate such an approach, an aggressive chemo-immunotherapy regimen is utilized to achieve remission. This typically is followed by high dose chemotherapy with autologous stem cell rescue. This approach is too toxic for the majority of patients presenting with MCL given the advanced age at diagnosis. Other approaches have been studied with bendamustine and rituximab (BR) currently considered a standard induction regimen for patients unwilling or ineligible for aggressive therapy.

BR was first studied by the German cooperative group study evaluating RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) vs. BR in indolent NHL. The MCL cohort included 94 patients and BR had an improved median progression-free survival (PFS) over RCHOP (35.4 vs 22.1 months, Hazard Ratio (HR) 0.49, p=0.0044).[3] Superiority of BR over RCHOP was also confirmed in the US through the BRIGHT study.[4] Another study through the German cooperative group compared FR (fludarabine and rituximab) to BR in indolent NHL. The MCL cohort in this study was 47 patients and again showed improved median PFS to BR over FR (17.6 vs. 4.7 months, p=0.01).[5] These studies support BR as the standard of care for MCL patients unable to be treated with aggressive measures.

Bendamustine and rituximab is generally well tolerated in this patient population. The only elderly MCL study assessing BR showed a Serious Adverse Event (SAE) rate of 2/63 during induction; however, there were deaths during the maintenance phase of this study (3 of 62).[6] Other studies, which include other NHL histologies, show a similar rate of SAE or Grade 3/4 non-hematologic toxicities that occasionally prompts withdrawal prior to completion of recommended 6 cycles.[3,4,5] Deaths during induction are rare. However, in a retrospective study of CLL patients, dose reductions to 70 mg/m^2 occurred in half of patients over the age of 65, mostly due to neutropenia and infections.[7] Of those over the age of 75, 69% of patients required dose reduction to 70 mg/m^2. [7] This has prompted some providers to start all patients of very advanced age (over 80) and others with comorbid conditions at 70 mg/m^2 instead of 90 mg/m^2 day 1 and 2.

Maintenance rituximab is more controversial in MCL. Most providers extend maintenance rituximab after chemo-immunotherapy induction to MCL patients as it has been shown to be superior to observation alone in other histologies of NHL.[8] However, the German group evaluated maintenance rituximab vs. observation after BR induction in MCL. They found no statistical benefit to maintenance rituximab and a suggestion of increased toxicity.[9] However, this study was small and the report was early and only presented in abstract form.

In a conflicting study, a meta-analysis showed superiority of maintenance rituximab in MCL.[10] At this time, a consensus on this has not been reached.

1.3 Pending Studies with Bendamustine and Rituximab in MCL

Many groups have added agents active in relapsed MCL to BR with the goal of inducing deeper remissions and prolonging the interval of treatments. The E1411 intergroup study, which recently finished accrual, evaluated BR with or without bortezomib.[11] The industry-sponsored SHINE study, which also recently finished accrual, evaluated BR with or without ibrutinib.[12] The Nordic LENA-BERIT study evaluated BR with the addition of lenalidomide,[13] and the Italian R-BAC studies have evaluated BR with different doses of cytarabine.[14] The results of the induction portion of these studies, which are expected within 2 years, will set the stage for a Phase III study comparing the most promising BR based regimens. However, there are other promising therapies, including venetoclax that will likely be important in MCL within this two year time frame. This study evaluates venetoclax in combination with bendamustine and rituximab. If there is promise in this study, this combination will be considered in a larger Phase III study for induction therapy in MCL planned through the US cooperative groups.

Safety in the reported combination studies with BR indicate increased toxicity with additional drugs. The LENA-BERIT (BR+ Lenalidomide) study mentioned previously had a Grade 3-5 infection rate of 42% (21 of 51) with a death rate during induction of 3 of 51. This was considered overly toxic, though the efficacy was high in this study.[13] The addition of bortezomib and dexamethasone to BR (RiBVD) in 76 older MCL patients showed 4 deaths during induction; 1 infection, 1 progressive multifocal leukoencephalopathy (PML) and 2 cardiac arrests.[14] The rate of febrile neutropenia on this study was 11% (11 of 74) and 24 episodes of infection were identified as SAEs.[14] Therefore, there is a suggestion that studies combining novel agents with BR show more toxicity than BR alone and should be evaluated closely for toxicity including deaths and infection. It is known that bendamustine can cause delayed lymphocyte recovery and thus atypical infections, such as *Pneumocystis Jiroveci* Pneumonia (PJP), Cytomegalovirus (CMV) and Herpes Simplex Virus (HSV) are possible and have been reported and seen by investigators.[15,16,17]

1.4 Venetoclax (ABT-199, GDC-0199)

Venetoclax is a novel, oral, highly selective BCL2 inhibitor which is currently Food and Drug Administration (FDA) approved in relapsed chronic lymphocytic leukemia (CLL).[18] Inhibition of BCL2, an anti-apoptotic protein that is overexpressed in many NHL's, allows for apoptosis to proceed and induces rapid cell kill.[19] Venetoclax has been studied in various NHL histologies as a single agent and in combination with chemotherapy and other targeted agents.

1.4.1 Clinical Efficacy and Safety in MCL and NHL

Response to single-agent venetoclax has been documented in 28 relapsed MCL patients in a Phase I study evaluating all histologies of NHL. The MCL cohort had an overall response rate (ORR) of 75% (n=21) with few complete responses (CRs) (n=6, 21%).[20] Given the risk of TLS, the dose of venetoclax was increased from 20 mg to the target dose over several weeks. The ending dose was 200 mg (n=1), 400 mg (n=9), 600 mg (n=4), 800 mg (n=7), 900 mg (n=1) and 1200 mg (n=6). There was no difference in efficacy between these doses and the target dose going forward for MCL is 400 mg orally (PO) daily. Additional studies evaluating combinations of venetoclax with chemotherapy and other targeted agents are on-going.

Venetoclax is generally safe though the majority of patients will experience a treatment emergent adverse event. Common side effects in NHL are mostly hematologic including neutropenia (Grade 3 or 4: 14.8%), febrile neutropenia

(Grade 3 or 4: 2.2%), thrombocytopenia (Grade 3 or 4: 9.6%), and anemia (Grade 3 or 4: 14.8%). Gastrointestinal (GI) toxicities including nausea and diarrhea are also common but tend to be low grade (all grade 47%, Grade 3 or 4 <1%). Infections, mostly being upper respiratory can also be seen with venetoclax. Please see the Investigator Brochure (IB) and prescribing information for more detail.[21,22]

1.4.2 Venetoclax Clinical Pharmacology[21]

Venetoclax is dosed daily with good bioavailability. In NHL, plasma concentrations peaked at approximately 4-8 hours after doses between 50 and 400 mg daily and had a half-life of 14.1 to 18.2 hours. Absorption is improved with a meal or snack. Venetoclax and its metabolites are metabolized by CYP34A and is excreted through the bile duct and feces. There is minimal renal excretion. A Phase I study evaluating venetoclax with bendamustine did not suggest a change in pharmacokinetics with bendamustine administration.

1.4.3 Dose Rationale

Preclinical studies have evaluated venetoclax as a chemotherapy sensitizer, suggesting that venetoclax can sensitize cancer cells to chemotherapy.[23,24,25] An interim analysis of a clinical trial in follicular lymphoma has demonstrated that BR plus venetoclax is tolerable and active, though more Grade 3-4 events occurred in the venetoclax containing arm.[26] The activity of venetoclax in MCL combined with the preclinical rationale and the safety data in follicular lymphoma suggest that a Phase II study of BR + venetoclax is warranted in MCL. Dosing with chemotherapy has not been optimized. The follicular lymphoma study utilized continuous dosing of venetoclax with BR and demonstrated a Grade 3-4 Adverse Event (AE) rate of 78% compared to 46% without venetoclax.[24] We hypothesize that intermittent dosing of venetoclax will still improve efficacy over BR alone but will be better tolerated.

Venetoclax can induce clinically significant TLS in CLL with the first dose of drug.[19] The risk of TLS necessitates careful dose titration of the drug and sometimes admission for hydration and TLS monitoring. Tumor lysis has also been seen in MCL, but to a lesser degree and usually in the setting of high tumor burden (verbal communication, unpublished data). Thus, in MCL, careful upward dose titration is still needed. In this study, we will start with 20 mg of venetoclax and increase the dose weekly to a maximum dose of 400 mg by Cycle 2, Day 1.

1.5 MRD Monitoring in MCL

The absence of Minimal Residual Disease (MRD) is a powerful predictor of outcome after induction in MCL. MRD can be measured in many ways but the most sensitive is a polymerase-chain reaction (PCR) based test quantifying the presence of a clonal immunoglobulin heavy chain re-arrangement or t(11;14).[27,28] A combined analysis of transplant eligible and ineligible patients (MCL Younger and MCL Elderly studies) showed MRD positive patients consistently had an adverse PFS after all induction treatment (chemotherapy in MCL Elderly and chemotherapy followed by autologous stem cell transplant (SCT) in MCL Younger).[29] Patients in clinical remission after induction also have a survival advantage if there is no MRD detected at that time.[29] Thus, MRD is a quick, meaningful surrogate of PFS and overall survival (OS) after induction therapy in MCL patients.

1.6 Summary of Rationale for Proposed Study

To summarize, there are several pending studies combining various agents with what is considered a standard therapy, bendamustine and rituximab, in MCL patients ineligible for aggressive therapy. This study seeks to add venetoclax, a promising single agent in MCL, to BR with plans to add this regimen, if promising, to a larger Phase III study of various BR

combinations in MCL.

Given the risk of TLS in MCL, venetoclax dose will be escalated through Cycle 1 with close monitoring of TLS. The monotherapy dose of venetoclax moving forward in MCL is 400 mg daily and there is no suggestion that combination with BR will change the pharmacokinetics of venetoclax. Thus, the maximum dose of 400 mg PO daily will be used from Cycle 2 onward. Given toxicity seen in the follicular lymphoma study combining BR with continuous venetoclax, we will utilize venetoclax as a chemosensitizer and only treat for 10 days with each cycle. Maintenance rituximab will be allowed per investigator discretion given the complexity of the issue in MCL after BR therapy.

We plan to utilize a CR rate of 70% as a historical control based on early evaluation of the induction therapy of E1411.[29] To be considered promising, we hope to improve this by 15% to 85%. CR is our primary outcome to allow for a quick readout and allow for potential inclusion in a future randomized study. We will also monitor MRD via PCR based methods throughout the study as an exploratory objective.

1.6.1 October 11, 2021: Revised Summary of Rationale

Preliminary data from a similar cohort of patients as that enrolled in this study indicates that post-induction CR rate is 60%, not 70% as initially assumed. In addition, the observed study accrual rate (1.1 patients/month) is significantly lower than the planned/expected study accrual rate of 2.3 patients/month. For both reasons, the study was redesigned to reflect the current historical CR rate and with a lowered sample size for prompt primary endpoint readout. Accrual before this redesign is 25 patients.

A 17% increase in CR rate from 60% (null) to 77% (alternate) is of interest.

2. Study Objectives

2.1 Primary Objective

To determine the CR rate of BR + venetoclax in untreated MCL patients over the age of 60 years.

2.2 Secondary Objectives

- Evaluate the safety of the combination, with particular attention to TLS incidence with Cycle 1.
- To determine the overall response rate (complete response [CR] + partial response [PR]) of BR + venetoclax in untreated MCL patients over the age of 60 years.
- To determine the survival (progression-free survival [PFS] and overall survival [OS]) of MCL patients treated with BR + venetoclax induction.

2.3 Exploratory Objectives

- Bone marrow aspirate and peripheral blood assessed minimal residual disease (MRD) negative rate of BR + venetoclax in untreated MCL patients over the age of 60 years.
- Evaluate the utility of morphologic assessment of bone marrow biopsy and aspiration when combined with peripheral blood MRD and PET assessments on CR rate at end of treatment.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

PrECOG Patient No. _____

Patient's Initials (F, M, L) _____

Physician Signature and Date _____

NOTE: PrECOG does not allow waivers to any protocol specified criteria. All eligibility criteria listed in Section 3 must be met, without exception. All questions regarding clarification of eligibility criteria must be directed to the Medical Monitor or PrECOG Study Contact.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

_____ 3.1 Patients must have histologically confirmed (biopsy-proven) diagnosis of mantle cell lymphoma (MCL), with documented cyclin D1 (BCL1) expression by immunohistochemical stains and/or t(11;14) by cytogenetics or FISH.[30]

Date of Diagnosis: _____

_____ 3.2 Patients must have measurable or evaluable disease as defined as a lymph node measuring >1.5 cm in any dimension or splenomegaly with spleen >15 cm in craniocaudal dimension.

_____ 3.3 Age ≥ 60 years.

_____ 3.4 No intention to undergo consolidation with high dose chemotherapy and autologous stem cell rescue (Autologous Stem Cell Transplant) in first remission.

_____ 3.5 ECOG performance status of 0-2 (Appendix I).

Performance Status: Please circle 0 1 2 Date: _____

_____ 3.6 Ability to understand and willingness to sign IRB-approved informed consent.

_____ 3.7 Willing to provide mandatory tissue samples (if sufficient tissue available), bone marrow and blood samples for research purposes (Section 13).

_____ 3.8 Adequate organ function as measured by the following criteria, obtained ≤ 2 weeks prior to registration:

- Absolute Neutrophil Count (ANC) ≥ 1000/mm^3 unless there is bone marrow involvement or splenomegaly

  ANC: _____ Date of Test: _____
- Hemoglobin >8.0 g/dL

  Hemoglobin: _____ Date of Test: _____
- Platelets >75,000/mm^3 or >50,000/mm^3 if there is bone marrow involvement or splenomegaly

  Platelets: _____ Date of Test: _____

- Creatinine Clearance ≥ 40 mL/min

  Creatinine Clearance: _____ Date of Test: _____

  NOTE: Acceptable Measures of Creatinine Clearance: Cockcroft-Gault formula (Appendix II or direct measured creatinine clearance [by 24 hour urine collection or other methods]).

- Total Bilirubin ≤ 1.5x upper limit of normal (ULN) or ≤ 3x ULN for patients with documented Gilbert's syndrome

  Total Bilirubin: _____ ULN: _____ Date of Test: _____

- Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 2.5x ULN

  AST: _____ ULN: _____ Date of Test: _____

  ALT: _____ ULN: _____ Date of Test: _____

_____ 3.9 All females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a blood test to rule out pregnancy within 2 weeks prior to registration.

Is the patient a woman of childbearing potential? _____ (yes/no)

If yes, Date of Test: _____ Results: _____

_____ 3.10 Women must not be pregnant or breastfeeding. Females of childbearing potential who are sexually active with a non-sterilized male partner and sexually active men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) prior to study entry, for the duration of study participation, and for 12 months after last dose of therapy. Method of contraception must be documented.

NOTE: Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

_____ 3.11 Patients should not have prior chemotherapy, radiotherapy or immunotherapy for lymphoma.

- Corticosteroids used for other non-lymphomatous conditions will be allowed.
- Corticosteroids no greater than 1 mg/kg prednisone (or equivalent) given for ≤ 14 days will be allowed for treatment of lymphoma related symptoms.

_____ 3.12 Patients must have no recent (<1 year) history of malignancy except for the following:

- adequately treated non-melanoma skin cancer
- adequately treated Stage I melanoma of the skin
- *in situ* cervical cancer
- low grade prostate adenocarcinoma (Gleason grade ≤ 6) managed with observation and stable for 6 months.

NOTE: Any malignancy treated with curative intent and disease free without treatment for ≥ 1 year prior to enrollment may be included.

_____ 3.13 Patients should not have known evidence of central nervous system (CNS) lymphoma.

_____ 3.14 Patients must not have received a prior allogeneic stem cell transplant or solid organ transplant (except for cornea) for any indication.

_____ 3.15 Patients must have no active, uncontrolled infections.

_____3.16 Patients must not have active hepatitis B or be chronic carriers of hepatitis B. This is defined as patients with hepatitis B surface antigen (HBsAg) positive. Patients with prior exposure to hepatitis B (hepatitis B core antibody (anti-HBc) positive AND HBsAg negative) are allowed with a protective level hepatitis B surface antibody AND a negative hepatitis B viral load by polymerase-chain reaction (PCR).

_____3.17 Patients must not have active hepatitis C (HCV) as defined by a hepatitis C viral load detectable by PCR. Patients with a negative HCV antibody are assumed to have a negative HCV viral load. Patients with a positive HCV antibody must have a negative hepatitis C viral load by PCR. Prior treatment for an active HCV infection will be allowed as long as the hepatitis C viral load by PCR is negative.

_____3.18 Patients must not have known active Human Immunodeficiency Virus (HIV). Testing not required in absence of clinical suspicion.

_____3.19 Patients must not have evidence of significant, uncontrolled concomitant diseases, including psychiatric diseases, that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient.

_____3.20 Patients must not have conditions that preclude oral administration or absorption of medications through the GI tract, including but not limited to the inability to swallow pills or malabsorption syndromes.

_____3.21 Patients must not have known allergies to both xanthine oxidase inhibitors and rasburicase.

_____3.22 Patients must not require the use of warfarin. Blood thinners of other classes are permitted.

_____3.23 Patient may not receive the following agents within 7 days prior to the first dose of venetoclax:

- Strong and moderate CYP3A inhibitors
- Strong and moderate CYP3A inducers
- Strong and moderate P-gp inhibitors

NOTE: Continuous use of strong and moderate CYP3A inhibitors, CYP3A inducers or P-gp inhibitors is not allowed. If a subject requires continuous use of these drugs they will need to be excluded. Please refer to Section 6.2.2 and Appendix III "Additional Excluded and Cautionary Medications" for further details.

_____3.24 Patients must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax.

4. Registration Procedures

4.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization/Good Clinical Practice (ICH/GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

4.2 Regulatory Requirements

Before a site may enroll patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once required documents are received, reviewed, and approved by PrECOG or their representative, a Study Reference Manual (SRM) will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. Once PrECOG activates a site, enrollment may occur. No patients will begin protocol therapy without formal registration as per the process below.

4.3 Patient Registration

After written informed consent has been obtained, protocol-required assessments will be performed.

Patients must meet all of the eligibility requirements listed in Section 3 prior to registration. Patients must not start protocol treatment prior to registration. Treatment should begin ≤ 10 working days from study entry (date of registration).

An eligibility checklist is included in Section 3. A confirmation of eligibility assessment by the investigator and/or site will be performed during the registration process.

Upon determination that a subject meets eligibility criteria, the subject will be registered in the study by site personnel via an electronic data capture (eDC) system.

Full information regarding registration procedures and guidelines can be found in the SRM provided. Correspondence regarding patient registration must be kept in the study records.

4.4 Research Tissue, Bone Marrow and Blood Samples

Pre-treatment, diagnostic pathology specimens (organ or lymph node biopsy or excision) obtained in the course of standard biopsy or surgery are required for enrollment (if sufficient tissue is available, submission is mandatory). However, if there is insufficient tissue available for sample submission (i.e. <10 slides) patients may still be enrolled to the trial.

NOTE: If blocks and/or slides are unavailable and bone marrow is involved with mantle cell lymphoma, obtain two 2 mL EDTA tubes of bone marrow aspirate (one for baseline MRD analysis and one for future research). If blocks/slides and bone marrow are unavailable and peripheral blood is involved with mantle cell lymphoma obtain one 4 mL and one 6 mL EDTA tubes of peripheral blood (one for baseline MRD analysis and one for future research). If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

If bone marrow procedure is completed per standard of care, mandatory bone marrow aspirate sample for MRD analysis will be collected at the end of treatment. Please note, if bone marrow is positive for mantle cell lymphoma at baseline, an end of treatment bone marrow must be collected to confirm response.

Mandatory peripheral blood samples for MRD analysis will be collected at the end of treatment.

Optional peripheral blood samples will also be collected for future research.

Optional: At time of progression, biopsy and peripheral blood samples are requested to be sent for correlative studies and banked for future research.

NOTE: No bone marrow biopsy/aspirate or tissue biopsy should be performed solely for the purposes of obtaining research samples.

Time points for tissue, bone marrow and blood samples are outlined in the study parameters (Section 10) and specific requirements are outlined in the correlative section of this protocol (Section 13) and the PrE0405 lab manual.

5. Treatment Plan

5.1 Overview

Eligible patients will be treated in a single arm with venetoclax, bendamustine and rituximab as induction therapy for 6 cycles of 28 ± 3 day length as outlined in Table 5-1. After 6 cycles, maintenance rituximab may be administered per physician discretion. The recommended schedule for maintenance rituximab is every 8 ± 2 weeks for 12 doses or 24 months (whichever comes first).

Table 5-1: Treatment Overview

Agent	Route	Dose	Days
Venetoclax	Oral	20 mg 50 mg 100 mg 200 mg 400 mg	Day 1-7 (Cycle 1 only) Day 8-14 (Cycle 1 only) Day 15-21 (Cycle 1 only) Day 22-28 (Cycle 1 only) Day 1-10 (Cycle 2-6)
Bendamustine	IV	90 mg/m^{2}[a]	Day 1 and 2 (Cycle 1-6)
Rituximab[b]	IV SQ (optional)	375 mg/m^2 1400 mg (optional)	Day 1 (Cycle 1-6[b]) Day 1 (Cycle 3-6) (optional)

[a] Per investigator discretion, bendamustine may be started at 70 mg/m^2 in patients over the age of 75 years with comorbid conditions or patients over the age of 80 years without comorbid conditions.

[b] Rituximab should be administered as 375 mg/m^2 IV on day 1 of each cycle. If the first two cycles of rituximab (or two consecutive cycles) are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units subcutaneous (SQ) rituximab/hyaluronic acid on Day 1 of Cycles 3-6 (or after 2 consecutive cycles are well tolerated), per rituximab/hyaluronic acid package insert. Biosimilars for rituximab are permitted.

All doses are based on actual body weight.

Prophylactic filgrastim, pegfilgrastim or pegfilgrastim on body injector (OBI) or biosimilars will be administered for all patients on study per Section 5.5.

Pneumocystis Jiroveci Pneumonia (PJP) and antiviral prophylaxis will be initiated in all patients (Section 5.6).

Section 5.7 for Monitoring of Cytomegalovirus (CMV).

Premedication: Acetaminophen and diphenhydramine should be administered prior to each infusion or injection of rituximab, per institution guidelines. Other prophylactic medications may be administered per institution guidelines.

Antiemetic Therapy: Standard anti-emetic therapy may be given to patients prior to administration of bendamustine per institutional guidelines. However, 5-HT3 serotonin receptor agonist and steroids are strongly recommended.

Tumor lysis syndrome (TLS) is an event of interest and will be monitored closely during therapy. TLS will be assessed by the Data Safety and Monitoring Board (DSMB) among the first 19 patients accrued to this study who received venetoclax treatment for at least 3 cycles with no hold to accrual.

5.2 Treatment and Administration Schedule

Venetoclax must be administered before bendamustine and/or rituximab. Bendamustine and rituximab may be given in any order (venetoclax, bendamustine, rituximab or venetoclax, rituximab, bendamustine). One cycle=28 days.

5.2.1 Venetoclax Administration

Venetoclax will be administered once daily and, given risk of tumor lysis syndrome in MCL, will be dose escalated with Cycle 1, as per Table 5-1 and Table 5-2. In Cycles 2-6, venetoclax will be given at 400 mg oral daily for 10 days starting on day 1. Venetoclax should be given prior to administering bendamustine or rituximab on day 1 of each cycle. Venetoclax will be supplied in 10 mg, 50 mg and 100 mg tablets and administration instructions are listed in Table 5-2.

Table 5-2: Venetoclax Dosing

Days	Total Daily Dose	Administration Instructions
Cycle 1		
Day 1-7	20 mg PO daily	Take two 10 mg tablets PO daily
Day 8-14	50 mg PO daily	Take one 50 mg tablet PO daily
Day 15-21	100 mg PO daily	Take one 100 mg tablet PO daily
Day 22-28	200 mg PO daily	Take two 100 mg tablets PO daily
Cycle 2-6		
Day 1-10	400 mg PO daily	Take four 100 mg tablets PO daily
Day 11-28	No venetoclax administered.	

Venetoclax should be administered with a meal and swallowed whole with an 8-ounce glass of water. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given.

If patient misses a dose of venetoclax within 8 hours of when it is usually taken, the patient should take the dose as soon as possible and resume normal daily dosing schedule. Should the dose be missed by greater than 8 hours, the dose should be skipped and patient should resume normal daily dosing the following day. This dose should not be made up.

Patient compliance in taking assigned daily dose of venetoclax will be assessed by pill counts and IRB reviewed medication diary (provided to sites). Bottles containing venetoclax tablets will be given to patients at regularly scheduled visits. Previously distributed bottles will be returned to the clinic. A medication diary will be given to document compliance.

5.2.1.1 Adherence

Medication diaries will be maintained on all patients taking venetoclax. Diaries will be completed by patients and subsequently reviewed by the research staff with the patient at the following visits (Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2-6 Day 1). Pill counts of venetoclax will also be performed and recorded at Cycle 1 Day 8, Cycle 1 Day 15, Cycle 1 Day 22, Cycle 2-6 Day 1 by the research staff and documented on the

drug accountability record. If the pill count is discrepant with the drug diary, the pill count will be used to determine adherence status. Patients may be counseled by the study doctor regarding adherence issues.

5.2.2 Bendamustine Dosing

Bendamustine will be administered as 90 mg/m^2 as IV infusion on days 1 and 2 of each 28 day cycle per institution guidelines. Subjects with advanced age or other comorbid conditions are known to have more side effects with bendamustine at 90 mg/m^2.[7] Per investigator discretion, bendamustine may be administered as 70 mg/m^2 is IV infusion on days 1 and 2 in patients over 75 years with comorbid conditions or over 80 years without comorbid conditions.

Bendamustine must be given after venetoclax but may be given before or after rituximab.

5.2.3 Rituximab Administration

Rituximab should be administered on day 1 of each 28 day cycle after administration of venetoclax. Rituximab should be given as a "standard" IV infusion at 375 mg/m^2 for Cycle 1 per institution guidelines and package insert. For patients that do not have a Grade 3-4 infusion related adverse event, Cycle 2-6 may be given as a "rapid" IV infusion at 375 mg/m^2 per institution guidelines and package insert. Patients that do have a Grade 3-4 infusion related adverse event should receive the "standard" infusion rate for the subsequent cycle. Patients may receive the "rapid" infusion schedule if the prior infusion was not associated with a Grade 3-4 infusion related adverse event. Biosimilars for rituximab are permitted.

Patients who did not have a Grade 3-4 infusion related adverse event with the first 2 cycles of IV rituximab (or two consecutive cycles), may be switched to SQ rituximab/hyaluronic acid at a dose of 1400 mg/23,400 units on Day 1 of Cycles 3-6 (or after 2 consecutive cycles are well tolerated) according to package insert and institution guidelines. This is per patient and institution preference. Patients may be switched back to IV rituximab at any time and switching to SQ rituximab is not required.

All doses of rituximab should be administered with acetaminophen and diphenhydramine (or another anti-histamine) pre-medication per institution guidelines. Other pre-medications may be utilized per institution guidelines. Rituximab must be given after venetoclax but may be given before or after bendamustine.

After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab IV or SQ (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

5.3 Tumor Lysis Prophylaxis

TLS is a risk for MCL patients treated with venetoclax. The highest risk for TLS occurs within the first 24 hours of a dose escalation. Ramp up dosing helps to mitigate this risk however, careful prophylaxis of TLS is required, including the following:

- Allopurinol 300 mg PO daily MAY be given if the risk of TLS is thought to be higher than the risk of Steven-Johnson syndrome. If Allopurinol is given, we recommend starting 24 hours prior to Cycle 1, Day 1 and continue through at least Cycle 2, Day 10. Allopurinol can continue longer per treating physician discretion.
- One liter of IV fluids on Day 1 of Cycle 1 and Cycle 2 of chemotherapy.

- Encourage oral hydration of at least 2 liters of any form of fluid per day starting 24 hours prior to Cycle 1, Day 1 and continuing until Cycle 2, Day 10.
- Rasburicase is allowed per institutional guidelines.
- Additional IV fluids and monitoring for TLS is allowed per treating physician discretion.
- What is listed in the protocol are minimum standards.
    - Admission to the hospital is allowed for advanced treatment and monitoring of TLS per treating physician discretion/institutional standards.

NOTE: Defined risks for TLS are not clear in MCL but some higher risk situations include:

- Bulky disease (any lymph node mass >10 cm)
- Circulating mantle cell lymphoma with Absolute Lymphocyte Count (ALC) >25 x 10^9/L
- Borderline renal function
- Rapidly progressing disease.

5.4 Tumor Lysis Monitoring

Tumor lysis syndrome (TLS) has been documented in patients treated with single agent venetoclax in other studies. Tumor lysis is most common within the first 24 hours of a dose increase of venetoclax. It is an outcome of interest in the current study and will be monitored closely in patients with Cycle 1 and Cycle 2.

Tumor lysis laboratory studies include the following: Basic Metabolic Panel (Sodium, Potassium, Chloride, Bicarbonate (HCO_3), BUN, Creatinine, Calcium), Albumin, Uric Acid, and Phosphorus. Monitoring for TLS is listed in Table 5-3.

Table 5-3: Tumor Lysis Monitoring

Days	Dose of Venetoclax	TLS Lab Timing
Cycle 1		
Day 1	20 mg PO	– Prior to dosing Venetoclax – 6-8 hours after dosing Venetoclax
Day 2	20 mg PO	Prior to dosing Venetoclax and Bendamustine
Day 8	50 mg PO	– Prior to dosing Venetoclax – 6-8 hours after dosing Venetoclax
Day 9	50 mg PO	Prior to dosing Venetoclax [a]
Day 15	100 mg PO	– Prior to dosing Venetoclax – 6-8 hours after dosing Venetoclax
Day 16	100 mg PO	Prior to dosing Venetoclax [a]
Day 22	200 mg PO	Prior to dosing Venetoclax
Day 23	200 mg PO	Prior to dosing Venetoclax [a]
Cycle 2		
Day 1	400 mg PO	– Prior to dosing Venetoclax – 6-8 hours after dosing Venetoclax
Day 2	400 mg PO	Prior to dosing Venetoclax and Bendamustine

Cycle 3-6		
Day 1	400 mg PO	Prior to dosing Venetoclax
[a] Can be performed locally. Venetoclax dose may be given prior to results returning on Cycle 1: Days 9, 16, 23; and Cycle 4-6: Day 1. Venetoclax should not be administered prior to results returning on Cycle 1: Days 1, 2, 8, 15, 22; Cycle 2: Days 1 and 2; and Cycle 3: Day 1.		

5.5 Neutropenic Sepsis Prophylaxis

Bendamustine and venetoclax can cause neutropenia. Prophylaxis for neutropenic sepsis and febrile neutropenia is required with one of the following (Growth Colony Stimulating Factors [GCSFs]) to be administered 24-72 hours after the last dose of bendamustine for each cycle.

- Pegfilgrastim SQ 6 mg once
- Pegfilgrastim SQ 6 mg via on-body injector (OBI) once
- Filgrastim or filgrastim-sndz SQ 300 or 480 mcg for 5 days
- Biosimilars are also allowed for prophylaxis for neutropenic sepsis and febrile neutropenia

5.6 Infection Prophylaxis

All patients must be initiated on prophylaxis for PJP at the time of Cycle 2 of venetoclax, bendamustine and rituximab. However, PJP prophylaxis may be administered with Cycle 1 if the treating physician feels the risk of PJP is higher than the risks during the venetoclax dose ramp up. Trimethoprim-sulfamethoxazole (Bactrim) is the preferred treatment of choice for PJP prophylaxis. PJP prophylaxis should continue until 6-8 weeks from Day 1 of last completed induction cycle. PJP prophylaxis may be discontinued at that time, or continued at the discretion of the treating physician .If the patient will not be able to take trimethoprim-sulfamethoxazole then alternatives include: Dapsone, Pentamidine (aerosol) or Atovaquone. (The myelosuppressive effects of trimethoprim-sulfamethoxazole when administered in prophylactic doses is minimal.)

Patients must also be initiated on acyclovir or valcyclovir as prophylaxis against Herpes Simplex and Varicella Zoster viral infections. Antiviral prophylaxis should continue for a minimum of 6 months after completion of induction, and may be discontinued at that time, or continued at the discretion of the treating physician.

If lymphopenia is documented (absolute lymphocyte count <500), then the investigator may choose to continue prophylactic medications for a longer duration.

NOTE: The above mentioned prophylactic medications have no known interactions with the study drugs.

5.7 Monitoring for Cytomegalovirus (CMV)

Patients will be monitored for CMV reactivation using Quantitative PCR assay for CMV DNA.

Induction Phase: Quantitative PCR will be checked once a month and at the end of induction.

Maintenance Phase: Treating physician discretion or per institutional standards; however, if the CMV level at the end of induction is detectable, it is recommended to continue monitoring CMV PCR per institutional standards.

There are four possible results:

- Not detected
- CMV DNA detected <137 IU/mL
- CMV DNA detected between 137 and 9,100,000 IU/mL
- CMV DNA detected >9,100,000 IU/mL

If CMV PCR is reported as >137 IU/mL, then the frequency of testing for the PCR needs to be changed to weekly monitoring.

If CMV PCR is >500 IU/ml and the trend is rising, on subsequent weekly measurements then:

- The study treatment will be held
- Preemptive CMV therapy will be initiated as per institutional guidelines in conjunction with Infectious disease specialists

NOTE: CMV testing will likely be reported in ~ 48-72 hours and the patient may have received all the study drugs and may or may not be receiving venetoclax.

Study drugs may be restarted without dose reduction after resolution of **asymptomatic** CMV reactivation if all the following conditions are met:

- CMV reactivation is resolved as determined by the investigator
- The CMV reactivation was **NOT** associated with any known end organ disease (for example: pneumonitis, hepatitis, gastroenteritis, retinitis, encephalitis)
- Patient is deemed clinically appropriate to restart therapy

Once treatment is restarted, secondary prophylaxis must be maintained per institutional guidelines.

If there is associated end organ damage, patient will be removed from study.

6. Dose Delays & Modifications

All toxicities should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE V5.0). A copy of the CTCAE V5.0 can be downloaded from the CTEP website (http://www.ctep.cancer.gov).

A 3 day window is allowed for scheduled therapy, tests and/or results except as noted for TLS monitoring. Delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

If administration of venetoclax, bendamustine or rituximab is delayed on day 1 of a cycle, the administration of all the agents should be delayed for the same timeframe. For example, if bendamustine is delayed, administration of venetoclax and rituximab should also be delayed so that they are given together beginning on Day 1 of the same cycle (Cycle 1 cannot be more than 49 days).

NOTE: For CMV reactivation and infection management, please refer to Section 5.7

If any of the study drugs are permanently discontinued (i.e., Grade 4 infusion-related reaction with rituximab), the patient will be removed from study and followed per Section 7.2.

NOTE: TLS will be considered as laboratory or clinical TLS per Appendix IV.

6.1 Dose Modifications

6.1.1 Hematologic Toxicities

Table 6-1: Dose Modifications and Delay for Hematologic Toxicity

- **GCSF will be administered to all patients per Section 5.5.**
- **If a cycle is delayed by >28 days, then patient will discontinue study treatment.**
- **Best supportive care should be offered to all patients per Section 6.2.**
- **Refer to Table 6-4 for Dose Modifications.**

Event	Dose Delays or Modifications
During Cycle 1: • Febrile neutropenia • Grade 4 thrombocytopenia • Grade 3 thrombocytopenia with bleeding	– Hold venetoclax until febrile neutropenia resolves, ANC recovers to >1000/mm^3 and/or platelets recover to >50,000/mm^3. Resume venetoclax dosing. – There may be a prolongation of Cycle 1 by up to 28 days. In general, after resuming venetoclax, please allow for 7 (+/- 1) days with each dose increase. Cycle 1 cannot be more than 49 days.
At Start of Cycle 2-6: • Grade 3 or 4 neutropenia or thrombocytopenia	– Hold all protocol therapy and delay cycle for at least 7 days and up to 28 days. – Once ANC resolves to >1000/mm^3 and/or platelets resolve >75,000/mm^3, resume cycle as below: o For first occurrence: ▪ If hold was ≤ 10 days, resume cycle at Dose Level 0. ▪ If hold was >10 days, resume cycle at Dose Level -1. o For second occurrence of any length: ▪ Resume cycle at Dose Level -1. o For any occurrence after a cycle at Dose Level -1. ▪ Resume cycle at Dose Level -2. o For any occurrence after a cycle at Dose Level -2. ▪ Subject will discontinue study treatment.
During Cycle 2-6: • Febrile neutropenia • Thrombocytopenia with bleeding	– If taking venetoclax (Days 2-10), hold venetoclax until next cycle AND – For subsequent cycles, resume at Dose Level -1. – If recurrence, dose subsequent cycles at Dose Level -2. – For third recurrence, subject will discontinue study treatment.

6.1.2 Non-Hematologic Toxicities

Table 6-2: Dose Modifications and Delay for Non-Hematologic Toxicity

- **Dose modifications should occur only for treatment emergent and related toxicities.**
- **Dose reductions should be made to the attributed drug. No dose reductions in rituximab are permitted. If both venetoclax and bendamustine are attributed to the AE of interest, venetoclax must be dose reduced; however, bendamustine may also be dose reduced per investigator discretion.**
- **If a cycle is delayed by >28 days, then patient will discontinue study treatment.**
- **Best supportive care should be given to all patients according to Section 6.2.**
- **Refer to Table 6-5 and Table 6-6 for Dose Modifications.**

Event	Dose Delays and Modifications
Grade 3 to 4 Non-Hematologic Toxicity (not otherwise described) • excluding alopecia	– During Cycle 1, hold all study treatment and resume once Grade ≤ 1. o Resume venetoclax treatment and dose escalation at the dose the toxicity occurred. o There may be a prolongation of Cycle 1 by up to 28 days. In general, after resuming venetoclax, please allow for 7 (+/- 1) days with each dose increase. Cycle 1 cannot be more than 49 days. o Re-challenge may occur twice during Cycle 1, a third occurrence will require subject discontinue study treatment. – During Cycle 2-6, hold all study treatment and delay subsequent cycle until resolves to Grade ≤ 1. o If delay in cycle is required but ≤ 10 days, no dose modification is required. ▪ However, dose reduction of venetoclax or bendamustine is allowed per investigator discretion depending on attribution. o If delay in cycle is >10 days, then reduce to Dose Level -1 (or Dose Level -2 if toxicity occurred after Dose Level -1) of attributed drug. o If toxicity occurs at Dose Level -2 of attributed drug, subject may dose reduce the other drug. o If toxicity occurs with venetoclax at 200 mg PO for 5 days and bendamustine 50 mg/m^2 IV day 1 and 2, subject must discontinue study treatment.
Grade 2 Non-Hematologic Toxicity • excluding alopecia, nausea/vomiting, diarrhea, and fatigue	– During Cycle 1, hold all study treatment and resume once Grade ≤ 1. o Resume venetoclax treatment and dose escalation at the dose the toxicity occurred. o There may be a prolongation of Cycle 1 by up to 28 days. In general, after resuming venetoclax, please allow for 7 (+/- 1) days with each dose increase. Cycle 1 cannot be more than 49 days. o Re-challenge may occur twice during Cycle 1, a third occurrence will require subject discontinue study treatment. – During Cycle 2-6, if occurs at the start of a cycle, delay cycle for at least 7 days and up to 28 days. Resume at same dose level when toxicity resolves to Grade ≤ 1. o If toxicity recurs and causes a delay in a cycle, subsequent cycles should be dose reduced to Dose Level -1 of the attributed drug. o If toxicity occurs at Dose Level -1, modify subsequent cycles to Dose Level –2 of the attributed drug. o If toxicity occurs at Dose Level -2 of the attributed drug, subject may dose reduce the other drug. o If toxicity occurs with venetoclax at 200 mg PO for 5 days and bendamustine 50 mg/m^2 IV day 1 and 2, subject must discontinue study treatment.

	– If taking venetoclax when toxicity occurs and toxicity is attributed to venetoclax, hold dose until next cycle and administer without dose modification. o If toxicity recurs during venetoclax treatment (Days 2-10) and is attributed to venetoclax, hold venetoclax dose and reduce venetoclax next cycle to Dose Level -1. o If toxicity occurs at Dose Level -1, modify subsequent cycles to Dose Level –2 of venetoclax if attributed to venetoclax. o If toxicity occurs at Dose Level -2 of venetoclax, consider dose reduction of bendamustine.

6.1.3 Tumor Lysis Syndrome Management

Table 6-3: Tumor Lysis Syndrome Management

Dose Patient Taking When TLS Occurs	If Tumor Lysis Is Suspected[a]	Restart Instructions[d]
Venetoclax 20 mg	-Hold venetoclax -Strongly consider admission for IV fluids and monitoring -Give supportive care[b] -Recheck TLS labs every 6 hours until resolved[c]	If TLS is absent and investigator feels safe: -Resume venetoclax at 20 mg. -Dose escalate on schedule if no signs of TLS 24 hours after re-dosing per protocol.
Venetoclax 50 mg	-Hold venetoclax -Strongly consider admission for IV fluids and monitoring -Give supportive care[b] -Re-check TLS labs every 6 hours until resolved[c]	If TLS is absent and investigator feels safe: -Resume venetoclax at 20 mg. -Dose escalate on schedule if no signs of TLS 24 hours after re-dosing per protocol.
Venetoclax 100 mg	-Hold venetoclax -Strongly consider admission for IV fluids and monitoring -Give supportive care[b] -Recheck TLS labs at least daily until resolved[c]	If TLS is absent and investigator feels safe: -Resume venetoclax at 50 mg. -Dose escalate per protocol if no signs of TLS.
Venetoclax 200 mg	-Hold venetoclax -Give supportive care[b] -Recheck TLS labs every 2-3 days until resolved[c]	If TLS is absent and investigator feels safe: -Resume venetoclax at 100 mg. -Re-check TLS labs after 2 days. -Dose escalate per protocol if no signs of TLS.
Venetoclax 400 mg	-Hold venetoclax for rest of cycle -Give supportive care[b] -Recheck TLS labs every 2-3 days until resolved[c]	If TLS absent and patient is not clinically progressing and investigator feels safe: -Give venetoclax at 400 mg for subsequent cycle. -Re-check TLS labs after 2 days.

[a] See Appendix IV for Definitions of Tumor Lysis Syndrome.[31]

[b] Recommend aggressive IV and oral hydration, electrolyte management, and depending on severity, rasburicase per institutional standards. Depending on severity, consider hospital admission.

[c] If TLS does not improve after 14 days, with good supportive care, patient must discontinue study treatment.

[d] After a TLS event, there may be a prolongation of Cycle 1 by up to 28 days. In general, after resuming venetoclax, please allow for 7 (+/- 1) days with each dose increase. Cycle 1 cannot be more than 49 days.

6.1.4 Dose Level Reductions

Table 6-4: Dose Modifications for Hematologic Toxicity
- **Note that dose escalations after a dose reduction are not allowed.**

Dose Level	Venetoclax	Bendamustine	Rituximab
0	400 mg PO daily x 10 days	90 mg/m^2 IV days 1 and 2 (70 mg/m^2 if starting dose is such per Section 5.2.2)	No dose modifications
-1	400 mg PO daily x 5 days	90 mg/m^2 IV days 1 and 2 (70 mg/m^2 if starting dose is such per Section 5.2.2)	No dose modifications
-2	400 mg PO daily x 5 days	70 mg/m^2 IV days 1 and 2 (50 mg/m^2 if starting dose is such per Section 5.2.2)	No dose modifications

Table 6-5: Dose Modifications for Non-Hematologic Toxicity—Venetoclax
- **Note that dose escalations after a dose reduction are not allowed.**

Dose Level	Venetoclax	Rituximab
0	400 mg PO daily x 10 days	No dose modifications
-1	400 mg PO daily x 5 days	No dose modifications
-2	200 mg PO daily x 5 days	No dose modifications

Table 6-6: Dose Modifications for Non-Hematologic Toxicity—Bendamustine
- **Note that dose escalations after a dose reduction are not allowed.**

Dose Level	Bendamustine	Rituximab
0	90 mg/m^2 IV day 1 and 2	No dose modifications
-1	70 mg/m^2 IV day 1 and 2 [a]	No dose modifications
-2	50 mg/m^2 IV day 1 and 2	No dose modifications
[a] 70 mg/m^2 maybe the initial dose for some subjects per Section 5.2.2.		

6.2 Concurrent Therapies

6.2.1 Permitted Concurrent Therapies

Concurrent therapy includes any prescription or over-the-counter medication used by a patient between the 7 days preceding the study entry evaluation and the end of treatment/study termination visit.

All supportive measures consistent with optimal patient care will be given throughout the study. Transfusion of blood products per institutional guidelines is permitted.

Prior to Cycle 1, Day 1, systemic (IV or PO) corticosteroids no greater than 1 mg/kg prednisone (or equivalent) given for less than or equal to 14 days will be allowed for treatment of lymphoma related symptoms. While on study, systemic (IV, IM, or PO) corticosteroids used for non-lymphomatous conditions will be allowed;

however, systemic (IV, IM, or PO) corticosteroids will not be allowed to control lymphoma related symptoms after Cycle 1 Day 5. Inhaled and topical corticosteroids are allowed.

Prevention and treatment of reactions to rituximab and bendamustine are allowed per intuitional standards.

6.2.2 Not Permitted

The use of live viral vaccines during study treatment is not allowed. Use of live viral vaccines within 28 days prior to the initiation of study treatment or within 30 days of the last treatment is not allowed.

Effectiveness of inactivated vaccines, recombinant vaccines, and cell-wall vaccines are unreliable in NHL patients but are allowed on this protocol per treating physician discretion.

The following treatments are prohibited from 7 days prior to initiation of treatment, during the study treatment, and within 30 days of the last study treatment:

- Immunotherapy other than prescribed in the treatment plan.
- Any FDA-approved or experimental therapy intended for the treatment of lymphoma including systemic corticosteroids, unless otherwise listed.
- Warfarin (novel anticoagulants are allowed so long as there are no other drug-drug interactions).
- Strong to moderate inhibitors or inducers of CYP3A per Appendix III.
    - Weak inhibitors and inducers are allowed
    - Please contact PrECOG for more guidance if needed
- Strong to moderate P-gp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor (Appendix III).
- Grapefruit and grapefruit juice, Seville oranges (including marmalade/jam) and star fruit are known inhibitors of CYP3A and should be avoided.
- In cycles 2-6 when venetoclax will not be administered (i.e., Days 11-28), avoid the use of strong or moderate CYP3A inhibitors or P-gp inhibitors 2 to 3 days prior to the next cycle of venetoclax treatment.
- In cycles 2-6 when venetoclax will not be administered (i.e., Days 11-28), avoid the use of strong or moderate CYP3A inducers at least 7 days prior to the next cycle of venetoclax treatment.

NOTE: Continuous use of strong and moderate CYP3A inhibitors, CYP3A inducers or P-gp inhibitors is not allowed. If a patient requires continuous use of these drugs they will need to be excluded.

Concomitant medications that fall into the categories below could potentially lead to adverse reactions and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator must assess and document the use of medications known or suspected to fall in the following medication categories:

- P-gp substrates such as digoxin, everolimus, and sirolimus due to inhibition potential at therapeutic dose levels.

  - P-gp substrate should be avoided. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.
- CYP2C8 substrates such as thiazolidinediones (glitazones) and select statins (because of expected inhibition of the metabolism of CYP2C8 substrates) by venetoclax.
- CYP2C9 substrates such as tolbutamide (because of expected inhibition of the metabolism of CYP2C9 substrates by venetoclax). It is recommended to exclude CYP2C9 substrates with a narrow therapeutic index such as phenytoin.

Additionally, caution should be exercised, or alternative treatments considered, when co-administering bendamustine with a CYP1A2 inhibitor or CYP1A2 inducer.

Refer to Appendix III: “Additional Excluded and Cautionary Medications” for additional information.

7. Study Duration and Discontinuation of Therapy

7.1 Study Duration

Patients will receive protocol therapy until:

1. Any of the study drugs are permanently discontinued (i.e., Grade 4 infusion-related reaction with rituximab), the patient will be removed from study.
2. Subject completes 6 cycles of treatment per Section 5.
3. Disease progression per Lugano staging[26] or clinical parameters.
4. Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications.
5. Development of an inter-current illness that prevents further administration of study treatment.
6. Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
7. Patient withdraws consent or is unable to comply with study procedures.

7.2 Duration of Follow-Up

Patients will be followed for adverse events for 30 days after their last dose of study medication. Patients should be followed every 3-6 months or per institutional guidelines for up to 5 years from treatment discontinuation or study closure for progression and survival. Initiation of first anti-cancer therapy will be documented.

If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment with the exception of allowed maintenance rituximab.

For patients who are registered but do not receive any protocol therapy, baseline and follow-up information per Section 10 will be collected.

7.3 Criteria for Removal from Study Treatment

A genuine effort will be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial, should this occur. It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued, the reason will be recorded on the appropriate electronic case report form. Reasons that a patient may discontinue treatment in a clinical study are considered to constitute one of the following:

1. Recurrence of disease or documented progression of disease.
2. Intercurrent illness that prevents further administration of treatment per investigator discretion.
3. Unacceptable adverse events.
4. Treatment interruption of more than 4 weeks (28 days).
5. Investigator and/or patient decision to discontinue treatment.
6. Pregnancy.
7. Develops a second malignancy (except for non-melanoma skin cancer or cervical carcinoma in-situ) that requires treatment, which would interfere with this study.
8. The patient may choose to withdraw from the study at any time for any reason.

9. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.
10. Severe non-compliance to protocol as judged by the investigator.
11. Lost to follow-up.
12. Death.
13. Closure of study by PrECOG.

Any patient who receives at least one dose of study drug (bendamustine, rituximab or venetoclax) will be included in the safety analysis. Patients who discontinue study treatment early should be followed for response assessments, if possible. Follow-up will continue per Section 10, as applicable.

8. Adverse Event Reporting

8.1 Collection of Safety Information

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed).

After informed consent, but prior to initiation of study treatment (bendamustine, rituximab or venetoclax), only AEs/SAEs caused by a protocol-mandated intervention not considered standard of care will be collected (e.g., SAEs related to invasive procedures such as biopsies). After the initiation of study treatment, all identified AEs and SAEs must be recorded and described on the appropriate page of the electronic Case Report Form (eCRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product (see definitions below); treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more-frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5x the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF unless their severity, seriousness, or etiology changes.

Severity

The categories and definitions of severity used for clinical trials AEs are defined in the NCI's Common Terminology Criteria (CTCAE) V5.0 (http://www.ctep.cancer.gov).

Attribution

The following categories and definitions of causal relationship or attribution to study drug should be used to assess Adverse Events:

- Definite: There is a reasonable causal relationship between the study drug and the event. The event response to withdrawal of study drug (dechallenge) and recurs with rechallenge, if clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the event. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is a reasonable causal relationship between the study drug and the event. Dechallenge information is lacking or unclear.

- Unlikely: There is doubtful causal relationship between the study drug and the event.
- Unrelated: There is clearly not a causal relationship between the study drug and the event or there is a causal relationship between another drug, concurrent disease, or circumstances and the event.

Categories 'definite', 'probable' and 'possible' are considered study drug related. Categories 'unlikely' and 'unrelated' are considered not study drug-related.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

Expected/Unexpected: Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator's Brochure (IB).

Unexpected AEs are those not listed in the Package Insert or current IB or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the Package Insert or IB. For example, under this definition, hepatic necrosis would be unexpected if the Package Insert or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

Attribution and expected/unexpected should be assessed against the study drug(s). The investigator will determine if event is due to bendamustine, rituximab or venetoclax, disease, etc.

AEs related to bendamustine, rituximab or venetoclax should be followed for 30 days after last dose of study therapy until ≤ grade 1 or stabilization, and reported as SAEs if they become serious.

Any AE's (serious or not) that occur after the above time periods but are deemed to be at least possibly related to study therapy shall be reported.

8.2 Serious Adverse Events

A ***serious AE*** is any untoward medical occurrence occurring after initiation of study treatment or that at any dose:

- results in death (i.e., the adverse event actually causes or leads to death)
- is life-threatening (defined as an event in which the study patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (i.e., the adverse event 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 (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

NOTE: Patients admitted for monitoring of tumor lysis is NOT considered an SAE.

8.3 Adverse Events of Special Interest (AESI)

The following adverse events are considered of special interest and must be reported to PrECOG as serious adverse events (Section 8.5 for reporting instructions), irrespective of regulatory seriousness criteria.

Non Drug Specific AESIs (applicable to Venetoclax and Rituximab)

- Drug-Induced Liver Toxicity

  Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:

  - Treatment-emergent ALT or AST >3x baseline value in combination with total bilirubin >2x ULN (of which >35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3x baseline value in combination with clinical jaundice

    Criteria for Hy's Law (FDA Guidance 2009)

    - The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
    - Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3x ULN, one or more also show elevation of serum total bilirubin to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
    - No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Venetoclax Events of Special Interest

- Any grade tumor lysis syndrome (TLS)
  - Definitions for TLS is described in Appendix IV: "Definition of Tumor Lysis Syndrome"[31]. Please note that, if the clinical scenario fits for TLS, use these criteria for evaluating renal and electrolyte imbalances occurring at the same time.
    - Laboratory TLS (2 or more metabolic abnormalities present) = Grade 3
    - Clinical TLS (laboratory TLS must also be present) = Grade 4
    - Fatal = Grade 5

Rituximab Events of Special Interest

- None

8.4 Special Situation Reports

8.4.1 COVID-19 Reporting

All positive COVID-19 test results must be reported with the type of test performed recorded.

Coding for COVID-19 adverse events will be as follows.

- Infections and infestations - Other, specify
- Specify = COVID-19

The categories and definitions of severity used for COVID-19 AEs are defined in NCI's CTCAE V5.0 (http://www.ctep.cancer.gov).

COVID-19 adverse events that qualify as Serious Adverse Events per Section 8.2 must be reported as such, per Section 8.5. The following information will be captured:

- Narrative: Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following: Presumptive vs confirmed diagnosis. If presumptive, please update narrative if/when diagnosis is confirmed, including timelines.
  - Treatment information
  - Recovery information, including timelines
  - Outcome information/status

All deviations or withdrawals due to COVID-19 will documented as such in the eCRF.

8.4.2 Other

In addition, the following Special Situation Reports should be collected and reported to PrECOG on a PrE0405 SAE Form even in the absence of an AE and PrECOG will transmit to Genentech within thirty (30) calendar days:

- Data related to the product usage during pregnancy or breastfeeding (Section 8.7).
- Data related to overdose, abuse, misuse, error (including potentially exposed or intercepted medication errors).
  - For any symptomatic overdose, **even if not fulfilling a seriousness criterion**, a SAE form should be completed and reported to PrECOG within 24 hours of the investigator's knowledge of the overdose.
- Data related to a "suspected transmission of an infectious agent via a medicinal product.

8.5 SAE Reporting Requirements

Serious adverse events (SAE) are defined above. The investigator should inform PrECOG of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on the PrECOG SAE form. This form must be completed and supplied to PrECOG within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up PrECOG SAE report form. A

final report to document resolution of the SAE is required. The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation. A copy of the email of the SAE report to PrECOG should be attached to the SAE and retained with the patient records.

SAEs should be scanned and emailed to PrE0405SAE@qdservices.com as per the instructions found in study materials provided to the investigator site.

[redacted]
Medical Monitor
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Phone: 484-574-2367
Email: [redacted]

Manager, Clinical Safety
During normal business hours
(8:30 am-5:00 pm EST):
Phone: 610-354-0404
After normal business hours:
Cell: 484-574-2367

PrECOG will notify Genentech of any SAE's and AEs of Special Interest (regardless of causality) within 1 business day of the Awareness Date. All non-serious adverse events will be provided to Genentech quarterly. Relevant follow-up information will be provided to Genentech as soon as it becomes available.

Investigators should also report event(s) to their IRB as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

All SAEs, regardless of causality, must be collected which occur within 30 days of last dose of study treatment. This includes all deaths within 30 days of last dose of bendamustine, rituximab or venetoclax regardless of attribution. In addition, the Investigator should notify PrECOG or designee of any SAE that may occur after this time period which they believe to be definitely, probably or possibly related to investigational product.

NOTE: After study closure, study-drug related SAEs should be reported voluntarily by the treating physician to the manufacturer.

Serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by PrECOG (or designee) in accordance with 21CFR312.32, local requirements and international regulations, as appropriate. FDA reporting requirement timelines will be followed. PrECOG will also concurrently forward any such reports to Genentech.

8.6 Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Product Complaints (with or without an AE) for venetoclax originating from the Study will be collected and reported to PrECOG on a PrE0405 Product Complaint Reporting Form even in the absence of an AE (if product complaint is an SAE, the PrE0405 SAE form will also be completed). PrECOG will transmit product complaints to Genentech for venetoclax within fifteen (15) calendar days. Product complaints for bendamustine and rituximab will be reported per each sites standard procedures.

8.7 Reporting of Other Second Primary Cancers

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

All cases of new primary cancers that occur during or after protocol treatment must be reported to PrECOG on a Second Primary Cancer form within 30 days of diagnosis, regardless of relationship to protocol treatment. Secondary primary malignancies should also be reported as a SAE. The SAE form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report, if applicable, should be sent, if available.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted.

8.8 Procedures in Case of Pregnancy

Prior to study enrollment, women of childbearing potential (WOCBP) and male patients with a female partner of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, documented in the informed consent. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

Pregnancy of a female patient or the female partner of a male patient occurring while the patient is receiving study drug or within 12 months after the patient's last dose of study drug will be reported to PrECOG on a Pregnancy Form within 24 hours of the investigator's knowledge of the pregnancy.

All reports of congenital abnormalities/birth defects and spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth including health of the newborn or congenital abnormality) must be followed and documented on the Pregnancy Form even if the subject was discontinued from the study treatment. Should pregnancy occur during a subject's participation, the subject will immediately be discontinued from the treatment and followed per protocol.

The study-specific Pregnancy Form can be found in the Study Reference Manual.

PrECOG will notify Genentech of any pregnancy within 1 business day of the Awareness Date.

9. Measurement of Effect

9.1 Response Assessments

Patients should have a baseline PET/CT. Repeat imaging in the form of CT or PET/CT before Cycle 3 or 4 should be done per institution guidelines. End of treatment PET/CT should be performed 6-8 weeks after the final cycle of therapy (6-8 weeks after Cycle 6 Day 1) and is the primary endpoint for this study. Bone marrow biopsy and aspiration will be performed at the end of treatment when it is standard of care.

Any progression on therapy should be confirmed with PET/CT.

After the End of treatment PET/CT, all other imaging will be per institution standards. Patients will be followed until progression or for up to 5 years from treatment discontinuation or study closure.

9.2 Lymphoma Response Criteria (Lugano Classification)[32]

Response and progression will be evaluated in this study using international criterial proposed by the 11th International Conference on Malignant Lymphoma in Lugano Switzerland (Lugano Classification).[32]

The criteria use Complete Response (CR), Partial Response (PR), Stable disease (SD) or Progressive Disease (PD) to evaluate response. PET/CT is the primary modality to measure response and will be utilized for the primary outcomes; however, CT without PET component may be adequate at other measurements.

Tumor measurements will be recorded at baseline for at least 6 dominant nodes or extranodal masses. If there are less than 6 measurable lesions, all lesions must be measured and followed. Selection of masses to follow should maintain that they are clearly measurable in 2 perpendicular directions, and should be from different regions of the body whenever possible. Measurements should be in centimeters to the nearest one tenth and in two planes, one being the longest diameter and the other its perpendicular counterpart. Measurements of lesions will be done at baseline and at each disease assessment.

Non-target lesions can be utilized also. These may be dominant lesions over 6 nodes identified or lesions which are seen but difficult to measure (i.e., a bone lesion with FDG activity but no clearly defined borders). Non-target lesions will be recorded as present or absent.

Spleen size, in cranio-caudal cross sectional measurement, should be recorded at each disease assessment.

Full criteria can be found in Appendix V: Revised Criteria for Response Assessment.[32]

End of treatment PET/CT is the primary response assessment. A 5-point scale, also known as the Deauville criteria, (Table 9-1) should be utilized to measure FDG uptake and treatment response via PET. Each target lesion should have a Deauville score at the end of treatment.[33]

Table 9-1: Deauville Criteria for Target and Non-Target Lesions	
Score	**Criteria**
1	No uptake
2	Uptake less than or equal to the mediastinal blood pool
3	Uptake greater than the mediastinal blood pool but less than the liver
4	Uptake moderately higher than the liver
5	Uptake markedly higher than the liver and/or new lesions
X	Areas of uptake unlikely to be related to lymphoma

9.2.1 Complete Response Definition

CR rate per Lugano criteria, utilizing the PET/CT criteria listed in Appendix V, is the primary outcome for this study. It is defined as a complete metabolic response via PET/CT as well as a morphologically negative bone marrow biopsy and aspiration. Bone marrow flow cytometry should not be utilized in CR assessments. If bone marrow biopsy and aspiration was not involved by MCL at screening, a repeat bone marrow biopsy and aspiration is not required to assess CR status (PET/CT imaging alone will suffice).

All other responses, including PR, SD, PD and CT based criteria are indicated in the Lugano Criteria, listed in Appendix V Revised Criteria for Response Assessment.[32]

9.3 Minimum Residual Disease (MRD) Measurements

MRD negative rate at the end of treatment assessment are exploratory endpoints in this study. MRD will be measured using PCR based markers through Adaptive Biotechnologies (clonoSEQ) on tumor tissue (baseline only), liquid marrow aspirate and peripheral blood samples.

Baseline tumor tissue sample will be obtained. If tumor tissue is not available, bone marrow aspirate or peripheral blood may be substituted, if involved with mantle cell lymphoma, for baseline comparison sample. If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

Bone marrow aspirate for MRD testing will be collected at the end of treatment per standard of care. Please note, if bone marrow is positive for mantle cell lymphoma at baseline, an end of treatment bone marrow must be collected to confirm response.

Peripheral blood for MRD assessments will be collected at the end of treatment.

10. Study Treatments, Parameters, and Assessments

1. All pre-study scans and biopsies should be done ≤ 6 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 2 weeks prior to registration, unless otherwise noted.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycle 2 and Subsequent Cycles*				Prior to Cycle 3 or 4	End of Treatment Visit[25]	Follow-Up[27]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 10	Day 11-28			
Windows (+/- days):	-28 to -1		1	1	1	1	3	1			7	14	
Administrative Procedures													
Written Informed Consent	X												
Disease Characteristics[1]	X												
Medical/Surgical History	X												
Assessment of Baseline Signs & Symptoms	X												
Prior and Concomitant Medication Review	X	X					X					X	
Clinical Procedures/Assessments													
Height	X												
Physical Exam including Weight	X	X					X					X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X	X	X	X	X	X					X	
Body Surface Area (BSA)	X	X					X						
ECOG Performance Status	X	X					X					X	
Review Adverse Events		X		X	X	X	X					X[26]	
Laboratory Assessments													
CBC/Differential/Platelets[2]	X	X		X	X	X	X					X	
Chemistry[3]	X	X	X	X	X	X	X	X[4]				X	
Liver Function[5]	X	X					X					X	
LDH	X											X	

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycle 2 and Subsequent Cycles*				Prior to Cycle 3 or 4	End of Treatment Visit[25]	Follow-Up[27]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 10	Day 11-28			
Windows (+/- days):	-28 to -1		1	1	1	1	3	1			7	14	
Tumor Lysis Labs[6]		X	X	X	X	X	X	X[4]					
Beta-2 Microglobulin	X											X	
Hepatitis B and C Testing[7]	X												
Serum Pregnancy Test[8]	X												
CMV Monitoring[9]	X						X					X[9]	
Treatments[10]													
Oral Hydration[11]		X	X	X	X	X	X[11]						
Intravenous Hydration[12]		X					X[12]						
Venetoclax (dose in mg)[13]		20	20	50	100	200	400	400	400	0			
Bendamustine[14]		X	X				X	X					
Rituximab[15]		X					X						
Growth Factor Support[16]			X					X					
PJP & Antiviral Prophylaxis[17]							X	X	X	X		X	
Subject Calendars													
Venetoclax Medication Diary		X	X	X	X	X	X	X	X				
Disease Assessments/Measurements													
PET/CT	X											X[18]	
Bone Marrow Biopsy & Aspirate	X											X[19]	
CT Chest/Abdomen/Pelvis											X[20]		
Disease and Survival Status											X	X	X
Correlative Study Samples													
Archived Tissue Procurement (Mandatory)[21]	X											X[22]	X[22]
Research Blood Specimens (Optional)[23]		X					X[23]					X	
MRD testing[24] (Mandatory)	X											X	

* **Scheduled Visits:** In general +/- 3 day window for therapy/tests/visits during therapy except as noted for TLS monitoring. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

1 Record date of diagnosis, primary tumor type, histology, stage, and MCL international prognostic index (MIPI). MIPI calculator can be accessed using the website at https://qxmd.com/calculate/calculator_149/mipi-mantle-cell-lymphoma-prognosis[34] or https://www.mdcalc.com/mantle-cell-lymphoma-international-prognostic-index-mipi[35].[36,37]

2 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hgb, and Hct. Required prior to each dose of treatment, and results known prior to treatment administration.

3 BUN/creatinine, sodium, potassium, chloride, bicarbonate (HCO_3), glucose, and calcium. Refer to Section 5.4, Table 5-3 "Tumor Lysis Monitoring" for additional time points and days not captured on Study Calendar.

4 Cycle 2, Day 2 only.

5 Albumin, total protein, alkaline phosphatase, AST, ALT, and total bilirubin.

6 Basic Metabolic Panel (Sodium, Potassium, Chloride, Bicarbonate (HCO3), BUN, Creatinine, Calcium), Albumin, Uric Acid, and Phosphorus. Refer to Section 5.4, Table 5-3 "Tumor Lysis Monitoring" for additional time points and days not captured on Study Calendar. See Appendix IV for "Definitions of Tumor Lysis Syndrome[31]".

7 Hepatitis B (HBV), Hepatitis B surface antigen (HBsAg), and Hepatitis C (HCV) testing within 6 weeks of registration. Patients who are chronic carriers of HBV with positive HBsAg+ and positive HCV serology are excluded. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are allowed with protective hepatitis B surface antibody AND a negative hepatitis B viral load by PCR. If enrolled, patients must be willing to undergo monthly HBV DNA testing.

Patients with positive HCV antibody must be negative for HCV by PCR to be eligible for study participation. Prior treatment for an active hepatitis C infection will be allowed so long as the hepatitis C viral load by PCR is negative.

8 Required for females of child-bearing potential.

9 Patients will be monitored for CMV reactivation using Quantitative PCR Assay for CMV DNA. If CMV PCR is reported as >137 IU/mL increase frequency of testing to weekly. See Section 5.7: Monitoring for Cytomegalovirus (CMV) for additional monitoring parameters and guidelines.

Induction: Once a month and end of induction.

Maintenance: Treating physician discretion or per institutional standards; however, if detectable, recommend continued monitoring per institutional standards.

10 Standard pre-medications and antiemetic therapy per institutional guidelines are allowed per Section 5.1. Also, refer to Section 5.3 for details on prophylaxis for TLS.

11 Encourage at least 2 liters of oral fluids per day starting 24 hours prior to Cycle 1, Day 1 and continuing until Cycle 2, Day 10. Refer to Section 5.3 for details.

12 At least 1 liter of IV hydration should be given on Day 1 of Cycle 1 and Cycle 2. Additional IV fluids and monitoring for TLS is allowed per treating physician discretion. Refer to Section 5.3 for details.

13 Venetoclax will be administered orally. **Cycle 1:** 20 mg on Day 1-7; 50 mg on Day 8-14; 100 mg on Day 15-21; and 200 mg on Day 22-28. **Cycle 2-6:** 400 mg on Day 1-10. One cycle = 28 days. On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. See Section 5 for dosing instructions and tumor lysis prophylaxis/monitoring and Section 6 for dose delays/modifications.

14 Bendamustine is given as 90 mg/m^2 IV day 1 and 2 before or after rituximab. See Section 5 for dosing instructions and Section 6 for dose delays/modifications.

NOTE: Per investigator discretion, bendamustine may be started at 70 mg/m^2 in patients over the age of 75 years with comorbid conditions or patients over the age of 80 years without comorbid conditions.

15 Rituximab 375 mg/m^2 is given on Day 1 of each cycle before or after bendamustine. If the first two cycles (or two consecutive cycles) of rituximab are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units SQ rituximab/hyaluronic acid on Day 1 of Cycles 3-6 (or after 2 consecutive cycles are well tolerated), per investigator and patient preference. Biosimilars for rituximab are permitted. See Section 5 for dosing instructions and Section 6 for dose delays/modifications.

NOTE: After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

16 Growth factor support should be given 24-72 hours after the last dose of bendamustine for each cycle per Section 5.5.

17 All patients must be initiated on prophylaxis at the start of Cycle 2 of venetoclax, bendamustine and rituximab.

PJP Prophylaxis: Trimethoprim-sulfamethoxazole (Bactrim) for PJP prophylaxis and should continue until 6-8 weeks from Day 1 of last completed induction cycle. PJP prophylaxis may be discontinued at that time, or continued at the discretion of the treating physician.

Antiviral Prophylaxis: Acyclovir or valcyclovir for antiviral prophylaxis. Antiviral prophylaxis should continue for a minimum of 6 months after completion of induction, and may be discontinued at that time, or continued at the discretion of the treating physician.

See Section 5.6: Infection Prophylaxis for additional parameters and guidelines.

18 PET/CT 6-8 weeks after Day 1 of last completed cycle. Each target lesion should have Deauville score at end of treatment. Refer to Section 9.2, Table 9-1 and Appendix V for details.

19 Bone marrow biopsy and aspirate per standard of care but must be performed if PET/CT shows CR and bone marrow biopsy was positive at screening to confirm CR. Mandatory sample submission for research when collected per standard of care.

20 Repeat imaging before Cycle 3 or 4 per institutional guidelines. CT scans or PET/CT scans may be used at this time point per institution standards. Any progression should be confirmed by PET/CT.

21 Pre-treatment, diagnostic pathology specimens (organ or lymph node biopsy or excision) obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory). Formalin-Fixed Paraffin-Embedded (FFPE) blocks and 5 FFPE slides or up to 15 FFPE slides plus H&E slide (if tissue is limited, then minimum of 10 slides) will be required. Procurement of tissue will be mandatory for enrollment, but if additional tissue from initial biopsy is not available, repeat biopsy will not be required. **Optional:** Any leftover tissue banked for future research. See Section 13.1 and PrE0405 Lab Manual for details.

NOTE: If blocks and/or slides are unavailable and bone marrow is involved with mantle cell lymphoma, obtain two 2 mL EDTA tubes of bone marrow aspirate (one for baseline MRD analysis and one for future research). If blocks/slides and bone marrow are unavailable and peripheral blood is involved with mantle cell lymphoma obtain one 4 mL and one 6 mL EDTA tubes of peripheral blood (one for baseline MRD analysis and one for future research). If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

22 **Optional:** At time of progression, biopsy samples are requested to be sent for correlative studies and banked for future research. See Section 13.1 and PrE0405 Lab Manual for details.

23 **Optional Research Bloods:** See Section 13.3 and PrE0405 Lab Manual for details.

Cycle 1, Day 1 (prior to treatment)

Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

Cycle 2, Day 1 (prior to treatment)
Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

Cycle 4, Day 1 (prior to treatment)

Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

End of Treatment Visit

Peripheral Blood: One 10 mL red top tube and one 6 mL in EDTA tube

At Time of Progression

Peripheral Blood: One 10 mL red top tube, one 4 mL and one 6 mL in EDTA tube

24 **Mandatory MRD Samples:** See Section 13.1, 13.2, 13.3 and PrE0405 Lab Manual for details.

Screening/Study Entry
FFPE: 3-5 FFPE slides from lymph node (preferred)

NOTE: If FFPE unavailable, either bone marrow aspirate (2 mL EDTA tube) or peripheral blood (4 mL EDTA tube) are acceptable as long as they are involved with mantle cell lymphoma. If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

End of Treatment Visit
Peripheral Blood: One 4 mL in EDTA tube
Bone Marrow Aspirate (per standard of care)*: One 2 mL in EDTA tube

*Bone Marrow Aspirate: Submission is mandatory when collected per standard of care. Please note, if bone marrow is positive for mantle cell lymphoma at baseline, an end of treatment bone marrow must be collected to confirm response.

25 6-8 weeks after Day 1 of last completed cycle.

26 Patients will be followed for adverse events for 30 days after their last dose of study medication.

27 Every 3-6 months or per institutional guidelines for up to 5 years from treatment discontinuation for progression and survival. Imaging to be done per institution standards and/or physician discretion. Maintenance rituximab is allowed and will be documented but will not constitute additional therapy. Initiation of first anti-cancer therapy will also be documented.

NOTE: If patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment with the exception of allowed maintenance rituximab for up to 5 years or study closure.

11. Drug Formulation and Procurement

11.1 Venetoclax[21,22]

11.1.1 Other Names

GDC-0199, ABT-199, RO5537382.

11.1.2 Classification

Oral Bcl-2 family protein inhibitor.

11.1.3 Storage and Stability

Venetoclax will be supplied in bottles with 10 mg, 50 mg, and 100 mg tablets.

The 10 mg film-coated tablets are round, biconvex shaped, pale yellow debossed with “V” on one side and “10” on the other side.

The 50 mg film-coated tablets are oblong, biconvex shaped, beige debossed with “V” on one side and “50” on the other side.

The 100 mg film-coated tablets are oblong, biconvex shaped, pale yellow debossed with “V” on one side and “100” on the other side.

The tablets must be stored at 15°C–25°C (59°F–77°F).

11.1.4 Dose Specifics

In Cycle 1, venetoclax is dispensed in a 1-week supply. There will be a gradual dose escalation in Cycle 1 (Table 5-2).

In Cycle 2-6, venetoclax is dispensed in a 4-week supply. Cycle 2-6, patients will take four tablets (400 mg) daily on days 1-10 for each 28 day cycle. Tablets should not be chewed, crushed or broken.

On days when venetoclax is given with bendamustine and rituximab, venetoclax should be given first.

If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given.

If patient misses a dose of venetoclax within 8 hours of when it is usually taken, the patient should take the dose as soon as possible and resume normal daily dosing schedule. Should the dose be missed by greater than 8 hours, the dose should be skipped and patient should resume normal daily dosing the following day. This dose should not be made up.

Refer to Section 5.2 for details.

11.1.5 Drug Interactions

Drug-drug interactions may occur with venetoclax. Co-administration of venetoclax with strong to moderate inhibitors or inducers of CYP3A or P-gp inhibitors is prohibited. Co-administration with weak CYP3A inhibitors and inducers is allowed. P-gp substrate should be avoided. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

In cycles 2-6 when venetoclax will not be administered (i.e., Days 11-28), avoid the use of strong or moderate CYP3A inhibitors or P-gp inhibitors 2 to 3 days prior to the next cycle of venetoclax treatment. Also avoid the use of strong or moderate CYP3A inducers at least 7 days prior to the next cycle of venetoclax treatment.

See Section 6.2.2 and Appendix III: Additional Excluded and Cautionary Medications for a list of medications that are to be excluded or used with caution in patients receiving venetoclax.

11.1.6 Availability

Venetoclax will be supplied by Genentech.

The initial supply of venetoclax will be sent directly to the site upon site activation. As needed, venetoclax may be requested by the Principal Investigator (or their authorized designees) at each participating institution. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return/destruction (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site) of venetoclax.

11.1.7 Agent Ordering

PrECOG will be responsible for ordering drug for re-supply to the site. Requests for shipments of venetoclax will be coordinated between PrECOG and Genentech.

11.1.8 Agent Accountability

Venetoclax will be stored in a secure location. Only authorized pharmacy and study staff will have access to this agent. Drug accountability will be performed by PrECOG.

Please refer to the current Investigator's Brochure for additional information.

11.1.9 Side Effects

11.1.9.1 Tumor Lysis Syndrome

TLS is a risk for patients with MCL who are treated with high cell-killing agents, including venetoclax. The highest risk for TLS occurs within the first 24 hours of a dose escalation caused by rapid reduction of the tumor. Refer to Section 5.3 for Tumor Lysis Prophylaxis and Section 5.4 for Tumor Lysis Monitoring.

NOTE: Defined risks for TLS are not clear in MCL but some higher risk situations include:

- Bulky disease (any lymph node mass >10 cm)
- Circulating mantle cell lymphoma with ALC >25 x 10^9/L
- Borderline renal function
- Rapidly progressing disease.

11.1.9.2 Neutropenia

Neutropenia is an important identified risk for venetoclax, specifically in CLL. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program.

11.1.9.3 Infections

Infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types

of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies and are similar across all indications.

Infections should be closely monitored in this study. Recommendations for anti-infective prophylaxis are per standard of care (e.g., National Comprehensive Cancer Network guidelines [NCCN] for oncology subjects).

11.1.9.4 Anemia

Anemia has been reported in the oncology studies with slightly higher frequency in some studies in which venetoclax is combined with other chemotherapeutic agents; however, most of the events were nonserious and confounded by disease factors and prior therapies.

11.1.9.5 Thrombocytopenia

Thrombocytopenia adverse events have been reported in the oncology studies, with slightly higher frequency in studies in which venetoclax is combined with other chemotherapeutic agents. However, most of the events were nonserious and assessment of these events is confounded by the patients' underlying disease states, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia, in several patients.

11.1.9.6 Lymphopenia

Lymphopenia has been observed in nonclinical studies with venetoclax. While opportunistic infections have been reported in the clinical program, data are confounded by patients' underlying disease and prior therapies.

If clinically indicated, anti-infective prophylaxis should be implemented, including appropriate prophylaxis for viral, fungal, bacterial, or *Pneumocystis jiroveci* pneumonia infections.

11.1.9.7 Reproductive System Effects

Based on nonclinical studies, there is a potential for decreased spermatogenesis. Male patients considering preservation of fertility should bank sperm before treatment with venetoclax. Long-term effects of venetoclax on female reproductive potential are unknown.

11.1.9.8 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported across the oncology program. No pattern has been was observed. As venetoclax is being evaluated in patients with relapsed/refractory (R/R) disease who had previously been treated with various cytotoxic agents, second primary malignancies should be closely monitored.

11.1.9.9 Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal.

11.1.9.10 Drug-Drug Interaction

Co-administration of venetoclax with strong to moderate inhibitors or inducers of CYP3A or P-gp inhibitors is prohibited. Co-administration with weak CYP3A inhibitors and inducers is allowed. P-gp substrate should be avoided. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

In cycles 2-6 when venetoclax will not be administered (i.e., Days 11-28), avoid the use of strong or moderate CYP3A inhibitors or P-gp inhibitors 2 to 3 days prior to the next cycle of venetoclax treatment. Also avoid the use of strong or moderate CYP3A inducers at least 7 days prior to the next cycle of venetoclax treatment. (Section 6.2.2 and Appendix III: Additional Excluded and Cautionary Medications).

Live attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs.

11.1.9.11 Overdose

There is no specific antidote for venetoclax. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt venetoclax and monitor carefully for signs and symptoms of TLS along with other toxicities.

11.1.10 Nursing/Patient Implications

1. TLS: Inform patient to immediately report any signs and symptoms associated with TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizure, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle pain, and/or joint discomfort) to their doctor.
2. Neutropenia: Monitor blood counts and for signs of infection; manage as medically appropriate.
3. Advise patients to avoid consuming grapefruit products, Seville oranges, or starfruit during treatment with venetoclax. Advise patients to inform their doctor of the use of any prescription medication, over-the-counter drugs, vitamins and herbal products.

11.2 Bendamustine[38]

Bendamustine will be obtained by the individual study sites as standard of care treatments from commercial stock. Refer to commercial package inserts for full prescribing information.

11.2.1 Other Names

Bendamustine hydrochloride, Treanda, Bendeka.

11.2.2 Classification

Alkylating neoplastic agent.

11.2.3 Storage and Stability

Bendamustine for injection, is supplied in multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow ready-to-dilute solution. Store intact vials in refrigerator, 2°-8°C (36°- 46°F). Vials should be retained in the original package until time of use to protect from light.

Admixture Stability: Bendamustine contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5%

Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of bendamustine must be completed within this period.

11.2.4 Dose Specifics

Induction: Bendamustine will be administered at 90 mg/m² intravenously on Day 1 and Day 2 of every 28 day cycle for 6 cycles.

NOTE: Per investigator discretion, bendamustine may be started at 70 mg/m^2 in patients over the age of 75 years with comorbid conditions or patients over the age of 80 years without comorbid conditions.

11.2.5 Preparation

Refer to commercial package insert or institutional guidelines for preparation of bendamustine.

11.2.6 Route of Administration

Bendamustine will be administered as an IV infusion per institutional guidelines and package insert at a dose of 90 mg/m^2 on days 1 and 2 of each 28-day cycle.

NOTE: Per investigator discretion, bendamustine may be started at 70 mg/m^2 in patients over the age of 75 years with comorbid conditions or patients over the age of 80 years without comorbid conditions.

If medical conditions necessitate, e.g., fluid management issues or infusion reactions, the infusion may be given over a longer period of time. In–line filters are not required for administration. Unless there are extenuating circumstances, all of the drug should be administered to the patient with the exception of what remains in the line. Be sure to document any problems you may encounter with the infusion. If for any reason the drug cannot be entirely administered, please measure the remaining volume in the infusion bag and record on your source documentation.

11.2.7 Dosage in Renal or Hepatic Failure

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 40-80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL <40 mL/min. These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL <40 mL/min.

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5x ULN, and/or ALP ≥ ULN to 5.0x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment. These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with AST or ALT ≥ 3.0x ULN and total bilirubin ≥ 1.5x ULN.

11.2.8 Drug Interactions

Bendamustine is a substrate for the cytochrome P450(CYP) 1A2 isoenzyme.

Bendamustine is metabolized to minimally active metabolites by CYP1A2. Concurrent administration of a CYP1A2 inhibitor such as atazanavir, cimetidine, ciprofloxacin, fluvoxamine, mexiletine, tacrine, thiabendazole, zileuton, norfloxacin, and/or ethinyl

estradiol may increase bendamustine concentrations in plasma. Caution should be exercised, or alternative treatments considered, when co-administering bendamustine with a CYP1A2 inhibitor.

Bendamustine is metabolized to minimally active metabolites by CYP1A2. Concurrent administration of a CYP1A2 inducer such as barbiturates, carbamazepine, and/or rifampin may cause a decrease in bendamustine plasma concentrations and a potential *decrease* in cytotoxicity. The parent compounds are believed to be primarily responsible for the cytotoxicity of this agent. Caution should be exercised, or alternative treatments considered, when co-administering bendamustine with a CYP1A2 inducer.

Bendamustine is metabolized to minimally active metabolites by CYP1A2. Smoking tobacco has been shown to induce CYP1A2, and may cause a decrease in bendamustine plasma concentrations and a potential decrease in cytotoxicity. The parent compound is believed to be primarily responsible for the cytotoxicity of this agent. Caution should be exercised, or smoking cessation considered, when co-administering bendamustine with a CYP1A2 inducer.

11.2.9 Incompatibilities

No incompatibilities are known (no data is available).

11.2.10 Side Effects

Please refer to Package Insert.

11.2.11 Nursing/Patient Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm^3 and increased risk of bleeding with platelet counts less than 20,000 cells/mm^3. Advise patients to call the clinic if they develop a fever above 101^oF or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia, although this is very uncommon with bendamustine therapy.
3. Assess hydration and fluid balance. Patients should be encouraged to have at least 1 liter of fluids per day for 72 hours after administration.
4. Consider premedication with antiemetics.
5. Observe for possible phlebitis at injection site.

11.3 Rituximab[39,40]

Rituximab will be obtained by the individual study sites as standard of care treatments from commercial stock. Refer to commercial package inserts for full prescribing information.

Biosimilars for rituximab are permitted.

11.3.1 Other Names

IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody, Rituxan.

11.3.2 Classification

Antibody

11.3.3 Storage and Stability

Rituximab IV: Store vials in the refrigerator at 2ºC–8ºC (36ºF–46ºF). Protect vials from direct sunlight. Once diluted to a concentration of 1 to 4 mg/mL in polyvinylchloride or polyolefin IV bags containing normal saline or 5% dextrose, the product is stable for up to 24 hours at 2ºC–8ºC (36ºF–46ºF), and at room temperature for an additional 12 hours after refrigeration (for a maximum period of 36 hours) if protected from light.

Rituximab SQ: Store vials in the refrigerator at 2ºC–8ºC (36ºF–46ºF) in the original carton to protect from light. Do not freeze.

Biosimilars for rituximab are permitted. Refer to package insert for storage and stability parameters.

11.3.4 Dose Specifics

Induction: Rituximab will be administered at 375 mg/m² intravenously every 28 days for 6 cycles.

NOTE: For patients that do not have a Grade 3-4 infusion related adverse event, Cycle 2-6 may be given as a "rapid" IV infusion at 375 mg/m^2 per package insert.

Additionally, if the first two cycles (or two consecutive cycles) of rituximab are well tolerated, IV rituximab may be replaced with 1400 mg/23,400 units SQ rituximab/hyaluronic acid on Day 1 of Cycle 3-6 (or after 2 consecutive cycles are well tolerated), per rituximab/hyaluronic acid package insert.

Maintenance: After 6 cycles of venetoclax, bendamustine and rituximab, subjects responding to therapy may receive maintenance rituximab IV or SQ (one dose every 8 ± 2 weeks for 12 doses or 24 months whichever comes first) per physician and patient preference.

Biosimilars for rituximab are permitted. Refer to package insert for dose specifics.

11.3.5 Preparation

Rituximab IV: Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

Rituximab preparation may also be done per institutional standards.

Rituximab SQ: Subcutaneous injection is supplied as a sterile preservative-free liquid solution in a single-dose vial.

Biosimilars for rituximab are permitted. Refer to package insert for preparation instructions.

11.3.6 Route of Administration

Rituximab IV: Rituximab should be given as a "standard" IV infusion at 375 mg/m^2 for Cycle 1 per institution guidelines and package insert. For patients that do not have a Grade 3-4 infusion related adverse event, Cycle 2-6 may be given as a "rapid" IV infusion at 375 mg/m^2 per institution guidelines and package insert. Patients that do have a Grade 3-4 infusion related adverse event should receive the "standard" infusion rate for the subsequent cycle. Patients may receive the "rapid" infusion schedule if the prior infusion was not associated with a Grade 3-4 infusion related adverse event.

Rituximab SQ: 1400 mg/23,400 units SQ rituximab/hyaluronic acid on Day 1 of Cycle 3-6 (or after two consecutive cycles are well tolerated), per rituximab/hyaluronic acid package insert.

Biosimilars for rituximab are permitted. Refer to package insert for route of administration instructions.

11.3.7 Incompatibilities

Rituximab IV: Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Rituximab Biosimilars: Refer to package insert for incompatibilities.

11.3.8 Side Effects

Please refer to Package Insert.

11.3.9 Nursing/Patient Implications

1. Monitor blood pressure, pulse, respiration, and temperature every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued or per standard of care.
2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.
3. Monitor and alter infusion rates in the presence of toxicities.

12. Statistical Considerations

12.1 Study Design, Sample Size Considerations & Statistical Analyses

12.1.1 Primary Endpoint

The primary endpoint of this single arm Phase II study is CR rate after 6 cycles of BR + venetoclax. A 15% improvement in the historical post-induction CR rate of 70% to 85% is of interest. A total of 56 patients will be enrolled, 53 of whom are expected to be eligible and treated. There will be 90% power to detect the 15% improvement in CR rate from 70% using one-sided exact binomial test with 10% Type I error. This treatment combination will be considered worthy of further investigation if 42 or more eligible and treated patients achieve CR. The efficacy population consists of all eligible and treated patients.

12.1.1.1 Revised Study Design

Preliminary data from a similar cohort of patients as that enrolled in this study indicates that post-induction CR rate is 60%, not 70% as initially assumed. In addition, the observed study accrual rate (1.1 patients/month) is significantly lower than the planned/expected study accrual rate of 2.3 patients/month. For both reasons, the study was redesigned to reflect the current historical CR rate and with a lowered sample size for prompt primary endpoint readout. Accrual before this redesign is 25 patients as of 10/11/2021.

With a revised accrual goal of 33 patients, 32 patients expected to be eligible and treated, there is 81.8% power and 11.6% alpha using exact binomial test to detect a 17% difference in CR rate from 60% to 77%. The null hypothesis will be rejected, and treatment combination declared positive if ≥ 23 (71.9%) CRs are observed among 32 eligible and treated patients.

12.1.2 Secondary Endpoints

Secondary endpoints include progression free survival (PFS) and overall survival (OS). PFS is defined as time from registration to disease progression or death from any cause, whichever occurs first. Patients that are alive and progression free at the time of analysis will be censored at the date of last disease assessment. OS is defined as time from registration to death; patients will be censored at the time of last study contact. PFS and OS will be estimated using Kaplan-Meier methodology and 90% confidence interval (CI) around estimates will be presented. Appropriate descriptive measures will be used to describe clinical and demographic variables.

12.2 Planned Analyses

12.2.1 Toxicity Monitoring Plan

12.2.1.1 Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS) is an event of interest in this study. TLS risk factors are listed in Section 5.3, TLS monitoring plan is detailed in Section 5.4 and “Definitions for Tumor Lysis Syndrome” noted in Appendix IV. The risk for TLS will be assessed among the first 19 patients accrued to this study who received venetoclax treatment for at least 3 cycles with no hold to accrual. Given the expected clinical TLS rate of 5%, the probability of observing at least one clinical TLS among 19 patients is 62%, and 82% among 33 patients.

A TLS incidence rate of no more than 15% (≤ 3 out of 19 patients) is permissible on this study. If the observed TLS is ≥ 21% (≥ 4 out of 19 patients) then a detailed review of TLS cases will be conducted by the Data Safety Monitoring Board (DSMB). This is the boundary and the DSMB could recommend closing the study due to high incidence of TLS. If the true incidence of TLS is 30% or higher, there is at least 87% probability of crossing the boundary. Whereas, if the true incidence of TLS is 10% there is only 11% chance of crossing the boundary.

12.2.1.2 Non-Disease Related Death on Treatment

Deaths during induction have been reported in prior studies with BR and novel combinations, particularly bortezomib and lenalidomide.[13,14] The combined rate of non-disease related death in these studies is approximately 5.5%, which is considered unacceptable. Non-disease related death, defined as death from any cause not due to mantle cell lymphoma and occurring at any time from Cycle 1, Day 1 to end of treatment, will be monitored during the study and each event will be reported to the DSMB. In addition to reporting each non-disease related death event to the DSMB for review, the cumulative observed number of events will be assessed, based on the presented operating characteristics, at specific accrual stages specified in the table below. These accrual stages include after 19, 28, and 33 patients enrollment. If at any of the accrual stages the specified boundary for that stage is crossed, the study will pause enrollment and await DSMB review and recommendations. During the review, the DSMB may decide that a death event is not related to treatment and may exclude the event from further calculations (i.e. accident or suicide).

From the table, at the 19 patient enrollment and treatment milestone, the expected number of non-disease related death is 1 (based on the 5.5% rate reported from referenced studies). If ≥ 2 such death events occur (i.e. boundary is crossed) among 19 patients then the DSMB will review all non-disease related death cases. There is 8.1%, 28.1%, 45.6%, 58.0%, 68.3%, and 80.2% probability of crossing the boundary if the true underlying non-disease related death rate is 2.5%, 5.5%, 8%, 10%, 12%, and 15% respectively.

If at any time there are greater than 5 non-disease related deaths during induction, the study may close for safety. If the true non-disease related death rate is 5.5% then the probability of observing >5 events among 33 patients is only 0.8%. Whereas the probability of observing >5 events is 10.6% if the true non-disease related death rate is 10%, and 67.1% if the true underlying death rate is 20%.

Table12-1: Operating Characteristics of Non-Disease Related Death on Treatment				
	Accrual Stage (Number of Expected Eligible and Treated Patients			
Total Accrual (N=33)	19	28	33	
***Expected # of deaths based on 5.5% estimate**	1	2	2	
Boundary (defined as expected # of deaths + 1)	2	3	3	
Probability of crossing boundary given true death rate of				
a) 2.5%	8.1%	3.2%	4.9%	
b) 5.5%	28.1%	19.8%	27.2%	
c) 8%	45.6%	39.1%	49.8%	
d) 10%	58.0%	54.1%	65.4%	
e) 12%	68.3%	67.0%	77.5%	
f) 15%	80.2%	81.3%	89.1%	

Rounded to the nearest whole number

12.2.1.3 Other Toxicity

Toxicity and adverse events for all enrolled patients will be monitored throughout the conduct of the study. Toxicity rates, with 90% exact binomial CIs, will be estimated for all enrolled patients who received at least one cycle of treatment, irrespective of eligibility. These rates will be estimated for Grade 3 or higher treatment-related toxicities using CTCAE Version 5.0. If all 33 patients are treated, the maximum width of a 90% exact CI on the rate of Grade 3 or higher treatment-related toxicities will be no wider than 31%. The probability of observing at least one rare toxicity event (given a true rate of 5%) is 81.6%. The DSMB will review safety data and may halt the study for safety if any grade 4 or higher specific toxicity occurs with an incidence rate of >30%.

12.2.1.4 Study and Safety Monitoring Plan

This study will be monitored by the PrECOG DSMB. The DSMB meets twice each year, or as frequently as deemed necessary by the DSMB. For each meeting, all monitored studies are reviewed for toxicity and progress toward completion. If a safety concern is identified, the DSMB may recommend halting or permanently stopping the trial at any time.

12.2.2 Analyses of Correlative Studies

Minimum Residual Disease (MRD) will be analyzed as a binary endpoint and 90% exact CI around the estimated MRD negative rate will be reported. This estimate will also be reported within levels of response to BR + venetoclax treatment.

13. Laboratory and Pathology Correlative Studies

13.1 Correlative Studies: Mandatory Tumor Samples (if sufficient tissue available)

13.1.1 Research Tumor Sample Collection

Pre-treatment, diagnostic pathology specimens (organ or lymph node biopsy or excision) obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory).

Formalin-fixed paraffin-embedded (FFPE) blocks and 5 FFPE tissue on unstained (5 um) slides or if blocks are not available, up to 15 FFPE tissue on unstained (5 um) slides plus H&E slide (if tissue is limited, then minimum of 10 slides).

NOTE: If additional tissue from initial biopsy is not available, repeat biopsy will not be required (no biopsy should be performed solely for the purposes of obtaining research samples).

Five slides per patient will be sent to Adaptive Biotechnologies for baseline calibration (obtained from a patient at the time of diagnosis and before treatment has begun) measurement for MRD.

If blocks and/or slides are unavailable and bone marrow is involved with mantle cell lymphoma, obtain two 2 mL EDTA tubes of bone marrow aspirate (one for baseline MRD analysis and one for future research). If blocks/slides and bone marrow are unavailable and peripheral blood is involved with mantle cell lymphoma obtain one 4 mL and one 6 mL EDTA tubes of peripheral blood (one for baseline MRD analysis and one for future research). If baseline samples (blocks/slides, bone marrow, and/or peripheral blood) are not submitted at baseline for MRD (i.e., not involved with mantle cell lymphoma), then patients will be allowed to remain on study but MRD samples will not be collected during the study.

Optional: Any tumor biopsy samples obtained during treatment or post-treatment (FFPE blocks or up to 15 FFPE tissue on unstained (5 um) slides plus H&E slide) will be requested for research if conducted due to concerns for progressive disease and banked for future research.

Blocks or remaining slide samples will be sent to the ECOG-ACRIN Central Biorepository Pathology Facility (CBPF) for storage.

13.1.2 Pathology Sample Processing and Shipment

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits will be supplied. Instructions and shipping address will be provided. Refer to the PrE0405 Lab Manual for details.

13.1.2.1 MRD Pathology Samples to Adaptive Biotechnologies

Sites should submit 5 FFPE slides (minimum of 3 slides) from a tumor tissue block. Thickness of the sections should be at 5 micron.

Samples should be shipped **Monday-Thursday**. Samples will be shipped ambient via overnight courier approximately every 6 months on a set schedule. For all patients the initial shipment should include Baseline (tissue sample) and End of Treatment (bone marrow, if collected and peripheral blood) samples.

13.1.2.2 Remaining Pathology Samples to Central Lab

Sites should submit FFPE diagnosis tumor tissue blocks or up to 10 FFPE slides plus H&E slide from a tumor tissue block within 6 months of patient registration. Thickness of the sections should be at 5 micron.

Sites should submit any optional tumor samples obtained during treatment or post-treatment (formalin-fixed paraffin-embedded (FFPE) blocks or up to 15 FFPE tissue (5 microns) on unstained slides plus H&E slide) within 3 months of procedure.

A copy of the pathology report from initial diagnosis and/or subsequent tumor sampling should be sent when the sample is shipped. Samples should be shipped **Monday-Thursday**. Samples will be shipped ambient via overnight courier to the CBPF approximately every 6 months.

13.2 Correlative Studies: Mandatory Bone Marrow Samples

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits will be supplied. Instructions and shipping address will be provided. Refer to the PrE0405 Lab Manual for details.

13.2.1 Research Bone Marrow Sample Collection

- **Screening (only if FFPE tumor samples are not available and bone marrow involved with mantle cell lymphoma)**
  - One 2 mL EDTA tube for MRD calibration sample
  - One 2 mL EDTA tube for future research
- **End of Treatment (submission is mandatory if collected)**
  - One 2 mL EDTA tube for MRD analysis

Please note, if bone marrow is positive for mantle cell lymphoma at baseline, an end of treatment bone marrow must be collected to confirm response.

13.2.2 Research Bone Marrow Processing and Shipment

13.2.2.1 MRD Bone Marrow Aspirate Samples to Adaptive Biotechnologies

Store 2 mL EDTA tube in the freezer at ≤ -80°C or colder until shipped to Adaptive Biotechnologies.

Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier approximately every 6 months on a set schedule. For all patients the initial shipment should include Baseline (tissue sample) and End of Treatment (bone marrow aspirate, if collected and peripheral blood) samples.

13.2.2.2 Remaining Bone Marrow Aspirate Samples to Central Lab, if applicable

Store 2 mL EDTA tube in the freezer at ≤ -80°C or colder until shipped to ECOG-ACRIN CBPF.

Bone marrow aspirate samples should be submitted approximately every 6 months, as applicable. A copy of the BM report should be sent when the sample is shipped. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier to the CBPF.

13.3 Correlative Studies: Mandatory and Optional Peripheral Blood Samples

All samples collected will be labeled with a unique numeric identifier that will be coded for patient privacy protection.

Kits will be supplied. Instructions and shipping address will be provided. Refer to the PrE0405 Lab Manual for details.

MRD Samples are mandatory. Samples for future research are optional except screening sample is mandatory, as applicable.

13.3.1 Research Blood Sample Collection

- **Screening (only if FFPE tumor and BM samples are not available and peripheral blood involved with mantle cell lymphoma)**
  - One 4 mL EDTA tube for MRD calibration sample
  - One 6 mL EDTA tube for future research
- **Cycle 1, Day 1**
  - One 10 mL red top tube for future research
  - One 6 mL EDTA tube for future research
- **Cycle 2, Day 1 (If sample drawn and cycle delayed, this sample may be used, do not need to repeat)**
  - One 10 mL red top tube for future research
  - One 6 mL EDTA tube for future research
- **Cycle 4, Day 1 (If sample drawn and cycle delayed, this sample may be used, do not need to repeat)**
  - One 10 mL red top tube for future research
  - One 6 mL EDTA tube for future research
- **End of Treatment**
  - One 4 mL EDTA tube for MRD analysis
  - One 10 mL red top tube for future research
  - One 6 mL EDTA tube for future research
- **At Time of Progression**
  - One 4 mL EDTA tube for future research
  - One 10 mL red top tube for future research
  - One 6 mL EDTA tube for future research

13.3.2 Research Blood Sample Processing and Shipment

13.3.2.1 MRD Peripheral Blood Samples to Adaptive Biotechnologies

Store 4 mL EDTA tube in the freezer at ≤ -80°C or colder until shipped to Adaptive Biotechnologies.

Samples should be shipped **Monday-Thursday**. Baseline and End of Treatment samples must be shipped on dry ice via overnight courier approximately every 6 months on a set schedule. For all patients the initial shipment should include Baseline (tissue sample) and End of Treatment (bone marrow aspirate, if collected and peripheral blood) samples.

NOTE: 4 mL EDTA tube sample collected at time of progression for future research will be stored at site. PrECOG will instruct sites when to ship these samples to the CBPF (approximately every 6 months).

13.3.2.2 Remaining Peripheral Blood Samples to Central Lab

Red Top Tube (10 mL) Processing for Serum

Gently mix the blood sample by inversion 5 times (do not shake). Allow the sample to sit at room temperature for 30-60 minutes in vertical positon until a clot has formed. If the blood is not centrifuged immediately after the clotting time (30-60 minutes at room temperature), the tubes should be refrigerated (4°C) for no longer than 4 hours.

Once the clot has formed, the sample is ready for centrifugation. Centrifuge for 15 minutes at room temperature at 1200 RPM or per institutional practices. Immediately aliquot and store the resulting serum into two (2) properly labeled polypropylene tubes. Be careful to not disturb the clot. Store the samples in the freezer at -80°C until they are shipped to the CBPF.

EDTA Tube (6 mL) Processing for Plasma and Buffy Coat

****Samples should be processed within 4 hours, but at limit of processing being same day****

- Gently mix blood sample by inversion 10 times (do not shake).
- Place tube immediately on wet ice for 5 minutes.
- Centrifuge at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes) or per institutional practices. Immediately place the tube on wet ice after centrifugation.

After centrifugation, the plasma layer will be at the top half of the tube. The nucleated cells (WBC) will be in a whitish layer, called the “buffy coat”, just under the plasma and above the red blood cells.

Plasma Preparation:

- Using a transfer pipette take the top two-thirds of the plasma and transfer plasma into a 15 mL conical centrifuge tube, be careful not to disturb the buffy coat layer in the EDTA tube (**NOTE:** see below for buffy coat processing instructions). Centrifuge the 15 mL conical tube at 1200 RPM for 15 minutes at 4°C. If a refrigerated centrifuge is not available, spin sample at room temperature (1200 RPM for 15 minutes). Immediately place the conical tube on wet ice after centrifugation.
- Transfer equal amounts of plasma into two (2) properly labeled polypropylene tubes for cryopreservation being careful not to disturb the small PBMC/pellet.
- Store the two aliquots of plasma samples in the freezer at ≤ -80°C or colder until they are shipped to the CBPF.

Buffy Coat Preparation:

- From the EDTA tube remove and aliquot the “buffy coat”; be careful not to disturb the layer of red blood cells.
- Store the aliquot of cells in one (1) properly labeled polypropylene tube for cryopreservation.
- Store the sample in the freezer at ≤ -80°C or colder until it is shipped to the CBPF.

Plasma and buffy coat samples should be batched together and shipped approximately every 6 months. Individual patients should only be included in the shipment if all of their samples have been completed through the End of Treatment sample. Samples should be shipped **Monday-Thursday**. Samples must be shipped on dry ice via overnight courier to the CBPF.

13.4 Assay Methodology

13.4.1 MRD Analysis

Adaptive's NGS MRD Assay is a process for measuring minimal residual disease (MRD) and will be used to analyze calibration samples and end of treatment samples from patients. Exploratory analyses of B-cell receptor repertoire loci will be performed to (i) determine disease-correlated clonotypes from each of the calibration samples and (ii) assess the levels of Index Clonotypes (and therefore levels of MRD) in end of treatment samples.

13.4.2 Planned Analysis for Future Research Samples

Analysis may be performed depending on resources, sample quality and availability for possible future molecular and genomic testing.

14. Administrative

14.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with, and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval from PrECOG and/or representatives and the Institutional Review Board (IRB) of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the Amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to who investigators should send correspondence will be provided in additional study documents.

14.2 Institutional Review Board

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

14.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by

the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

14.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the IRB according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

14.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of investigational product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Monitoring of drug accountability will also occur.

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other study files. The Investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials.

14.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the eCRFs must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

14.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/ submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by the Principal Investigator.

Instructions for management of patients who do not receive any protocol therapy:

If a patient is registered and does not receive any assigned protocol treatment, baseline, Serious Adverse Event and follow-up data will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate electronic off treatment form.

14.8 Records Retention

FDA Regulations (21CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US Investigational New Drug (IND):

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, whichever is longer. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

15. References

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Appendix I: ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix II: Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [years]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age [years]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})} \times 0.85$$

NOTE: Actual body weight in kg.

Source: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992; 62:249

Appendix III: Additional Excluded and Cautionary Medications

The following is NOT a complete list of medications that are potentially incompatible with treatment on this protocol. As the list of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference. Please refer to the following website for more information:

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Clinically Relevant Drug Interactions: Inhibitors and Inducers of Isoenzyme CYP3A and P-gp Inhibitors

Continuous use of strong and moderate CYP3A inhibitors, CYP3A inducers or P-gp Inhibitors is not allowed. If a subject requires continuous use of these drugs they will be excluded. Consider alternative medications.

NOTE: In cycles 2-6 when venetoclax will not be administered (i.e., Days 11-28), avoid the use of strong or moderate CYP3A inhibitors or P-gp inhibitors 2 to 3 days prior to the next cycle of venetoclax treatment. Also avoid the use of strong or moderate CYP3A inducers at least 7 days prior to the next cycle of venetoclax treatment.

Co-administration with the use of weak CYP3A inducers and inhibitors is allowed. P-gp substrate should be avoided. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

CYP3A INHIBITORS
STRONG INHIBITORS boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice, idelalisib, indinavir, itraconazole, lopinavir, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, teleprevir, telithromycin, troleandamycin, voriconazole **MODERATE INHIBITORS** amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, darunovir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, isavuconazole, nifedipine, seville oranges, star fruit, tofisopam, verapamil
CYP3A INDUCERS
STRONG INDUCERS avasimibe, carbamazepine, enzalutamine, mitotane, phenobarbital, phenytoin, rifampin, St. John's Wort **MODERATE INDUCERS** bosentan, efavirenz, etravirine, modafinil, nafcillin, oxcarbazepine
P-gp INHIBITORS (STRONG & MODERATE)
STRONG & MODERATE INHIBITORS amiodarone, azithromycin, captopril, carvedilol, cyclosporine, dronedarone, elacridar, felodipine, ginkgo (ginkgo biloba), mibefradil, milk thistle (silybum marianum), nitrendipine, quercetin, quinidine, ranolzine, schisandra chinensis, telmisartan, ticagrelor, tipranavir, valspodar

Cautionary Use

CYP3A INHIBITORS
WEAK INHIBITORS
alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseed, isoniazid, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, ticagrelor, tipranavir, zileuton
CYP3A INDUCERS
WEAK INDUCERS
armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib
P-gp
P-gp SUBSTRATES
aliskiren, ambrisentan, colchicines, dabigatran etexilate, digoxin, everolimus, fexofenadine, indinavir, lapatinib, loperamide, maraviroc, nilotinib, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan

Appendix IV: Definitions for Tumor Lysis Syndrome[31]

Definitions of Tumor Lysis Syndrome		
Metabolic Abnormality	**Criteria for Classification of Laboratory Tumor Lysis Syndrome***	**Criteria for Classification of Clinical Tumor Lysis Syndrome***
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 µmol/liter) in adults.	
Hyperphosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/ liter) in adults.	
Hyperkalemia		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‡	N/A	Increase in the serum creatinine level of 0.3 mg/dl (26.5 µmol/liter) (or a single value >1.5x 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 of <0.5 mL/kg/hr for 6 hr.

* 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 days afterward (Grade 3). Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death (Grade 4 or Grade 5[death]).

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

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome if no other cause can be found.

Source: Howard SC, Jones, DP and Pui CH. The Tumor Lysis Syndrome. N Engl J Med 2011; 364: 1844-54. Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Appendix V: Revised Criteria for Response Assessment[32]

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

Response and Site	PET-CT–Based Response	CT-Based Response
No Response or Stable Disease	**No Metabolic Response**	**Stable Disease**
Target Nodes/ Nodal Masses, Extranodal Lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured Lesions	Not applicable	No increase consistent with progression
Organ Enlargement	Not applicable	No increase consistent with progression
New Lesions	None	None
Bone Marrow	No change from baseline	Not applicable
Progressive Disease	**Progressive Metabolic Disease**	**Progressive Disease requires at least 1 of the following**
Individual Target Nodes/Nodal Masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal Lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: – LDi >1.5 cm and – Increase by ≥ 50% from PPD nadir and – An increase in LDi or SDi from nadir o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions >2 cm – In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline – New or recurrent splenomegaly
Nonmeasured Lesions	None	New or clear progression of preexisting nonmeasured lesions
New Lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	– Regrowth of previously resolved lesions – A new node >1.5 cm in any axis – A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma – Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

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

  - Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.
  - Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.
  - In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS:

1. No uptake above background
2. Uptake ≤ mediastinum
3. Uptake >mediastinum but ≤ liver
4. Uptake moderately >liver
5. Uptake markedly higher than liver and/or new lesions
6. X: new areas of uptake unlikely to be related to lymphoma.

Source: Reprinted with permission. © 2014 American Society of Clinical Oncology. All right reserved. Cheson BD, Fisher RI, Barrington SF, Cavalli F, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: the Lugano Classification. Table 3. JCO. 2014 Sep 20; 32(27):3059-3068.

Appendix VI: Investigator's Statement

1. I have carefully read this protocol entitled **"Phase II Study of Bendamustine and Rituximab plus Venetoclax in Untreated Mantle Cell Lymphoma over 60 Years of Age"**, **Version 5.0 dated 10/11/2021 (Protocol Number PrE0405)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.
3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.
5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the FDA.

Principal Investigator (PI):

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

MM DD YYYY