PrECOG Protocol Number: PrE0403

Phase II Study of Venetoclax (ABT-199/GDC-0199) in Combination with Obinutuzumab and Bendamustine in Patients with High Tumor Burden Follicular Lymphoma as Front Line Therapy

NCT#:	NCT03113422
IND #:	134855
Protocol Version Number:	8.0
Version Date:	10/15/2021

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(Internal Use Only) Genentech US Ref. ID Number: ML39161

IND #: 134855

Version Number: 8.0

Version Date: October 15, 2021

Release/Revision History	
Version 1.0: 5/25/2017	Released to Sites
Version 2.0: 11/7/2017	Released to Sites
Version 3.0: 11/16/2017	Released to Sites
Version 4.0: 1/23/2018	Released to Sites
Version 5.0: 9/25/2018	Released to Sites
Version 6.0: 8//28/2019	Released to Sites
Version 7.0: 2/5/2020	Released to Sites
Version 8.0: 10/15/2021	Released to Sites

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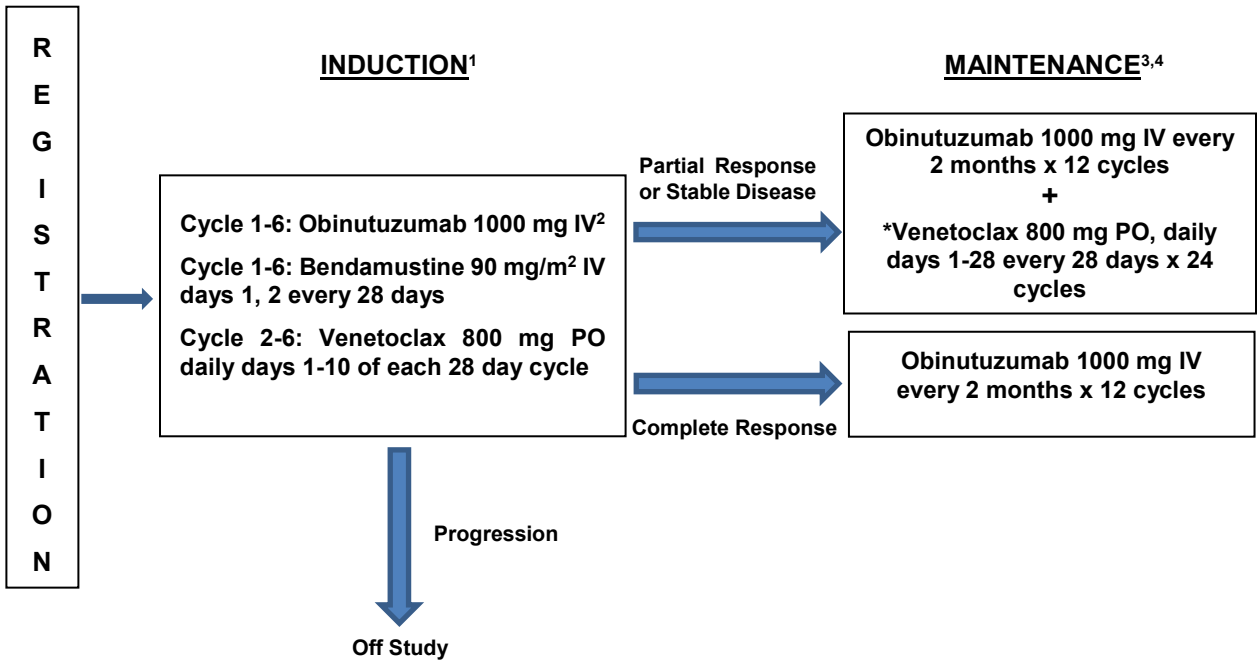
Brief Protocol Synopsis

See Protocol Document Sections for complete details

Study Schema

High Risk Follicular Lymphoma: GELF (High Tumor Burden) OR FLIPI (Score 3-5)



Accrual goal: 56 patients

Cycle length: 28 days (4 weeks)

[1] There will be a formal, detailed toxicity evaluation after 21 patients complete 3 cycles of treatment (including patients that come off treatment for any reason). Section 12.1 for details.

[2] Cycle 1 only obinutuzumab: 100 mg IV will be given on day 1 and 900 mg will be given on day 2. Cycle 1, day 8 and day 15, 1000 mg IV will be given. Starting with cycle 2 obinutuzumab 1000 mg will be given on Day 1 only.

[3] Patients will move on to the maintenance phase no earlier than 8 weeks and no later than 12 weeks post completion of cycle #6, day 28 of induction therapy.

[4] Further maintenance therapy was suspended on 9/16/2021. Refer to Section 1.6.3 for details.

* Patients with venetoclax dose reduction to 400 mg during induction phase will continue with 400 mg dosing during maintenance therapy for the 28 day cycle.

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

ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
anti-HBc or HBcAB	Hepatitis B Core Antibody
AST	Aspartate Aminotransferase
Bcl-2	B-Cell Lymphoma 2
BID	Twice a Day
BR	Bendamustine Rituximab
BSA	Body Surface Area
C	Celsius
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CI	Confidence Interval
Clb	Chlorambucil
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CMV	Cytomegalovirus
CR	Complete Response or Complete Remission
CrCl	Creatinine Clearance
Cru	Unconfirmed Complete Response
CT	Computerized Tomography
CTEP	Cancer Therapeutic Evaluation Program
dL	Deciliter
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eDC	Electronic Data Capture
EFS	Event-Free Survival
F	Fahrenheit

FC	Fludarabine Cyclophosphamide
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence In Situ Hybridization
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G	Obinutuzumab (GA101)
G-benda	Obinutuzumab-bendamustine
G-CHOP	Obinutuzumab in combination with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GELF	Groupe D'Etude des Lymphomes Follicularies
GI	Gastrointestinal
gm	Gram
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
Hct	Hematocrit
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIPPA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hr	Hour
HR	Hazard Ratio
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IgE	Immunoglobulin E
IHC	Immunohistochemistry
IND	Investigational New Drug
iNHL	Indolent Non-Hodgkin's Lymphoma
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-Related Reactions
ITT	Intent To Treat
IV	Intravenous
IWWM	International Workshop-Waldenstrom's Macroglobulinemia (Criteria)

JC Virus	John Cunningham Virus
Kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
M	Meter
m^2	Meter Squared
MCL	Mantle Cell Lymphoma
Mcl-1	Myeloid Cell Leukemia-1
mg	Milligram
mL	Milliliter
mm^3	Cubic Millimeter
mmol	Millimole
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
N	Number
NaCl	Sodium Chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
OBI	On Body Injector
ORR	Overall Response Rate
OS	Overall Survival
PCP	Pneumocystis Jiroveci Pneumonia
PCR	Polymerase-Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PJP	Pneumocystis Jiroveci Pneumonia
PML	Progressive Multifocal Leukoencephalopathy
PO	*per os*; By Mouth (orally)
PR	Partial Response or Partial Remission
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
R	Rituximab

R-CHOP	Rituximab in Combination with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
RNA	Ribonucleic Acid
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SD	Stable Disease
SPD	Sum of Products of the Diameter
SRM	Study Reference Manual
STiL	Study Group Indolent Lymphomas
TEN	Toxic Epidermal Necrolysis
TLS	Tumor Lysis Syndrome
TMA	Tissue Microarray
TTF	Time to Treatment Failure
TTP	Time to Progression
ULN	Upper Limit of Normal
µmol	Micromole
USA	United States of America
USPI	United States Product Insert
WBC	White Blood Cell
V+BR	Venetoclax + Bendamustine Rituximab
WHO	World Health Organization
WM	Waldenstrom's Macroglobulinemia
WNL	Within Normal Limits
WOCBP	Women of Childbearing Potential

1. Introduction- Background and Rationale

1.1 Follicular Lymphoma (FL) – Disease Overview

It is estimated that approximately 71,850 individuals were diagnosed with non-Hodgkin's lymphoma (NHL) and over 19,000 men and women died of the disease in 2015. Follicular lymphoma (FL) is the most common low-grade lymphoma comprising 70% of low-grade NHL and 22% of all cases of NHL.[1] The survival rates for patients with indolent NHL remained unchanged from the 1950s through the early 1990s, but recent evidence suggests that outcomes continue to improve. High-risk patients with FL, defined as having advanced stage and high tumor burden have significantly shorter progression free survival despite significant advances.[2,3,4]

The hallmark of FL is abnormal co-expression of Bcl-2 protein by germinal center-type (CD10+ and/or Bcl-6+) B cells, which implies the presence of the anti-apoptotic driver t(14;18) IgH/Bcl-2 rearrangement. Up to 90% of FL express Bcl-2 by immunohistochemistry with standard antibodies, more commonly in grade 1-2 (85-90%) compared to grade 3A tumors (50%).[5] Absence of bcl-2 protein expression can be a consequence of mutations in the *BCL2* gene preventing antibody recognition of the protein; true absence of t(14;18) is uncommon.[6]

1.2 Treatment of High Risk Follicular Lymphoma

1.2.1 Current Standard Approach to Frontline Therapy

Bendamustine is an alkylating agent that contains a bifunctional mechlorethamine derivative, a benzimidazole heterocyclic ring, and a butyric acid substituent. Bendamustine received approval in the United States of America (USA) in 2008 by the Food and Drug Administration (FDA) for the first-line treatment of patients with chronic lymphocytic leukemia (CLL), and for the treatment of patients with advanced indolent B-cell NHL that progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

The pivotal, multicenter, randomized Phase 3 study, conducted by the Study Group Indolent Lymphomas, Germany (StiL), enrolled 549 patients with advanced indolent NHL or mantle cell lymphoma (MCL) to treatment with either bendamustine in combination with rituximab (BR) or standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in the first-line setting. The primary objective was to prove non-inferiority of the BR regimen compared with the R-CHOP regimen, defined as a difference of less than 10% in progression-free survival (PFS) after 3 years but with an improved safety profile. The overall response rate (ORR) was 92.7% for BR and 91.3% for R-CHOP; however, complete response (CR) rate was improved for BR (40%) compared with R-CHOP (31%). Among all patients, BR was associated with a superior PFS compared with R-CHOP (BR: 54.9 vs. R-CHOP: 34.8 months (median), Hazard Ratio (HR)=0.57 (95% Confidence Interval (CI): 0.43-0.76; p=0.00012) as was the time to next treatment (BR: not reached vs. R-CHOP: 37.5 months (median), HR=0.52 (95% CI: 0.38-0.70), p=0.00002). No differences in overall survival (OS) were noted.[7] In terms of toxicity, significant differences in hematologic toxicities were observed for neutropenia grade 3/4 occurring in 46.5% of patients receiving R-CHOP vs. 10.7% with BR (p<0.0001). Other toxicities that were significantly increased with R-CHOP compared with BR included: Alopecia (all vs. <2% patients, p<0.0001), paresthesia (73 vs. 18, <0.0001), stomatitis (47 vs. 16, <0.0001), infectious complications (127 vs. 96, p=0.0025), sepsis (8 vs. 1 patient, p=0.0190). The only side effects more frequent with BR compared with R-CHOP were skin/erythema (42 vs. 23 p=0.0122) and allergic reaction (skin) (40 vs. 15, p=0.0003). In this final analysis, the combination of BR improved PFS and CR rates, while showing a better tolerability profile. These results established BR as a standard first-line treatment for patients with high tumor burden FL.

1.2.2 Maintenance Therapy with Monoclonal Antibody

To improve the response rate, duration of response, and potentially prolong OS, additional doses of rituximab have been administered as post-remission or maintenance therapy.

A randomized open label study (PRIMA) was undertaken in 1217 patients with previously untreated FL needing systemic therapy and were assigned to one of the three induction arms containing immunochemotherapy. 1019 patients achieved a complete or partial response and were randomized to receive a 2-year maintenance treatment with rituximab or observation. In the intention to treat analysis, the PFS was 74.9% in the rituximab maintenance arm compared with 57.6% in the group that were observed at a median follow up of 36 months ($p<0.0001$).[8]

1.3 Overview of Obinutuzumab[9]

Obinutuzumab (GA101, RO5072759, Gazyva®, Gazyvaro®) is a humanized glycoengineered type II anti-CD20 monoclonal antibody. It is characterized by high-affinity binding to a CD20 epitope that is different from the epitope targeted by rituximab, which is currently the widely used anti-CD20 monoclonal antibody.[10,11] Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high-affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction. Nonclinical studies with obinutuzumab in comparison with rituximab show significantly greater ADCC and ADCP, increased direct cell-death induction, and low CDC. Superior efficacy to rituximab has been demonstrated in various human lymphoma xenograft models.[10,12]

1.3.1 Clinical Experience with Obinutuzumab in NHL

As of 2 July 2015, obinutuzumab has been administered to 2105 patients with NHL in 4 monotherapy studies and 6 combination therapy studies. The combination therapy studies include the following:

- Study BO21000 (GAUDI): A Phase Ib, open-label study of obinutuzumab in combination with CHOP (G-CHOP), fludarabine/cyclophosphamide (FC), or bendamustine in patients with CD20+ B-cell FL. A total of 137 patients were enrolled, including 56 with relapsed/refractory (R/R) disease (obinutuzumab + FC: n=28; obinutuzumab + CHOP: n=28) and 80 first-line patients (obinutuzumab + bendamustine: n=41; obinutuzumab + CHOP: n=40).
- Study GAO4915g (GATHER): A Phase II, open-label study of obinutuzumab + CHOP in previously untreated advanced Diffuse Large B-Cell Lymphoma (DLBCL). A total of 100 patients were enrolled.
- Study GAO4753g (GADOLIN): A Phase III study of obinutuzumab + bendamustine (G-benda) vs. bendamustine alone in patients with rituximab-refractory CD20+ indolent NHL (iNHL). A total of 194 patients were randomized to the G-benda arm and 202 to bendamustine arm.
- Study BO21223 (GALLIUM): A Phase III study of G-chemo vs. R-chemo in patients with advanced iNHL. Enrollment to the study has completed with 1401 enrolled patients; the study is ongoing.
- Study BO21005 (GOYA): A Phase III study of G-CHOP vs. R-CHOP in patients with previously untreated CD20+ DLBCL. Enrollment to the study has completed with 1418 enrolled patients; the study is ongoing.
- Study JO29737 (GATS): A Phase II, open-label study of obinutuzumab (shorter duration of infusion) in patients with CD20+ NHL. Enrollment is ongoing, with 14 patients enrolled (planned enrollment of 36).

Details regarding all obinutuzumab studies, including the obinutuzumab monotherapy studies in NHL and studies in other indications are provided in the Obinutuzumab Investigator's Brochure (IB).

1.3.2 Clinical Efficacy of Obinutuzumab in NHL

In the monotherapy setting (studies BO20999, BO21003, YP25623, and JO21900), the proportion of patients who had a response (CR or partial response [PR]) at the end of treatment ranged from 28% (11/40 patients) to 58% (7/12 patients). Although patients had treatment-refractory (including rituximab-refractory) or relapsed disease, some patients in studies BO20999, BO21003 (Phase II), and JO21900 achieved a CR by the end of treatment assessment.

In the chemotherapy combination studies BO21000 and GAO4915g, the proportion of patients achieving a response exceeded 90% among FL patients and was 82% among DLBCL patients. The CR rate was also higher (35%–50% of patients with FL and 55% of patients with DLBCL) than in the monotherapy studies.

Data from the pivotal chemotherapy combination Phase III study (GAO4753g) in patients with FL showed that treatment with G-benda for 6 cycles (28 days per cycle) followed by 2-year monotherapy with obinutuzumab resulted in a clinically meaningful and statistically significant increase in PFS compared with bendamustine alone. The median Independent Review Committee (IRC)-assessed PFS in the bendamustine arm was 13.8 months. Median IRC-assessed PFS was not reached in the G-benda arm (PFS HR=0.48, 95% CI: 0.34–0.68; stratified log-rank test p-value <0.0001). An analysis conducted with 24.1 months of median observation time revealed that the median OS was not yet reached in either arm.

1.3.3 Clinical Safety of Obinutuzumab

As of 2 July 2015 (the safety data cutoff date for all studies except MO28543), obinutuzumab has been administered to a total of 3386 patients, including 1281 patients with CLL and 2105 patients with NHL, from doses of 50 mg to 2000 mg in monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil (Clb). Overall, the safety of monotherapy obinutuzumab, or obinutuzumab combination therapy with CHOP, FC, bendamustine, or Clb, was manageable.

The most frequent causes of death were disease progression and adverse events (AEs) of infectious diseases. This is consistent with the study population and the disease being treated.

Of particular interest, infusion related reactions (IRRs) were observed consistently in all obinutuzumab trials. In patients with CLL (study BO21004), the highest incidence of IRR was at the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence of IRR observed with combination therapy (FC, CHOP, or bendamustine) appears similar to that observed with monotherapy.

Adverse events of special interest include IRRs, tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia), neutropenia (including late-onset and prolonged neutropenia), prolonged B-cell depletion, infections including progressive multifocal leukoencephalopathy (PML) and hepatitis B virus (HBV) reactivation, worsening of pre-existing cardiac conditions, gastrointestinal (GI) perforation, and second malignancies.

1.3.4 Risks Associated with Obinutuzumab

Please see Section 11.2.11 for Risks Associated with Obinutuzumab and the current IB for more information.

1.4 Venetoclax Background[13]

1.4.1 Structure and Mechanism of Action

Venetoclax (GDC-0199, ABT-199, A-1195425.0, or RO5537382) is a selective, orally bioavailable, small-molecule Bcl-2 family protein inhibitor. Overexpression of Bcl-2 has been demonstrated in various hematologic and solid tumor malignancies and has been implicated as a resistance factor for certain therapeutic agents. Venetoclax helps restore the process of

apoptosis by binding directly to the Bcl-2 protein, displacing pro-apoptotic proteins like Bcl-2-like protein 11 (commonly called BIM), and triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in a variety of B cell and other hematologic malignancies.[14,15]

1.4.2 Clinical Experience with Venetoclax in NHL

As of 28 November 2015, six Phase I/II studies with venetoclax are ongoing in NHL, including three monotherapy and three combination studies.

- Study M12-175 (Arm B): A Phase I, first-in-human, open-label, dose-escalation study of venetoclax in patients with R/R CLL (Arm A) and NHL (Arm B). A total of 106 patients with R/R NHL received at least 1 dose of venetoclax in Arm B. Of these patients, 70 patients were enrolled during the dose-escalation portion of the study.
- Study M13-834: A Phase I study of venetoclax in Japanese subjects with hematological malignancies. As of 28 November 2015, 11 patients with NHL have received at least 1 dose of venetoclax and had available safety data in Arm A.
- Study M13-835: An extension study of venetoclax in patients with advanced NHL. As of 28 November 2015, 11 patients have been rolled over from Study M13-364 (drug-drug interaction study of ketoconazole) and had available safety data.
- Study M12-630: A Phase I study of venetoclax + bendamustine/rituximab (BR) in in patients with R/R NHL. A total of 58 patients received at least 1 dose of venetoclax and had available data.
- Study GO27878/CAVALLI: A Phase Ib/II study of venetoclax + R-CHOP or venetoclax + G-CHOP in patients with B-cell NHL and DLBCL. As of 28 November 2015, 54 patients have been enrolled (Section 1.5.2.1).
- Study BO29337 (CONTRALTO): A Phase II study of venetoclax + BR, BR alone, or venetoclax + R in patients with R/R follicular NHL. As of 28 November 2015, 103 patients have safety data available, including 9 patients in the run-in phase, 52 patients in Arm A (venetoclax + R), 21 patients in Arm B (venetoclax + BR), and 21 patients in Arm C (BR).

Details regarding all venetoclax studies, including the venetoclax monotherapy studies in NHL and studies in other indications are provided in the Venetoclax IB.

1.4.3 Clinical Efficacy of Venetoclax in NHL

As of 15 September 2015, efficacy data for Arm B of Study M12-175 are available for a total of 106 patients with R/R NHL enrolled in Arm B (70 in the dose-escalation cohorts and 36 in the safety expansion cohort). Patients were evaluated for objective response following the International Working Group criteria (patients with Waldenstrom's macroglobulinemia [WM] were evaluated using the International Workshop [IWWM] criteria). The investigator-assessed ORR for all FL patients and DLBCL patients, excluding DLBCL-Richter's transformation patients (across dose escalation and safety expansion), was 37.9% and 17.6%, respectively; CR was achieved by 4 patients in each group (13.8% and 11.8%, respectively).

Preliminary efficacy data are available for 48 patients with R/R NHL for Study M12-630 as of 17 September 2015. Median time on study was 5.3 months (range: 0.1 to 38.1 months). The ORR was 67.4% (31 of 48 evaluable patients), with CR in 13 patients (28.3%) and PR in 18 patients (39.1%). Three additional patients (6.5%) experienced stable disease (SD).

1.4.4 Clinical Safety Summary for Combination Studies M12-630 and BO29337

Safety data are available for 58 patients in Study M12-630 and 108 patients in Study BO29337. An overview of adverse events reported in these two venetoclax combination NHL studies is provided below. See the current Venetoclax IB for additional safety information.

Most patients receiving venetoclax in combination with BR in Study M12-630 (57/58, 98.3%) reported at least 1 adverse event. The most common adverse events were nausea (63.8%), neutropenia (55.2%), and diarrhea (50.0%). In this study, 46 patients (79.3%) had Grade ≥ 3 adverse events, 21 patients (36.2%) had serious adverse events, 9 patients (15.5%) had adverse events leading to discontinuation of study drug, and 4 patients (6.9%) had fatal adverse events (2 events of malignant neoplasm progression and 1 event each of disease progression and respiratory failure). None of the fatal events were considered to be related to venetoclax.

Most patients in Study BO29337 (90/108, 83.3%) reported at least 1 adverse event. The most common adverse events were nausea (28.7%), diarrhea (26.9%), and neutropenia (21.3%). The types of adverse events were similar across cohorts; however, patients in Arm C (BR) experienced fewer adverse events than patients in Arm A or Arm B. Grade ≥ 3 adverse events were reported in 45 patients (41.7%). Serious adverse events were reported in 18 patients (16.7%), including 3 patients in the run-in phase, 12 patients in Arm A, and 3 patients in Arm B (but no patients in Arm C). Serious adverse events occurring in 2 patients each were blood lactate dehydrogenase increased and TLS. All other events occurred in 1 patient each. Six patients (5.6%) experienced adverse events that led to study drug discontinuation. Nausea occurred in 2 patients each; all other events occurred in 1 patient each. Fatal events were reported in 2 patients in Arm A: 1 event of pulmonary hemorrhage and 1 event of colitis. Neither of the fatal events was considered related to venetoclax.

1.4.5 Overall Safety Summary for Venetoclax in NHL

As of 28 November 2015, a total of 346 patients with NHL have been treated in the venetoclax oncology clinical program: 131 patients received venetoclax as a single agent and 215 patients received venetoclax in combination with other agents, including rituximab, obinutuzumab, and bendamustine; R-CHOP; or G-CHOP.

Overall, most patients with NHL experience at least one adverse event when treated with venetoclax as a single agent or in combination with other therapies, with the most common events being nausea or diarrhea; whereas neutropenia and IRRs commonly occur in combination studies. Approximately half of patients in NHL clinical trials experienced Grade ≥ 3 adverse events, with most common being neutropenia, anemia, and thrombocytopenia. The frequency of thrombocytopenia and anemia are slightly higher in NHL combination trials; however, the numbers are small.

The incidence of TLS in NHL studies is low, with reported 2 cases (1.9%) of TLS in monotherapy Study M12-175 (Arm B), 3 cases of TLS (2.8%) in combination Study BO29337 (venetoclax + BR), and 3 cases of TLS (6.1%) in combination Study GO27878 (venetoclax + R-CHOP or G-CHOP). TLS remains an important identified risk for the NHL program.

Neutropenia has a similar frequency in the NHL clinical program as in the CLL population, with higher frequency in NHL combination studies. Serious adverse events of neutropenia and febrile neutropenia, although relatively rare, occurred with higher frequency in the combination studies and remain important identified risks. Infections, including serious infections, were observed in the NHL clinical program, with similar incidence in monotherapy and combination studies. There were no deaths due to infections in the NHL program. Infection remains a potential risk for the NHL clinical program.

1.4.6 Risks Associated with Venetoclax

See Section 11.1.8 for Risks Associated with Venetoclax and the current IB for more information.

1.5 Nonclinical Studies of Venetoclax and Obinutuzumab in Combination

Nonclinical pharmacology and pharmacokinetics, and product metabolism studies have been conducted with the combination of venetoclax and obinutuzumab. [redacted] When combined at optimal doses,

an additive effect of the two drugs was observed. [redacted] For details regarding nonclinical studies for each individual agent, refer to current version of the IB.

1.5.1 Clinical Studies of Venetoclax and Obinutuzumab

The combination of venetoclax and obinutuzumab is being evaluated in three clinical studies:

- Study GP28331: A Phase Ib study of venetoclax + obinutuzumab in patients with relapsed/refractory (R/R) CLL or previously untreated CLL
- Study BO25323 (CLL14): A Phase III randomized study of venetoclax + obinutuzumab vs. obinutuzumab + chlorambucil in patients with previously untreated CLL with coexisting medical conditions
- Study GO27878/CAVALLI: A Phase Ib/II, study of venetoclax + rituximab (R) or obinutuzumab (G) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with B-cell NHL and DLBCL

As of 28 November 2015, 51 patients with R/R CLL or previously untreated CLL have been treated in Study GP28331, 110 patients (both arms) with previously untreated CLL have been treated in Study BO25323, and 46 patients with untreated or R/R B-cell NHL (Phase I) and 8 patients with previously untreated DLBCL (Phase II) have been treated in Study GO27878/CAVALLI.

Data from Study GO27878/CAVALLI in patients with NHL are summarized below. Details regarding Study GP28331 and Study BO25323 in patients with CLL are provided in the Venetoclax and Obinutuzumab IBs.

1.5.2 Clinical Studies with Venetoclax and Obinutuzumab in Combination in NHL

1.5.2.1 Study GO27878 (CAVALLI)

Study GO27878 is a Phase Ib/II, open-label study evaluating the safety and pharmacokinetics of venetoclax in combination with rituximab (R) or obinutuzumab (G) plus CHOP in patients with B-cell NHL and DLBCL.

In the dose-finding Phase I portion of the study, two parallel treatment arms of up to 4 cohorts each explored venetoclax at doses ranging from 200 to 800 mg in combination with R-CHOP and G-CHOP. The maximum tolerated dose was not reached in Phase I, and a recommended Phase II dose of 800 mg for Arm A is being used in Phase II. Patients are treated for a total of 8 cycles (6 to 8 cycles of CHOP and 8 cycles of venetoclax + R or venetoclax + G). Each cycle is 21 days.

In order to mitigate the risk for TLS, CHOP was initiated before venetoclax and all patients receive TLS prophylaxis before the first dose of venetoclax, with those at higher risk of TLS hospitalized for the initial dose.

The planned enrollment for the study is 24–48 patients in Phase I and 180–200 patients in Phase II. As of 28 November 2015, 46 and 8 patients have been enrolled in the Phase I and Phase II portions of the study, respectively.

Two patients in Arm A experienced dose-limiting toxicity (DLT); one case of DLT occurred at the 200 mg dose in Cohort 1 (Grade 3 neutropenia) and the other case of DLT occurred at the 600 mg dose in Cohort 3 (Grade 4 TLS). For the latter case of DLT, the severity Grade of 4 was assigned by the investigator although the patient had laboratory abnormalities only, was not symptomatic, and had stable cardiac and renal function and vital signs. Three patients in Arm B experienced DLT; 2 cases of DLTs occurred at the 200 mg dose in Cohort 1 (Grade 3

pneumonia and Grade 3 infection). The third case of DLT occurred at the 600 mg dose in Cohort 3 (Grade 4 sepsis).

Preliminary Safety Summary:

As of 28 November 2015, 54 subjects have been enrolled in Study GO27878 and 49 subjects had available data. Most subjects (95.9%) across all cohorts in Study GO27878 experienced at least 1 treatment-emergent adverse event. The most common adverse events across cohorts in Study GO27878 were nausea (44.9%), diarrhea (38.8%), fatigue and neutropenia (36.7%), constipation (34.7%), vomiting (28.6%), and thrombocytopenia (26.5%). Serious adverse events have been reported for 26 patients (53.1%) in the study. The most common serious adverse event was febrile neutropenia in 10 patients (20.4%). Eleven patients (22.4%) experienced adverse events that led to withdrawal from any treatment. The most common events leading to study drug discontinuation were thrombocytopenia and peripheral neuropathy in 2 patients each; all other events leading to study drug discontinuation occurred in 1 patient each. No events resulted in death.

One case of drug-induced liver injury (Preferred Term) was reported in Study GO27878. Patient [redacted] had a slight elevation in liver function test (2x upper limit of normal [ULN]) on Cycle 3, Day 7. On Cycle 4, Day 1, liver function tests were 7 to 8x ULN with normal bilirubin. Venetoclax and other NHL treatments were discontinued because of this event. All viral studies were normal; however, the patient was taking concomitant [redacted] for [redacted]. A liver biopsy demonstrated relatively nonspecific features consistent with drug-induced hepatitis. [redacted] liver function tests continued to be abnormal during the subsequent 8 months following discontinuation of all cancer treatments. [redacted] was then discontinued, and [redacted] liver function tests as of [redacted] remained mildly elevated. The investigator considered this event to be related to venetoclax, G, and CHOP. In the investigator's opinion, other etiological factors for the event included concomitant medication.

1.6 Rationale for the Dosing, Study Design and Treatment Plan

1.6.1 Dosing Regimen Rationale

Bendamustine is an alkylating agent indicated for the treatment of FL. Dosing is based on the approved package insert.

Obinutuzumab dosing regimen is based on the dosing regimen currently being used in Phase III clinical trials.

Information from the ongoing Venetoclax development program in NHL has suggested that an intermittent administration of Venetoclax, when combined with chemotherapy, is better tolerated than continuous dosing. This has been demonstrated in trials M12-630 (Ven + BR, NCT01594229) and CAVALLI (Ven + R-CHOP, NCT02055820).

Venetoclax dosing is based on the CAVALLI (Section 1.5.2.1) and the M12-630 and CONTRALTO clinical trials (see below). The M12-630 trial included dosing up to 1200 mg. No maximum tolerated dose has been reached.

1.6.1.1 M12-630 and CONTRALTO Trial Overview

A phase 1 dose escalation trial (M12-630) combined Venetoclax with Bendamustine (90 mg/m^2) and Rituximab (375 mg/m^2) in patients with FL, DLBCL and MCL. Venetoclax doses were escalated from 50 mg (intermittent) to 1200 mg (continuous daily). No dose limiting toxicities have been identified.

In the 800 mg cohort (n=5) the following grade 3/4 AEs were noted: neutropenia (2), lymphocyte count decrease (1), leukopenia (1), anemia (1). One SAE (respiratory failure) occurred.

Thus, combination therapy with venetoclax and BR (V + BR) demonstrated a tolerable safety profile. A protocol amendment was implemented after cohort 5 to strongly encourage granulocyte-colony stimulating factor (G-CSF) prophylaxis during venetoclax administration, particularly in heavily pretreated patients.

The combination of venetoclax, bendamustine and rituximab and in patients with R/R follicular lymphoma is currently explored in a Phase Ib/2 study (Study BO29337, CONTRALTO). The recommended phase 2 dose of venetoclax is 800 mg given once daily continuously, in combination with bendamustine 90 mg/m^2 given on days 1 and 2 and Rituximab 375 mg/m^2 (V+BR) given on day 1.

In the randomized portion of that trial, per data cut Sept 27, 2016, 49 patients were evaluable for safety in the treatment arm (V+BR) and 50 in the control arm (BR). Three deaths occurred, 1 due to pneumonia in the V+BR arm and 1 each due to PD and hypoxia in the BR arm. In the V+BR arm laboratory tumor lysis syndrome was seen in 3 patients and was manageable. In the V+BR arm 16 pts (33%) discontinued at least one drug to adverse events. In the control arm one patient stopped BR due to an AE.[16]

Most frequent AEs (all grades) were neutropenia (73%), nausea (65%), thrombocytopenia (59%) and diarrhea (49%) in the V+BR arm and nausea (44%), neutropenia (38%), constipation (34%) and fatigue (28%) in the BR arm.

Grade 3/4 AEs occurring in more than 10% of patients were neutropenia (61% with V+BR, 30% with BR), thrombocytopenia (45%, 6%), anemia (14%, 2%) and febrile neutropenia (12%, 6%).

Based on the higher rate of grade 3/4 AEs and the more frequent drug discontinuations in V+BR compared to BR in the CONTRALTO Trial, a pulsatile administration of venetoclax given for 14 days per 28 day cycle is planned and is expected to improve the safety profile of V+BR. A similar approach has been followed in DLBCL, where venetoclax was given in combination with R-CHOP for 10 days per 21 day cycle, resulting in a promising CR rate including for patients with double-expressor DLBCL.[17]

1.6.2 Study Design and Treatment Plan

Bendamustine plus rituximab induction followed by rituximab maintenance therapy has been the most commonly used frontline approach for FL in the United States for several years. Genentech has sponsored an international study (GALLIUM trial) comparing R-chemotherapy (bendamustine most commonly used chemotherapy) with rituximab maintenance therapy to obinutuzumab-chemotherapy followed by obinutuzumab maintenance therapy. A press release in May of 2016 indicates the trial met its primary endpoint and shows superiority for the obinutuzumab-chemotherapy arm. This trial is highly likely to define a new standard of care in FL of obinutuzumab-bendamustine followed by obinutuzumab maintenance. The question now is can those outcomes be further improved? Given the central role of BCL2 overexpression in the biology of FL, targeting BCL2 with the addition of venetoclax to the new standard therapy (bendamustine-obinutuzumab) is logical.

Our hypothesis is that enhanced induction therapy and/or improved continuation treatment (post-induction) will improve CR rates and PFS for patients with high tumor burden low-grade lymphoma. Furthermore, these new novel therapeutic combinations will be safe and well tolerated among this patient population. Since venetoclax has not previously been combined with obinutuzumab and bendamustine in the front line setting, there will be a formal, detailed toxicity evaluation after 21 patients complete 3 cycles of treatment (including patients that come off treatment for any reason). Toxicity evaluation after 21 patients completed 3 cycles of treatment was reviewed on March 28, 2019, see Section 12.1.1 for details. Enrollment will not stop for safety analysis.

Our hypothesis will be tested in a single-arm phase II clinical trial with venetoclax, obinutuzumab and bendamustine induction followed by obinutuzumab continuation in patients achieving a CR. In patients achieving a PR or SD after induction therapy, both venetoclax and obinutuzumab will be continued.

NOTE: We observed a high incidence of tumor lysis syndrome (TLS) among the cases currently enrolled and treated with this agent combination. Currently, it is not clear if the TLS events are attributable to venetoclax therapy. The study and its treatment combination (including treatment dates, relevant labs, criteria that was met for TLS definition, clinical course and management of TLS event, patients' baseline disease stage) regarding the TLS events that have happened to date have been reviewed.

An updated definition of TLS (see Appendix IV), distinguishing between laboratory and clinical TLS event, is being implemented in this updated protocol. To mitigate the risk of clinical and/or of laboratory TLS, venetoclax will be withheld from cycle 1 and will be initiated in cycle 2, day 1 for all patients. Also, laboratory assessment will be conducted and reviewed for potential TLS events on day 2, day 8 and day 15 (if required) of cycle 1 and also on day 2 of cycle 2.

The synergistic effect of chemoimmunotherapy and venetoclax will be maintained through cycle 2-6.

On January 9, 2020 enrollment was suspended due to a report of an unexpected event of Grade 5 Cytomegalovirus (CMV) related Encephalitis infection probably related to the combination of the study drug regimen (venetoclax, obinutuzumab, and bendamustine). There have been no other adverse event reports to date for CMV and/or Encephalitis infection for this study.

As a safety measure, monitoring for CMV will now be performed. In addition, all patients will be initiated on Pneumocystis Jiroveci Pneumonia (PJP) and antiviral prophylaxis.

1.6.3 Maintenance Therapy Suspension as of 9/16/2021

Due to a recent Grade 5 event of myocarditis in a patient on maintenance therapy, the study investigators are concerned about atypical infections that have been seen after induction therapy on study. There have been four events of atypical infections as listed below:

- Treatment related death due to cytomegalovirus encephalitis as well as *Pneumocystis jiroveci* Pneumonia (PJP) occurring after cycle 6 of induction but before maintenance therapy.
- BK virus nephropathy leading to end stage renal disease and chronic hemodialysis in a patient following 6 doses of maintenance obinutuzumab.
- Respiratory syncytial virus pneumonia 30 days after cycle 6 of induction and later, after 2 cycles of maintenance obinutuzumab, developed PJP.
- The recent fatal myocarditis which is suspected, but not proven, to be viral in etiology.

Given these adverse events we are suspending any additional maintenance therapy for those patients on study. These patients will not receive any further treatment and move on to the two year survival follow-up portion of the study. All study-required follow-up activities remain unchanged.

Patients with follicular lymphoma are not thought to be cured with initial therapy and several other treatments are available. Maintenance therapy has never been shown to improve overall survival in follicular lymphoma, only progression free survival and thus, we feel comfortable stopping maintenance therapy at this time.

There are currently 7 patients on maintenance therapy. The site investigators with patients were contacted via e-mail and agree with the recommendation to stop additional maintenance therapy. Several patients have already been taken off of study during maintenance due to the COVID-19 pandemic and either developing COVID-19 or having cytopenias related to maintenance therapy.

The PrECOG Data Safety and Monitoring Board has also reviewed and agree with the recommendation to stop additional maintenance therapy.

2. Study Objectives

2.1 Primary Objective

To estimate the proportion of patients achieving a complete remission (CR) at the end of induction with the combination of venetoclax, obinutuzumab and bendamustine.

2.2 Secondary Objectives

- To determine the ORR of patients treated.
- To determine the proportion of patients who achieve a PR with induction therapy and later convert to CR with maintenance therapy.
- To evaluate PFS and OS in the intent to treat (ITT) population.
- To evaluate the compliance and toxicities of patients receiving induction and maintenance therapy.

2.3 Exploratory Objectives

- To compare Bcl-2 protein expression by immunohistochemistry (IHC) in pretreatment biopsies with response, PFS, and OS.
- To assess Bcl-2 family expression by mRNA expression including ratios of Bcl-2/BIM, Bcl-2/Mcl-1 and others with response, PFS and OS.
- To compare *BCL2* rearrangement status by fluorescence in situ hybridization (FISH) in pretreatment biopsies and correlate with response, PFS, and OS.
- To compare Mcl-1 and Bcl-X_L protein expression by IHC in pretreatment biopsies with response, PFS, and OS.
- To compare histologic features of pretreatment biopsies with response, PFS, and OS.

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: All questions regarding eligibility should be directed to the Medical Monitor or Study Site 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 Patient must have a histologically confirmed (biopsy-proven) diagnosis of follicular B-cell non-Hodgkin lymphoma (WHO classification: follicular center grades 1, 2, and 3a [3b patients are not eligible]), with no evidence of transformation to large cell histology.

Date of Diagnosis: _____ WHO Classification Grade: _____

_____ 3.2 Patient must meet criteria for High Tumor Burden (higher risk) as defined by **either** the Groupe D'Etude des Lymphomes Follicularies (GELF) criteria **OR** the follicular lymphoma international prognostic index (FLIPI):

- To meet GELF criteria, a patient must have at least one criterion (please answer yes or no for each criterion):

Nodal or extranodal mass >7 cm Record largest/longest single nodal/extranodal mass diameter: _____	☐ Yes ☐ No
At least 3 nodal masses: all >3.0 cm in diameter	☐ Yes ☐ No
Systemic symptoms due to lymphoma or B symptoms	☐ Yes ☐ No
Splenomegaly with spleen >16 cm by CT scan	☐ Yes ☐ No
Evidence of compression syndrome (e.g., ureteral, orbital, gastrointestinal) or pleural or peritoneal serous effusion due to lymphoma (irrespective of cell content).	☐ Yes ☐ No
Leukemic presentation (>5.0 x 10^9/L malignant circulating follicular cells)	☐ Yes ☐ No
Cytopenias (polymorphonuclear leukocytes <1.0 x 10^9/L, hemoglobin <10 gm/dL, and/or platelets <100 x 10^9/L)	☐ Yes ☐ No

- **FLIPI criteria:** a patient must have a score of 3, 4, or 5 (per FLIPI-1, one point each for below criterion; please answer yes or no for each criterion):

Age >60 years	☐ Yes ☐ No
Ann Arbor stage III-IV	☐ Yes ☐ No
Hemoglobin level <12 mg/dL	☐ Yes ☐ No
>4 nodal areas	☐ Yes ☐ No
Serum LDH level above normal	☐ Yes ☐ No
FLIPI Score: Please circle 3 4 5	

_____ 3.3 Patient must have Stage II, III or IV disease (Appendix I: Modified Ann Arbor Staging).

☐ Stage II OR ☐ Stage III OR ☐ Stage IV

_____ 3.4 Baseline measurements and evaluations (PET/CT) must be obtained within 10 weeks of randomization to the study. Patient must have at least one objective measurable disease parameter. Measurable disease in the liver is required if the liver is the only site of lymphoma. Please see Section 9.1 for definition of measurable disease.

_____ 3.5 Age ≥ 18 years.

_____ 3.6 ECOG performance status of 0-2 (Appendix II).

Performance Status: Please circle 0 1 2 Date: _____

_____ 3.7 Ability to understand and willingness to sign IRB-approved informed consent.

_____ 3.8 Willing to provide mandatory tissue samples (if sufficient tissue available) for research purposes (Section 13).

_____ 3.9 Adequate organ function as measured by the following criteria:

- Absolute Neutrophil Count (ANC) ≥ 1000/mm^3

  ANC: _____ Date of Test: _____

- Hemoglobin ≥ 8 g/dL

  Hemoglobin: _____ Date of Test: _____

- Platelets >75,000/mm^3

  Platelets: _____ Date of Test: _____

  NOTE: Patients with documented marrow involvement (with lymphoma) or hypersplenism secondary to involvement of the spleen by lymphoma at the time of randomization are not required to meet the above hematologic parameters.

- Creatinine clearance ≥ 50 mL/min, calculated with the use of 24-hour creatinine clearance or by Cockcroft-Gault formula (Appendix III).

  Creatinine: _____ ULN: _____ Date of Test: _____

- Total Bilirubin ≤ 1.5x 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: _____

- Alkaline Phosphatase <5x ULN

  Alkaline Phosphatase: _____ ULN: _____ Date of Test: _____

_____ 3.10 All females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a blood or urine 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: _____

_____ 3.11 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 18 months for females and 6 months for males 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.

_____ 3.12 Patient must have had no prior chemotherapy, radiotherapy or immunotherapy for lymphoma. For purposes of this trial, prednisone or other corticosteroids used for non-lymphomatous conditions will not be considered as prior chemotherapy. In addition, a prior/recent short course (<2 weeks) of steroids for symptom relief of lymphoma-related symptoms will not make a patient ineligible.

_____ 3.13 Patient must have no recent history of malignancy except for adequately treated basal cell or squamous cell skin cancer, Stage I melanoma of the skin, or in situ cervical cancer. Individuals in documented remission without treatment for ≥ 1 year prior to enrollment may be included at the discretion of the investigator.

_____ 3.14 Patient must have no active, uncontrolled infections.

_____ 3.15 Patients must be tested for hepatitis B virus (HBV), hepatitis B surface antigen (HBsAg+) and hepatitis C (HCV) antibody within 6 weeks of registration. Patients who are chronic carriers of HBV with positive HBsAg+ and positive HCV serology are excluded, as chemotherapy and B-cell depleting therapy have been associated with virus reactivation and fulminant hepatitis.

Hepatitis B: Results: _____ Date of Test: _____

Hepatitis C: Results: _____ Date of Test: _____

NOTE: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) may be included if HBV DNA is undetectable. If enrolled, patients must be willing to undergo monthly HBV DNA testing.

Patients with positive HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.

_____ 3.16 HIV positive patients are not excluded, but to enroll, must meet all of the below criteria:

- HIV is sensitive to antiretroviral therapy.
- Must be willing to take effective antiretroviral therapy if indicated.
- No history of CD4 prior to or at the time of lymphoma diagnosis <300 cells/mm^3.
- No history of AIDS-defining conditions.
- If on antiretroviral therapy, must not be taking zidovudine or stavudine.
- Must be willing to take prophylaxis for Pneumocystis jiroveci pneumonia (PCP) during therapy and until at least 2 months following the completion of therapy or until the CD4 cells recover to over 250 cells/mm^3, whichever occurs later.

_____ 3.17 Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient.

_____ 3.18 No major surgery within 2 weeks prior to cycle 1, other than for diagnosis.

_____ 3.19 A condition that precludes oral route of administration (venetoclax).

_____ 3.20 No known allergies to both xanthine oxidase inhibitors and rasburicase.

_____ 3.21 Patient must not require the use of warfarin (because of potential drug-drug interactions that may potentially increase the exposure of warfarin). Blood thinners of other classes are permitted.

_____3.22 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
- Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax.

NOTE: Please refer to Section 6.3.2 and Appendix VI "Additional Excluded and Cautionary Medications" for further information.

_____3.23 Patient must not have serious medical or psychiatric illness likely to interfere with participation in this clinical study.

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 enter 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. No patients will begin protocol therapy without formal registration as per the process below.

4.3 Patient Registration

Patients must not start protocol treatment prior to registration.

Patients must meet all of the eligibility requirements listed in Section 3 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. Confirmation of registration will be displayed in the 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 Mandatory Research Tissue Samples (if sufficient tissue available)

Pre-treatment, diagnostic pathology specimens 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. **Optional:** Any tumor biopsy samples during treatment or post-treatment will be requested and leftover tissue (pre-treatment, during treatment or post-treatment) banked for future research.

Time points for tissue 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 lab manual.

5. Treatment Plan

5.1 Overview

Eligible patients will receive induction therapy with obinutuzumab and bendamustine for cycle 1-6 with the addition of venetoclax for cycle 2-6. There will be a formal, detailed toxicity evaluation after 21 patients complete 3 cycles of treatment (including patients that come off treatment for any reason). Toxicity evaluation after 21 patients completed 3 cycles of treatment was reviewed on March 28, 2019, see Section 12.1.1 for details.

Patients with progressive disease will not continue on the maintenance arm. Patients who achieve a CR will receive obinutuzumab every 2 months for a total of 12 cycles. Patients who achieve partial response or stable disease will receive therapy with obinutuzumab (12 cycles) and venetoclax (24 cycles).

Table 5-1: Induction Phase

Cycle	Agent	Dose	Route	Day(s)	Cycle Length
Cycle 1-6	Obinutuzumab	100 mg 900 mg 1000 mg 1000 mg	IV	1 (Cycle 1) 2 (Cycle 1) 8, 15 (Cycle 1) 1 (starting Cycle 2)	28 days
Cycle 1-6	Bendamustine	90 mg/m^2	IV	Days 1,2	28 days
Cycle 2-6	Venetoclax	800 mg	Oral	Days 1-10	28 days

All doses are based on actual body weight. In general +/- 3 day window for therapy/tests/visits during therapy except as noted for TLS monitoring. Alterations due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

Prophylactic filgrastim, pegfilgrastim or pegfilgrastim on body injector (OBI) will be administered in all patients.

Pneumocystis Jiroveci Pneumonia (PJP) and antiviral prophylaxis will be initiated in all patients (Section 5.1.2).

Section 5.1.3 for Monitoring of Cytomegalovirus (CMV).

Premedication: Acetaminophen (650 or 1000 mg orally) and diphenhydramine (25 or 50 mg oral or intravenous) is to be administered prior to starting each infusion of obinutuzumab or per institutional guidelines. In addition, cycle 1, days 1 and 2 should receive dexamethasone (20 mg) or methylprednisolone (80 mg) prior to obinutuzumab or per institutional guidelines. Since transient hypotension may occur during obinutuzumab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to obinutuzumab infusion.

Antiemetic Therapy: Standard anti-emetic therapy may be given to patients prior to administration of each chemotherapy cycle per institutional guidelines: 5-HT3 serotonin receptor antagonists (e.g., ondansetron 8-16 mg) +/- steroids (e.g., dexamethasone) are recommended.

5.1.1 Tumor Lysis Prophylaxis

TLS is a risk for patients with NHL who are treated with high cell-killing agents. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of treatment. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Patient characteristics that may suggest an increased risk of TLS include, but are not limited to, the following:

- Any lymph mass $\geq$ 10 cm on the screening imaging
- ALC >25 x 10^9/L

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Creatinine clearance <60 mL/min
- Extensive bone marrow involvement/skeletal involvement
- Dehydration

TLS Considerations:

- Allopurinol (300 mg daily or bid [twice a day]) 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 24-48 hours prior to cycle 1, day 1 and continue through cycle 1, day 10 or per treating physician discretion.
- Additional IV fluids are allowed per treating physician discretion.
- Patients should be encouraged to consume oral hydration of 1.5-2 L/day beginning 48 hours prior to treatment and to continue for 24 hours post treatment.
- Rasburicase is allowed per institutional guidelines.
- Chemistry and hematology will be obtained and reviewed by a health care provider:
    - Cycle 1
        - Day 1 approximately 6 hours after treatment initiation
        - Day 2 prior to initiating day 2 treatment
        - Day 8 prior to initiating day 8 treatment
        - Day 15 prior to initiating day 15 treatment, only if day 8 labs indicate continued testing is needed
    - Cycle 2
        - Day 1 approximately 6 hours after treatment initiation
        - Day 2 prior to initiating day 2 treatment
- Additional monitoring for TLS is allowed per treating physician discretion.

If clinically significant TLS is identified during treatment, manage patients according to institutional guidelines. Refer to Appendix IV for "Definitions of Tumor Lysis Syndrome"[18].

5.1.2 Infection Prophylaxis

All patients must be initiated on prophylaxis for Pneumocystis Jiroveci Pneumonia (PJP) within 2 weeks of initiating therapy with bendamustine and obinutuzumab. Trimethoprim-sulfamethoxazole (Bactrim) is the preferred treatment of choice for PJP prophylaxis. PJP prophylaxis should continue until first restaging visit after completion of induction. 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 simple 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.

5.1.3 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.

Maintenance Phase: Quantitative PCR will be checked once every 2 months.

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 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.

5.2 Induction Administration Schedule

Venetoclax (cycle 2-6) must be administered before obinutuzumab and/or bendamustine. Obinutuzumab and bendamustine may be given in any order (venetoclax, obinutuzumab, bendamustine or venetoclax, bendamustine, obinutuzumab). One cycle=28 days.

5.2.1 Obinutuzumab

Cycle 1-6: Obinutuzumab 100 mg will be administered on cycle 1, day 1. The remaining 900 mg is to be administered on cycle 1, day 2. A fixed dose of 1000 mg is to be administered on cycle 1, day 8 and 15, and on day 1 of cycles 2-6. For rate of infusion see Table 5-2 on next page and for management of infusion reactions please refer to Section 6.1.2.1 and Section 11.2.6.1. Obinutuzumab must be given after venetoclax but may be given before or after bendamustine.

Table 5-2: Obinutuzumab Rate of Infusion			
Cycle and Day of Administration		**Dose of Obinutuzumab**	**Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)**
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	

5.2.2 Bendamustine

Cycle 1-6: Bendamustine 90 mg/m^2 will be administered to patients by IV infusion on days 1, 2 of each 28 day cycle. The infusions are administered over a 15-30 minute period or per institutional guidelines. Bendamustine must be given after venetoclax but may be given before or after obinutuzumab.

5.2.3 Venetoclax

Cycle 2-6: Venetoclax 800 mg will be dispensed on day 1 of each 28 day cycle. On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. A pill diary will be given to document compliance (Appendix V).

Venetoclax will be taken once daily on days 1-10 and should be administered with a meal. 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. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose.

Patient compliance in taking the assigned daily dose of venetoclax will be assessed by standard pill counts. Bottles containing venetoclax tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

5.2.4 Restaging and Length of Therapy

Repeat cycles every 28 days for a total of six cycles. Patients may be evaluated more frequently if needed at physician discretion.

Patients will be restaged after 3 cycles of therapy. Patients who are in at least stable disease (SD, PR or CR) after 3 cycles will receive 3 additional cycles. Patients who have improved response or no interval change in their tumor measurements with restaging between cycles 3 and 6 will proceed to the maintenance phase. Patients who achieve a complete remission following six cycles of therapy, will receive therapy with obinutuzumab and patients who are declared to be in a partial remission or stable disease following six cycles of therapy, based on PET/CT imaging, will receive therapy with venetoclax and obinutuzumab during maintenance. Patients with progressive disease will discontinue study protocol.

Table 5-3: Patients with Complete Response				
Agent	**Dose**	**Route**	**Day**	**Cycle Length**
Obinutuzumab	1000 mg	IV	1	Every 2 months x 12 cycles

Table 5-4: Patients with Partial Response or Stable Disease				
Agent	**Dose**	**Route**	**Day**	**Cycle Length**
Venetoclax	800 mg	Oral	1-28	Every month x 24 cycles
Obinutuzumab	1000 mg	IV	1	Every 2 months x 12 cycles

The first dose of maintenance obinutuzumab should be given 8-12 weeks after completion of cycle 6, day 28 of induction therapy. Patients who do not start maintenance therapy by week 12 will be removed from study.

For patients with partial response or stable disease, a 28 day supply of venetoclax will be dispensed. Therefore, for patients receiving both venetoclax and obinutuzumab, patients will be seen every 28 days. If venetoclax was dose reduced to 400 mg during the induction phase, the same dose of 400 mg will continue during the maintenance phase for the 28 day cycle. (Patients on both venetoclax and obinutuzumab who convert to CR, will remain on both venetoclax and obinutuzumab for a total of 24 cycles and 12 cycles, respectively.)

Section 5.1.3 for Monitoring of Cytomegalovirus (CMV).

Premedication: Acetaminophen (650 or 1000 mg orally) and diphenhydramine (25 or 50 mg oral or intravenous) is to be administered prior to starting each infusion of obinutuzumab or per institutional guidelines. Since transient hypotension may occur during obinutuzumab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to obinutuzumab infusion.

5.3 Maintenance Administration Schedule

The following are to be administered during the maintenance phase.

Obinutuzumab: A fixed dose of 1000 mg is to be administered on day 1 every 2 months for a total of 12 cycles. Management of infusion reactions please refer to Section 6.1.2.1 and Section 11.2.6.1.

Venetoclax: Venetoclax 800 mg will be dispensed on day 1 every 28 days and taken once daily on days 1-28. A pill dairy will be given to document compliance (Appendix V). Venetoclax will only be administered for patients with a partial response or stable disease. On days when venetoclax is given with obinutuzumab, venetoclax should be given first. (Patients on both venetoclax and obinutuzumab who convert to CR, will remain on both venetoclax and obinutuzumab for a total of 24 and 12 cycles, respectively.)

NOTE: If venetoclax was dose reduced during the induction phase, the same dose reduction will continue during the maintenance phase for the 28 day cycle.

5.3.1 Maintenance Therapy Suspension as of 9/16/2021

Due to a recent Grade 5 event of myocarditis in a patient on maintenance therapy, the study investigators are concerned about atypical infections that have been seen after induction therapy on study. There have been four other events of atypical infections (Section 1.6.3 for details).

Given these adverse events we are suspending any additional maintenance therapy for those patients on study. These patients will not receive any further treatment and move on to the two year survival follow-up portion of the study. All study-required follow-up activities remain unchanged.

There are currently 7 patients on maintenance therapy. The site investigators with patients were contacted via e-mail and agree with the recommendation to stop additional maintenance therapy. Several patients have already been taken off of study during maintenance due to the COVID-19 pandemic and either developing COVID-19 or having cytopenias related to maintenance therapy.

6. Dose Modification

6.1 Dose Modifications & Toxicity Management – Induction Phase

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).

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

If administration of venetoclax, obinutuzumab or bendamustine 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 obinutuzumab should also be delayed so that they are given together beginning on Day 1 of the same cycle.

NOTE: If any of the study drugs are permanently discontinued (i.e., Grade 4 IRR with obinutuzumab), the patient will be removed from study.

6.1.1 Venetoclax

6.1.1.1 Hematologic Toxicities for Venetoclax, Obinutuzumab and Bendamustine during Induction

Table 6-1: Venetoclax, Obinutuzumab, and Bendamustine Dose Delay or Modifications for Hematologic Toxicity (G-CSF will be administered in all patients)

- **G-CSF will be used in all patients starting with cycle 1 of treatment and will be continued unless contraindicated.**
- **If a cycle is delayed by >28 days then patients will discontinue further treatment on protocol.**
- **Table 6-3 for Venetoclax Dose Reductions and Table 6-4 for Bendamustine Dose Reductions.**

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Cycle 2 Day 1 with or without infection or fever [a] **OR** First episode	• Delay doses of all study treatment by 7 days (+/-4 days) • If ANC recovers to ≥ 1000/mm^3 by Day 7 of the scheduled date for the next cycle, proceed with the previous dose levels • If ANC recovers to ≥ 1000/mm^3 on or after Day 8 of the scheduled date for the next cycle, change the dose of venetoclax to dose level -1. Bendamustine and obinutuzumab will be restarted at full dose. • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax. Decisions must be made in consultation with and with approval of PrECOG.
Recurrent Grade 3 or 4 neutropenia on Cycle 3 onwards	• Delay doses of all study treatment by 7 days (+/-4 days) • If ANC recovers to ≥ 1000/ mm^3 by Day 7 of the scheduled date for the next cycle, and the previous venetoclax dose change has been made (Dose Level -1) then, continue with bendamustine at 90 mg/m^2 (days 1,2). Obinutuzumab will be restarted at full dose. • If ANC is <1000/mm^3 on or after Day 7, postpone therapy by 7 days (+/-4 days) of the scheduled date for the next cycle and the previous venetoclax dose change was made (Dose Level -1), change the dose of venetoclax to dose level -2 and decrease bendamustine to 70 mg/m^2. Obinutuzumab will be restarted at full dose. • If recurrent grade 3 or 4 neutropenia requiring dose delays of >7 days with venetoclax dosing at Dose Level -2 and decreased bendamustine dose, patient will discontinue study treatment.
Recurrent Grade 4 neutropenia on Cycle Day 1	• If patient develops persistent Grade 4 neutropenia requiring dose delay despite growth factor support and following venetoclax dosing schedule changes and bendamustine dose reduction, and treatment is delayed by 28 days discontinue all study treatment permanently.

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia or cytopenias without infection or fever (between cycles)	• Continue dosing with venetoclax. Venetoclax need not be held if cytopenias are documented in between cycles.
Grade 3 or 4 neutropenia with infection	• Hold all study treatments until infection resolves following adequate treatment with antibiotics.
Grade 3 or 4 thrombocytopenia on Cycle Day 1[a] **OR** First Episode	• Delay doses of all study treatment. • If platelet count recovers to ≥ 75,000/mm^3 by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to ≥ 75,000/mm^3 on or after Day 8 of the scheduled date for the next cycle, change the dose of venetoclax to dose level -1. Bendamustine and obinutuzumab will be restarted at full dose. • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax.
Recurrent Grade 3 or 4 thrombocytopenia	• Delay doses of all study treatment. • If platelet count recovers to ≥ 75,000/mm^3 by Day 7 of the scheduled date for the next cycle, and the previous venetoclax dose change has been made (Dose Level -1) then, continue with bendamustine 90 mg/m^2 (days 1,2). Obinutuzumab will be restarted at full dose. • If platelet count recovers to ≥ 75,000/mm^3 on or after Day 8, postpone therapy by 7 days (+/-4 days) of the scheduled date for the next cycle and the previous venetoclax dose change has been made (Dose Level -1), change the dose of venetoclax to dose level -2 and decrease bendamustine to 70 mg/m^2. Obinutuzumab will be restarted at full dose. • If recurrent grade 3 or 4 thrombocytopenia requiring dose delays of >7 days with venetoclax dosing at Dose Level -2 and decreased bendamustine dose, the patient will discontinue study treatment.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.

[a] All based on laboratory results obtained within 72 hours prior to infusion of Day 1 of that cycle.

6.1.1.2 Non-Hematologic Toxicities for Venetoclax, Obinutuzumab and Bendamustine during Induction

Table 6-2: Venetoclax, Obinutuzumab and Bendamustine: Dose Delays and Modifications for Non-Hematologic Toxicity

Event(s)	Dose Delay or Modification
Grade 3 or 4 TLS (first episode and subsequent episodes)	• Refer to Appendix IV for "Definitions of Tumor Lysis Syndrome"[18]. • Hold all study treatments until TLS resolves. Resume treatment once TLS resolves. Missed doses may be administered to complete the intended treatment for that cycle. • Following complete resolution of TLS, if venetoclax was held for 14 days or less, venetoclax may be restarted at the same dose or changed to dose level -1 as determined by the investigator based on a risk assessment (including tumor burden status) in conjunction with prophylactic hydration and uricosuric agent; hospitalization for restarting the venetoclax dose may be considered at the discretion of the investigator. Dose escalation to the standard venetoclax should be considered in the following cycle. Obinutuzumab will be restarted at full dose and bendamustine will be resumed at the previous dose (dose before the delay) for the next infusion. • If clinically significant TLS is identified, manage patients according to institutional guidelines.
Grade 3 or 4 treatment-related non-hematologic toxicity not specifically described above (excludes alopecia)	• Delay attributable treatment until resolution for a maximum of 28 days. • First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax, obinutuzumab and bendamustine. • Missed doses of venetoclax will NOT be made up. • For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart attributable treatment with appropriate dose reduction. Venetoclax at dose level -1 (or dose level -2, if patient already at dose level -1) and/or bendamustine at 70 mg/m^2 (Table 6-3 and Table 6-4). Obinutuzumab will be restarted at full dose.
Grade 2 treatment-related non-hematologic toxicity except nausea/vomiting (see below) (excludes alopecia and fatigue)	• Delay treatment with venetoclax, obinutuzumab and bendamustine until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. After resolution, resume the full dose of venetoclax or dose before the delay. Obinutuzumab will be restarted at full dose and bendamustine will be resumed at the previous dose (dose before the delay) for the next infusion. • **NOTE:** Bendamustine should not be used in patients with AST or ALT ≥ 3.0x ULN and total bilirubin ≥ 1.5x ULN.
Grade 2 treatment-related nausea and vomiting despite antiemetic treatment	• Delay attributable treatment for a maximum of 28 days. • First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax, obinutuzumab and bendamustine. • For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart attributable treatment with appropriate dose reduction. Venetoclax at dose level -1 (or dose level -2, if patient already at dose level -1) and/or bendamustine at 70 mg/m^2 (Table 6-3 and Table 6-4). Obinutuzumab will be restarted at full dose.

TLS=Tumor Lysis Syndrome

Refer to Section 6.2 for Dose Modifications & Toxicity Management- Maintenance Phase.

6.1.1.3 Induction Phase Venetoclax Dose Reductions

Table 6-3: Induction Phase Venetoclax Dose Modifications	
Starting Dose Level	800 mg days 1-10
Dose Level -1	800 mg days 1-5
Dose Level -2	400 mg days 1-5

Patients who cannot tolerate dose level -2 dosing will be discontinued from study treatment.

6.1.2 Obinutuzumab

Dose delays as a result of adverse events should proceed on the basis of the principle of maintaining the dose intensity of immunochemotherapy. The determination of all schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment. There will be no dose reductions for obinutuzumab.

Please refer to Table 6-1: Venetoclax, Obinutuzumab, and Bendamustine Dose Delay or Modifications for Hematologic Toxicity and Table 6-2: Venetoclax, Obinutuzumab and Bendamustine: Dose Modifications for Non-Hematologic Toxicity. Refer to Section 6.2 for Dose Modifications & Toxicity Management- Maintenance Phase. In addition, refer to below for other adverse events and dose delays for obinutuzumab.

6.1.2.1 Infusion Related Toxicities

If a patient experiences an infusion-related reaction (IRR) of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any further infusion-reaction symptoms, the infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose per institutional guidelines. Permanently discontinue treatment if a patient experiences a Grade 3 infusion-related symptom at re-challenge.
- Grade 1–2 (mild to moderate): Reduce the infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion-reaction symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose per institutional guidelines.

Section 11.2.6.1 premedication requirements for patients who experience IRRs.

6.1.2.2 Hepatitis B Virus Reactivation

Patients who are both HBsAg negative and hepatitis B core antibody (anti-HBc) positive may be included in studies with obinutuzumab. These patients should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV DNA assay becomes positive and is above the World Health Organization's (WHO) cutoff of 100 IU/mL, treatment with immunochemotherapy should be held and the patient should be treated (for at least 1 year after the last dose of obinutuzumab) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume immunochemotherapy once HBV DNA levels decrease to undetectable levels.

If the HBV DNA assay becomes positive and is ≤ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, treatment with immunochemotherapy must be held and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of obinutuzumab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume immunochemotherapy once the HBV DNA levels decrease to undetectable levels.

If a patients HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, treatment with immunochemotherapy must be permanently discontinued.

If prophylactic antiviral medications for hepatitis B reactivation is the standard of care, patients may be treated prophylactically.

6.1.3 Bendamustine

Guidelines and dose modifications for bendamustine are below. Dose modifications will be made according to Table 6-1 Venetoclax, Obinutuzumab, and Bendamustine Dose Delay or Modifications for Hematologic Toxicity and Table 6-2: Venetoclax, Obinutuzumab and Bendamustine: Dose Modifications for Non-Hematologic Toxicity.

6.1.3.1 Hematologic and Non-Hematologic Toxicity

At the start of each cycle, ANC must be at least 1000/mm^3 and platelet count must be at least 75,000/mm^3 to proceed with treatment (unless the patient has documented marrow involvement with lymphoma suppressing blood counts). Granulocyte-colony stimulating factor (G-CSF) support is required.

NOTE: Bendamustine should not be used in patients with AST or ALT ≥ 3.0x ULN and total bilirubin ≥ 1.5x ULN.

Table 6-4: Bendamustine Dose Modification

Bendamustine Starting Dose	Bendamustine Dose Reduction (Dose Level -1)
90 mg/m^2	Reduce dose to 70 mg/m^2

Patients will be removed from study treatment if they require a dose reduction of bendamustine below 70 mg/m^2.

6.2 Dose Modifications & Toxicity Management – Maintenance Phase

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).

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

6.2.1 Obinutuzumab Maintenance for Patients Achieving a Complete Remission

Table 6-5: Obinutuzumab Dose Modification

Event	Dose Delay or Modification
Grade 3 or 4 Neutropenia	• First Episode: Delay treatment by minimum of 7 days for a maximum of 28 days. GCSF support may be offered per investigator discretion. If ANC recovers to Grade 2 or less, resume maintenance with obinutuzumab. • If ANC does not improve to Grade 2 or less, discontinue maintenance therapy with obinutuzumab. • For subsequent episodes: Discontinue maintenance with obinutuzumab.
*Hypogammaglobulinemia (asymptomatic)	• IgG <300mg/dl, discontinue obinutuzumab maintenance.
*Hypogammaglobulinemia (symptomatic) Defined as 2 or more ≥ grade 2 infections in a six month period after obinutuzumab treatment in the absence of neutropenia.	• IgG <500mg/dl, discontinue obinutuzumab maintenance, and consider IVIG replacement therapy.
Grade 3 or 4 infections with or without neutropenia	• Discontinue obinutuzumab maintenance.

6.2.2 Venetoclax and Obinutuzumab Maintenance for Patients Achieving a Partial Response or Stable Disease

Table 6-6: Venetoclax and Obinutuzumab Dose Modification

Event	Dose Delay or Modifications
Grade 3 or 4 Neutropenia	• First Episode: Delay treatment by minimum of 7 days for a maximum of 28 days. GCSF support may be offered per investigator discretion. If ANC recovers to Grade 2 or less, resume maintenance with venetoclax and obinutuzumab. • If ANC does not improve to Grade 2 or less, discontinue maintenance therapy. • For subsequent episodes: Discontinue maintenance therapy.
*Hypogammaglobulinemia (asymptomatic)	• IgG <300mg/dl, discontinue obinutuzumab maintenance. Continue venetoclax.
*Hypogammaglobulinemia (symptomatic) Defined as 2 or more ≥ grade 2 infections in a six month period after obinutuzumab treatment in the absence of neutropenia.	• IgG <500mg/dl, discontinue obinutuzumab maintenance, replace with monthly (IVIG 400 mg/kg) until IgG improves to >500-550mg/dl). Further therapy based on investigator discretion. Continue venetoclax.
Grade 3 or 4 infections with or without neutropenia	• Discontinue maintenance therapy.
Grade 2 or higher nausea/vomiting	• Reduce venetoclax to 400 mg daily. If 400 mg not tolerated, discontinue venetoclax.

*Hypogammaglobulinemia are not graded in the CTCAE Version 5.0. The current recommendations are modified from the American Academy of Allergy, Asthma and Immunology guidelines.

6.3 Concurrent Therapies

6.3.1 Permitted

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Effective contraception is required while receiving obinutuzumab. For women, effective contraception is required to continue for ≥ 18 months after the last dose of obinutuzumab. For men, effective contraception is required to continue for ≥ 6 months after the last dose of obinutuzumab.

Systemic steroid therapy other than the prednisone component of chemotherapy regimens will not be allowed during study treatment with the exception of inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease, infusions of steroids prior to obinutuzumab infusions or for IRRs, topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency.

For infusion related reactions and anaphylaxis, medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

6.3.2 Not Permitted

The use of live viral vaccines is contraindicated. Responses to inactivated vaccines, recombinant vaccines, and cell-wall vaccines are unreliable and suboptimal in NHL patients.

Receipt of live viral vaccines within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment.

Use of the following therapies are prohibited during the study:

- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of lymphoma whether FDA approved or experimental (outside of this study)

Use of the following concomitant medications is prohibited from 7 days prior to initiation of drug treatment and during the study:

- Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma or chronic obstructive pulmonary disease, prior to obinutuzumab infusions or for IRRs, topical steroids, or replacement/stress corticosteroids
- Warfarin or warfarin derivatives (Factor Xa is allowed)
- Co-administration with strong and moderate CYP3A inhibitors is not recommended. Consider alternative medications if necessary. If subject requires the use of these medications, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. If subject requires use of strong or moderate CYP3A inducers, use with caution and contact PrECOG for guidance. Co-administration with the use of weak CYP3A inducers and weak CYP3A4 inhibitors should be undertaken with caution.
- Avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.

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 inhibitors such as amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor
- P-gp substrates such as digoxin, everolimus, and sirolimus due to inhibition potential at therapeutic dose levels
- 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.

See Appendix VI “Additional Excluded and Cautionary Medications” for additional information.

6.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

7. Study Duration and Discontinuation of Therapy

7.1 Study Duration

Patients will receive protocol therapy unless:

1. Disease progression per Lymphoma Response Criteria (Cheson Criteria) guidelines or clinical progression.
2. Toxicities considered unacceptable by either the patient or the investigator, despite optimal supportive care and dose modifications.
3. Development of an inter-current illness that prevents further administration of study treatment.
4. Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
5. Patient withdraws consent or is unable to comply with study procedures.

7.2 Duration of Follow-Up

Adverse events will be captured for 30 days after the last dose of study medication. Patients will be followed every 6 months for up to 2 years from treatment discontinuation or study closure. Initiation of first anti-cancer therapy will also 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.

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

NOTE: Further maintenance therapy was suspended on 9/16/2021. Follow-up will continue as noted above.

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

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

Any patient who receives at least one dose of study drug (venetoclax, obinutuzumab, and/or bendamustine) 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 (venetoclax, obinutuzumab, and/or bendamustine), only AEs/SAEs caused by a protocol-mandated intervention 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 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 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 venetoclax, obinutuzumab, bendamustine, disease, etc.

AEs related to venetoclax, obinutuzumab, and/or bendamustine 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 Definition of 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.

Obinutuzumab and Venetoclax Combination Therapy Events of Special Interest:

- 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.

  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 drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prior 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 contamination of the study drug is suspected.

Venetoclax Events of Special Interest:

- Refer to Appendix IV "Definitions for Tumor Lysis Syndrome"[18]

Obinutuzumab Events of Special Interest:

- All Tumour Lysis Syndrome (irrespective of seriousness, causality or severity)
  - Refer to Appendix IV "Definitions for Tumor Lysis Syndrome"[18]
- Second Malignancies

Selected events (events for which additional data collection or analyses will be performed; no special case handling or follow-up is required) include the following:

- IRRs
- Infections (including PML)
- Neutropenia (including late-onset neutropenia, defined as neutrophil count <1000 cells/mm^3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia, defined as neutrophil count <1000 cells/mm^3, that does not resolve after 28 days (without obinutuzumab treatment)
- Thrombocytopenia (including acute thrombocytopenia occurring during and within 24 hours post obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events (cardiomyopathy, arrhythmias, myocardial infarction, etc.)
- Second malignancies (any malignancy other than basal cell carcinoma of skin, squamous cell carcinoma of skin, carcinoma -in -situ of the cervix)
- Gastrointestinal (GI) perforation

8.3 Special Situation Reports

8.3.1 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 8.4 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 Handling of Serious Adverse Events (SAEs)

8.4.1 SAE Definitions

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.

8.5 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 PrE0403SAE@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
[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 venetoclax, obinutuzumab, and/or bendamustine, 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 and obinutuzumab originating from the Study will be collected and reported to PrECOG on a PrE0403 Product Complaint Reporting Form even in the absence of an AE (if product complaint is an SAE, the PrE0403 SAE form will also be completed). PrECOG will transmit product complaints to Genentech for venetoclax and obinutuzumab within fifteen (15) calendar days. Product complaints for bendamustine 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 18 months for a female patient or 6 months for the female partner of a male patient 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.

8.9 Reporting Guidelines in the Case of Overdose

In the event of an overdose with any of the study drugs (venetoclax, obinutuzumab and/or bendamustine), defined as any dose higher than the patient allocated dose in the study, this should be captured as an adverse event. Both symptomatic and non-symptomatic overdose must be reported. For any accidental or intentional overdose with the study treatment that is symptomatic, **even if not fulfilling a seriousness criterion**, a SAE form should also be completed and reported to PrECOG within 24 hours of the investigator's knowledge of the overdose.

9. Measurement of Effect

Lymphoma Response Criteria (Cheson Criteria)

NOTE: These criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma.[19]

9.1 Lymphoma Response Cheson Criteria

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1 cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

9.1.1 Complete Response

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

For lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

If the pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (<1.5 cm in their greatest transverse diameter for nodes >1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and >1.0 cm in their short axis prior to treatment must have decreased to <1 cm in their short axis after treatment.

The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of >20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by IHC. A sample that is negative by IHC but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

9.1.2 Partial Response

The designation of PR requires all of the following:

A >50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

No increase in the size of other nodes, liver or spleen.

Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small cleaved cell lymphoma. No new sites of disease.

9.1.3 Stable Disease

Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease.

Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.

For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

9.1.4 Progression Disease/Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes <1 x <1 cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by >50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

Lesions should be PET positive if the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

9.2 Response

9.2.1 Duration of Response

This is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

9.2.2 Survival

Survival is defined as the date of study entry to the date of death.

9.2.3 Progression-Free Survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS is often considered the preferable endpoint in lymphoma clinical trials, especially those involving incurable histologic subtypes (e.g., follicular and low grade, MCL). PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed or the first date of unscheduled new anti-lymphoma treatment.

9.2.4 Time to Progression

Time to progression (TTP) is defined as the time from study entry until lymphoma progression or death due to lymphoma. In TTP, deaths from other causes are censored either at the time of death or at an earlier time of assessment, representing a random pattern of loss from the study. TTP is not as useful as PFS unless the majority of deaths on a study are unrelated to the lymphoma due to the efficacy of the treatment and/or prolonged follow-up.

9.2.5 Time to Treatment Failure

Time to treatment failure [TTF] (event-free survival [EFS]) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death. This composite endpoint is generally not encouraged by regulatory agencies because it combines efficacy, toxicity and patient withdrawal.

9.2.6 Disease-Free Survival

Disease-free survival is measured from the time of occurrence of disease-free state (e.g., the adjuvant setting following surgery or radiation therapy or attainment of a complete remission) to disease recurrence or death from lymphoma or acute toxicity of treatment. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the

lymphoma and there is controversy as to whether such deaths should be considered as events or censored at the time of occurrence. Whereas it is often possible to identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

9.2.7 Disease-Specific Survival

Disease-specific survival (e.g., lymphoma-specific survival, cause-specific survival) is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death from lymphoma, or from toxicity from the drug. Death from unknown causes should be attributed to the drug. For certain trials, time to next lymphoma treatment may be of interest, defined as time from the end of primary treatment until the initiation of the next therapy.

10. Study Parameters

1. All pre-study scans and bone marrow biopsy should be done ≤ 10 weeks prior to registration.
2. All other pre-study assessments should be done ≤ 4 weeks prior to registration, unless otherwise noted.

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycles 2-6*		Every 3 Cycles (every 12 weeks)	Maintenance[19]*	Follow-Up[20]
		Day 1	Day 2	Day 8	Day 15	Day 21 Break	Day 1	Day 2			
Written Informed Consent	X										
Documentation of GELF, FLIPI and FLIP2 criteria[1]	X										
Medical/Surgical History	X										
Assessment of Baseline Signs & Symptoms	X										
Height in cm	X										
Physical Exam	X	X		X	X		X			X	
Weight in kg	X	X					X			X	
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X		X	X		X			X	
Body Surface Area (BSA)	X	X					X			X	
Performance Status	X	X					X			X	
CBC/Differential/Platelets[2]	X	X	X	X	X		X			X	
Chemistry[3]	X	X		X			X			X	
Hepatitis B & C Testing[4]	X										
Beta-2 Microglobulin	X										
Immunoglobulin (IgG)[5]	X								X[5]	X[5]	

Procedures	Screening	Cycle 1* (1 cycle=28 Days)					Cycles 2-6*		Every 3 Cycles (every 12 weeks)	Maintenance[19]*	Follow-Up[20]
		Day 1	Day 2	Day 8	Day 15	Day 21 Break	Day 1	Day 2			
Serum or Urine Pregnancy Test[6]	X										
CMV Monitoring[7]	X						X			X	
Tumor Lysis Labs[8]		X	X	X	X[8]		X[8]	X[8]			
PET CT[9]	X								X[10]	X[11]	
Chest, Abdomen, and Pelvic CT[9]									X	X[11]	
Bone Marrow Biopsy	X								X[12]		
Archived Tissue Procurement (Mandatory)[13]	X						X[14]			X[14]	X[14]
Induction Treatment Administration[15]		X	X	X	X		X	X			
Maintenance Treatment Administration[16]										X[16]	
PJP & Antiviral Prophylaxis[17]		X	X	X	X	X	X	X			
Concomitant Medication Review	X	X	X	X	X		X	X		X	
Adverse Events Assessment		X	X	X	X		X	X		X[18]	
Survival Status											X

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

1 Record the GELF, FLIPI-1 (Appendix VII) and FLIPI-2 criteria (Appendix VIII).

2 CBC with differential and platelet count which includes WBC, ANC, Platelets, Hgb, and Hct. Required prior to each dose of chemotherapy (days 1, 2, 8 and 15 of cycle 1 and day 1 of cycle 2 and subsequent cycles), and results known prior to treatment administration.

3 Albumin, BUN/creatinine, uric acid, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, LDH and total protein.

4 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) may be included if HBV DNA is undetectable. If enrolled, patients must be willing to undergo monthly HBV DNA testing. Patients with positive HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.

5 Obtain quantitative immunoglobulins at end of induction and every 6 months during maintenance therapy.

6 Required for females of childbearing potential within 2 weeks of registration.

7 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 5.1.3: Monitoring for Cytomegalovirus (CMV) for additional monitoring parameters and guidelines.

Induction: Once a month.

Maintenance: Once every 2 months.

8 Labs for tumor lysis monitoring include uric acid, calcium, albumin, phosphorus, potassium, and serum creatinine. Information on prophylaxis for TLS and definitions for tumor lysis syndrome refer to Section 5.1.1 and Appendix IV.

- **Cycle 1**
  - Day 1 approximately 6 hours after treatment initiation
  - Day 2 prior to initiating day 2 treatment
  - Day 8 prior to initiating day 8 treatment
  - Day 15 prior to initiating day 15 treatment, only if day 8 labs indicate continued testing is needed
- **Cycle 2**
  - Day 1 approximately 6 hours after treatment initiation
  - Day 2 prior to initiating day 2 treatment

9 PET/CTs are the preferred imaging modality. Notably however, once a patient enters complete remission, then only CT's (chest/abdomen/pelvis) should be obtained (not both PET/CT and dedicated CTs) except as noted in footnote #9 below. MRI exams of the chest/abdomen/pelvis may be performed, if CTs of the chest/abdomen/pelvis cannot be obtained.

10 PET/CT to be obtained after cycle 6 (not required after cycle 3). CT of the chest/abdomen/pelvis will suffice at interim restaging i.e., after cycle 3.

11 Performed every 6 months or as per standard of care.

12 Performed after cycle 6. Bone marrow biopsy at the end of induction treatment needs to be obtained only if it was positive prior to initiation of therapy.

13 Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory): Formalin-Fixed Paraffin-Embedded (FFPE) blocks and 7-10 FFPE slides or if blocks are not available, up to 25 FFPE slides plus H&E slide (if tissue is limited, then minimum of 13 slides) will be required. Procurement of tissue will be mandatory for enrollment (submission of tissue is not required prior to registration), but 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).

14 **Optional:** Any tumor biopsy samples obtained during treatment or post-treatment (Formalin-Fixed Paraffin-Embedded (FFPE) blocks or up to 15 FFPE slides plus H&E slide) will be requested for research and any leftover tissue (pre-treatment, during treatment or post-treatment) will be banked for future research. See Section 13.1 for details.

15 **Cycle 1-6:** Patients will receive obinutuzumab by IV infusion on Cycle 1, days 1, 2, 8, and 15 of 28 day cycle and Cycles 2-6 on day 1 of each 28 day cycle (1 cycle=28 days).

Cycle 1-6: Bendamustine will be administered on days 1, 2 of each cycle.

Cycle 2-6: Venetoclax will be administered orally as continuous dosing days 1-10 of each 28 day cycle. On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first.

See Section 5 for dosing instructions and Section 6 for dose delays/modifications.

16 The maintenance phase will start no earlier than 8 weeks and no later than 12 weeks following completion of cycle 6, day 28 of induction therapy (patients who do not start maintenance therapy by week 12 will be removed from study). During the maintenance phase, patients who are in a complete remission will receive obinutuzumab every 2 months for a total of 12 cycles. Patients who are in a PR or stable disease will receive venetoclax and obinutuzumab for a total of 24 cycles and 12 cycles, respectively. Patients who receive venetoclax (orally as continuous dosing days 1-28) and obinutuzumab (obinutuzumab will be given every 8 weeks) will be seen every month (to dispense venetoclax). On days when venetoclax is given with additional anti-lymphoma agents, venetoclax should be given first. (Patients on both venetoclax and obinutuzumab who convert to CR, will remain on both venetoclax and obinutuzumab for a total of 24 cycles and 12 cycles respectively.)

NOTE: If venetoclax was dose reduced during the induction phase, the same dose reduction will continue during the maintenance phase for the 28 day cycle.

****Further maintenance therapy was suspended on 9/16/2021. Refer to Section 1.6.3 for details. Follow-up will continue as noted in footnote 20.**

17 All patients must be initiated on prophylaxis within 2 weeks of initiating therapy with bendamustine and obinutuzumab.

PJP Prophylaxis: Trimethoprim-sulfamethoxazole (Bactrim) for PJP prophylaxis and should continue until patients first restaging visit, after completion of induction. 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 5.1.2: Infection Prophylaxis for additional parameters and guidelines.

18 Adverse events will be captured for 30 days after their last dose of study medication.

19 Patients who receive obinutuzumab only will be seen every 2 months with indicated exams/testing performed. Patients who receive obinutuzumab and venetoclax will be seen every month with indicated exams/testing performed.

20 Every 6 months for up to 2 years from treatment discontinuation or until study closure. 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.

11. Drug Formulation and Procurement

11.1 Venetoclax[13]

For complete information, please refer to the current IB.

11.1.1 Other Names

GDC-0199, ABT-199, RO5537382.

11.1.2 Storage and Stability

Venetoclax will be supplied in bottles with 100 mg tablets. 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).

11.1.3 Dose Specifics

The recommended venetoclax dose for NHL is 800 mg daily orally. Venetoclax is dispensed in a 4-week supply. Patients will take eight tablets (800 mg) daily on days 1-10 for each 28 day cycle during Induction and days 1-28 during Maintenance. Tablets should not be chewed, crushed or broken.

On days when venetoclax is given with obinutuzumab and bendamustine, 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. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose.

Refer to Section 6.1 and Table 6-1, Table 6-2 and Table 6-3 for Dose Delays and Modifications details during Induction. Refer to Section 6.2 for Dose Modifications & Toxicity Management-Maintenance Phase.

11.1.4 Drug Interactions

Drug-drug interactions may occur with venetoclax. Co-administration of venetoclax with CYP3A4 inhibitors and strong inducers is prohibited. Co-administration with moderate/weak CYP3A4 inducers, CYP2C8 substrates, and CYP2C9 substrates should be undertaken with caution. See Section 6.3.2 and Appendix VI: Additional Excluded and Cautionary Medications for a list of medications that are to be excluded or used with caution in patients receiving venetoclax.

11.1.5 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.

11.1.6 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.

11.1.7 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.

11.1.8 Risks Associated with Venetoclax

11.1.8.1 Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing chemistry abnormalities prior to initiation of treatment.

Refer to Section 5.1.1 for "Tumor Lysis Prophylaxis" guidelines and Appendix IV for "Definitions of Tumor Lysis Syndrome"[18].

11.1.8.2 Neutropenia

Neutropenia is an important identified risk for venetoclax, specifically in CLL. Clinical data from oncology studies suggest the neutropenia AEs 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. SAEs of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program.

11.1.8.3 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 2016] for oncology subjects).

Serious infections, including cytomegalovirus (CMV) reactivations, have been reported in patients treated with venetoclax in combination with other agents, including obinutuzumab.

11.1.8.4 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. The dataset in non-CLL indications is small.

11.1.8.5 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. The dataset in non-CLL indications is small.

11.1.8.6 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 carinii* pneumonia infections.

11.1.8.7 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.

11.1.8.8 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 R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies should be closely monitored.

11.1.8.9 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.

11.1.8.10 Drug-Drug Interaction

Co-administration of venetoclax with inhibitors or strong inducers of CYP3A4 are not recommended. Co-administration with moderate/weak CYP3A4 inducers, CYP2C8 substrates, and CYP2C9 substrates should be undertaken with caution (Section 6.3.2 and Appendix VI: Additional Excluded and Cautionary Medications).

11.1.9 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 Obinutuzumab[9]

For complete information, please refer to the current IB.

11.2.1 Other Names

Gazyva™; GA101; RO5072759.

11.2.2 Formulation

Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 40 mL pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188.

11.2.3 Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2–20 mg/mL have been demonstrated for 24 hours at 2°C–8°C and an additional 24 hours at ambient temperature and ambient room lighting. The prepared diluted product should generally be used immediately per institutional standards. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in line filter because of potential adsorption.

11.2.4 Preparation

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.

One vial may be used to prepare both the 100 mg dose (equals 4 mL) and 900 mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900 mg bag for a maximum of 24 hours at 2°C–8°C. After allowing the diluted bag to come to room temperature, use immediately per institutional standards.

To prepare a 100 mg dose: The final drug concentration of a 100 mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250 mL infusion bag containing 0.9% NaCl, withdraw and discard 4 mL of the sodium chloride. Withdraw 4 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 900 mg dose: The final drug concentration of a 900 mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250 mL infusion bag containing 0.9% NaCl, withdraw and discard 36 mL of the sodium chloride. Withdraw 36 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1000 mg dose: The final drug concentration of a 1000 mg dose should be 4 mg/mL. Using a 250 mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the NaCl. Withdraw 40 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or peripherally inserted central catheter line is acceptable.

Do not use obinutuzumab beyond the expiration date stamped on the carton.

11.2.5 Dosage and Administration

Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):

- On Cycle 1, Day 1, 100 mg obinutuzumab will be administered
- On Cycle 1, Day 2, 900 mg of obinutuzumab will be administered
- On Cycle 1, Days 8 and 15, 1000 mg of obinutuzumab will be administered.
- On Cycles 2–6, Day 1, 1000 mg of obinutuzumab will be administered.
- Maintenance: Every 2 months x 12 cycles, 1000 mg of obinutuzumab will be administered.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 30 minutes from the end of infusion; if no AEs occur after 30 minutes, the IV line may be removed. During the maintenance phase, the IV access may be removed at the end of the infusion if no adverse events occurred during the infusion.

11.2.6 Premedication Requirements

11.2.6.1 Infusion Related Reactions

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below or per institutional guidelines:

- Cycle 1, Days 1 and 2, all patients require pre-medication with:
  - IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
  - An oral acetaminophen (650-1000 mg) and an antihistamine such as diphenhydramine (25-50 mg) administered before starting each obinutuzumab infusion.
- Cycle 1, Days 8 and 15; Cycles 2-6, Day 1; and Maintenance:
  - An oral acetaminophen (650-1000 mg) and an antihistamine such as diphenhydramine (25-50 mg) administered before starting each obinutuzumab infusion.
  - Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

11.2.6.2 Hypotension

Hypotension may be expected to occur during obinutuzumab infusions. Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.

11.2.7 Obinutuzumab Dosing

The first 1000 mg of obinutuzumab will be administered over 2 days. During Cycle 1, Day 1, 100 mg will be administered. On the following day (Cycle 1, Day 2), 900 mg will be administered (Table 11-1).

Table 11-1: Obinutuzumab Rate of Infusion			
Cycle and Day of Administration		**Dose of Obinutuzumab**	**Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)**
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

NOTE: Rates above are listed in mg/hr. Please remember to take into consideration the final concentration of the prepared dose if the rate will be converted into mL/hour for the infusion pump.

If a patient experiences any grade infusion reaction during infusion, adjust the infusion as below:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any further infusion-reaction symptoms, the infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose per institutional guidelines. Permanently discontinue treatment if a patient experiences a Grade 3 infusion-related symptom at re-challenge.
- Grade 1–2 (mild to moderate): Reduce the infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion-reaction symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose per institutional guidelines.

Refer to Section 6.1 and Table 6-1 and Table 6-2 for Dose Delays and Modifications details during Induction. Refer to Section 6.2 for Dose Modifications & Toxicity Management- Maintenance Phase.

11.2.8 Availability

Obinutuzumab will be supplied by Genentech.

The initial supply of obinutuzumab will be sent directly to the site upon site activation. As needed, obinutuzumab 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 obinutuzumab.

11.2.9 Agent Ordering

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

11.2.10 Agent Accountability

Obinutuzumab 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.

11.2.11 Risks Associated with Obinutuzumab

Important risks identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), prolonged B-cell depletion, infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions and GI perforation.

Please refer to the current IB for additional information.

11.2.11.1 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Screen all patients for HBV infection before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring, and consider HBV antiviral therapy.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving obinutuzumab, immediately discontinue obinutuzumab and any concomitant chemotherapy, and institute appropriate treatment. Resumption of obinutuzumab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming obinutuzumab in patients who develop HBV reactivation.

11.2.11.2 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to pre-existing neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

11.2.11.3 Infusion-Related Reactions

Obinutuzumab can cause severe and life-threatening IRRs; 65% of patients with CLL experienced a reaction to the first 1000 mg infused of obinutuzumab, and 38% of iNHL patients experienced a reaction on Day 1 of obinutuzumab infusion. IRRs within 24 hours of receiving obinutuzumab have occurred. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Other common symptoms include fatigue, dizziness, nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

- Pre-medicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed. Closely monitor patients during the entire infusion.
- For patients with any Grade 4 IRRs, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.
- For patients with Grade 1, 2, or 3 IRRs, interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.
- For patients with pre-existing cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because these patients may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab IRR. Consider withholding antihypertensive treatments for 12 hours prior to, during, and for the first hour after administration of each obinutuzumab infusion until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their hypertensive medication.

11.2.11.4 Tumor Lysis Syndrome

TLS, including fatal cases, has been reported in patients receiving obinutuzumab. Patients with high tumor burden, high circulating lymphocyte count ($>25 \times 10^9$/L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab. Continue prophylaxis prior to each subsequent obinutuzumab infusion, as needed.

During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

11.2.11.5 Infection

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Fatal infections have been reported. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

11.2.11.6 Neutropenia

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Patients with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection.

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Patients with severe or long-lasting (>1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

11.2.11.7 Thrombocytopenia

Severe and life threatening thrombocytopenia has been reported during treatment with obinutuzumab in combination with chlorambucil or bendamustine. Fatal hemorrhagic events during Cycle 1 have also been reported in patients with CLL treated with obinutuzumab.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of obinutuzumab and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

11.2.11.8 Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy have not been studied. Immunization with live-virus vaccines is not recommended during treatment and until B-cell recovery.

11.2.12 Nursing/Patient Implications

1. Monitor blood pressure, pulse, respiration, and temperature per institutional guidelines.
2. Medications (including oxygen, epinephrine for subcutaneous injections, corticosteroids, diphenhydramine for IV injection, and meperidine) and resuscitation equipment should be available for all infusions for immediate use in the event of an anaphylactic reaction or moderate to severe IRR.
3. Monitor and alter infusion rates in the presence of toxicities.
4. Cases of TLS have been reported in patients treated with obinutuzumab. Patients with a high tumor burden including those patients with a lymphocyte count ≥ 25 x 10^9/L (in particular patients with B-CLL and MCL) are at increased risk of TLS and severe IRRs. Aggressive intravenous hydration is the cornerstone of prevention of TLS and is recommended prior to therapy in all patients at intermediate or high risk for TLS. Prior to initiation of IV hydration, reversible forms of renal insufficiency (e.g., volume contraction, hypercalcemia, urinary tract obstruction) should be corrected. In addition, all patients considered to be at risk of TLS, should be premedicated with an agent to reduce uric acid (e.g., allopurinol or rasburicase). In addition, care should be taken to ensure that patients have adequate fluid intake. For subsequent infusions, patients at risk for TLS should receive TLS prophylaxis with anti-hyperuricemics and adequate hydration prior to each infusion.
5. Patients who experience Grade 3/4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The administration of transfusion of blood products according to institutional practice is at the discretion of the investigators. Use of G-CSF has been found to result in a rapid normalization of neutrophils similar to what has been observed in patients treated with rituximab. Obinutuzumab should not be administered in the presence of active severe infections. Physicians should exercise caution when considering the use of obinutuzumab in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections.

11.3 Bendamustine[20]

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.

11.3.1 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.

11.3.2 Preparation

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

11.3.3 Route of Administration

Bendamustine will be administered as a 10 minute or per institutional guidelines IV infusion at a dose of 90 mg/m^2 on days 1 and 2 of each 28-day cycle.

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.

Refer to Section 6.1 and Table 6-1, Table 6-2 and Table 6-4 for Dose Delays and Modifications details during Induction.

11.3.3.1 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.

11.3.4 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.

11.3.5 Incompatibilities

No incompatibilities are known (no data is available).

11.3.6 Side Effects

The adverse events specified below are also likely to be of clinical importance and may result in bendamustine dose delays or dose reductions.

11.3.6.1 Infection and Pneumonia

Infection, including pneumonia and sepsis, has been reported and, in rare cases, infection has been associated with hospitalization, septic shock, and death. Patients with myelosuppression following bendamustine treatment are susceptible to infections and should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms.

11.3.6.2 Infusion Reactions and Anaphylaxis

Infusion reactions with bendamustine have occurred commonly in clinical studies with symptoms that are generally mild and include fever, chills, pruritus, and rash. In rare instances, severe infusion reactions, described as anaphylactic and anaphylactoid reactions, have occurred, particularly in the second and subsequent cycles of therapy. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics, and corticosteroids should be considered in subsequent cycles in patients who have previously experienced infusion reactions.

11.3.6.3 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with bendamustine, with onset typically within the first treatment cycle. Tumor lysis syndrome may lead to acute renal failure and death without appropriate medical intervention. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry (particularly potassium and uric acid levels), and the use of allopurinol during the first 1 to 2 weeks of bendamustine treatment.

11.3.6.4 Skin Reactions

Skin reactions have been reported with the use of bendamustine, including non-specific rash, toxic skin reactions, and bullous exanthema. The relationship of skin reactions to bendamustine administration is often unclear as bendamustine is frequently administered with other anti-cancer therapies. A case of fatal toxic epidermal necrolysis (TEN) has been reported in 1 patient treated with a combination of bendamustine and rituximab.

TEN was considered possibly related to either agent. The relationship of this adverse event to bendamustine remains uncertain as TEN has also been reported with single-agent rituximab. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, bendamustine should be withheld or discontinued.

NOTE: There is the potential for overlapping skin reaction toxicity with concomitant administration of bendamustine with allopurinol. Allopurinol may be temporarily disrupted if safe from a tumor lysis standpoint.

11.3.6.5 Other Malignancies

Development of premalignant and malignant disorders following treatment with bendamustine has been reported. The reports are limited and included development of myelodysplastic syndromes, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. Because of

confounding effects of other previous chemotherapy in these patients, the relationship to bendamustine could not be determined.

11.3.7 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.
6. Administer antiemetics as indicated.

12. Statistical Considerations

12.1 Primary Endpoint

The study is a single arm phase II study combining venetoclax, obinutuzumab and bendamustine. Patients with a high tumor burden based on FLIPI or GELF criteria will be enrolled.

The primary objective of this study is CR after induction. We anticipate a 50% CR rate after induction treatment with obinutuzumab and bendamustine. With the addition of venetoclax (given concurrently), a CR rate of 65% (15% improvement from 50%) would be considered promising for the addition of venetoclax to the induction regimen. A total of 56 patients will be enrolled into the study, 51 of which are expected to be eligible and treated. Among 51 eligible, treated patients, this study will have 85% power to detect a 15% improvement in CR using a one-sided exact binomial test with 15% Type I error. This regimen combination of venetoclax + obinutuzumab and bendamustine will be considered worthy of further investigation if 30 or more patients achieve CR. CR rate will be estimated among all eligible, treated patients.

Given the study treatment combination, there will be a formal, detailed, toxicity evaluation. To maintain homogeneity, this toxicity evaluation will be performed after the first 21 enrolled patients (~38% of total accrual), treated on the same venetoclax schedule, have been on study and received 3 full treatment cycles. This includes patients who come off treatment for any reason. For all treatment-related Grade 3 or higher AEs, the formal evaluation will be done within each AE category and also for the overall AE rate. All treatment-related AEs information will be collected and tabulated by toxicity grade.

- It is expected that the proportion of any Grade 3 or higher, treatment-related, AEs will be no higher than 35% within each AE category. This includes expected, treatment-related, Grade 3 or higher toxicities including any cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia), infections, electrolyte changes, skin rash, hyper/hypotension, transient diarrhea, vascular disorders.

  If any event's observed Grade 3 or higher, treatment-related, AE proportion is higher than 45% (≥ 10 out of 21 patients), a detailed review of all treatment-related AE will be conducted and the study review team may decide if treatment modification is necessary. If the true proportion of any AE is 55% or higher there is at least 82% probability of exceeding the observed AE boundary. Whereas, if the true proportion of any AE is 35% there is 16% probability of crossing the toxicity boundary. The above decision boundary (45% or more observed events) will be followed for all treatment-related Grade 3 or higher events within each AE category.

- The expected overall toxicity rate for all Grade 3 or higher, treatment-related, AEs is approximately 40%. If the observed overall Grade 3 or higher, treatment-related, AEs proportion is higher than 50% (≥ 11 out of 21 patients), a detailed review of all treatment-related AE will be conducted and the study review team may decide if treatment modification is necessary. If the true proportion of overall AE is 60% or higher, there is at least 83% probability of exceeding the observed boundary. Whereas, if the true proportion is 40% there is 17% chance of crossing the toxicity boundary. This decision boundary will be followed for the overall treatment-related Grade 3 or higher AEs.

A detailed review of AEs could be triggered by the within-category or overall AEs based on the rules specified above.

12.1.1 Data Safety Monitoring Board (DSMB) Monitoring and Interim Safety Analysis

As at the time of this amendment #6, there have been 3 DSMB reviews for this study: June 2018, December 2018, and most recently in June 2019.

In addition, the DSMB convened an ad hoc web teleconference meeting March 28, 2019 to review the findings from the planned interim safety analyses which took place after the first 21 enrolled patients were treated on the same venetoclax schedule for 3 full treatment cycles (all patients

started venetoclax with Cycle 1). At the time of analyses, 19 of 21 patients experienced treatment-related worst toxicity Grade of 3 or higher for an adverse event proportion (Exact 90% CI) of 90.5% (72.9, 98.3). Twelve (12) unique patients experienced treatment-related Grade 3 or higher cytopenias for an adverse event proportion (Exact 90% CI) of 57.1% (37.2, 75.5). The proportion (Exact 90% CI) of TLS events was 38.1% (20.6, 58.3).

The observed proportion of overall and cytopenia AE exceeded the pre-specified thresholds in Section 12.1. Based on the data, the high proportion of overall AEs were found to be a result of high cytopenias which is common for this disease and treatment.

At the end of the meeting, the DSMB made three recommendations: continue a) close monitoring for TLS, b) to receive SAE Reports for TLS events in real time, and c) monitor neutropenia and sequelae.

NOTE: In Version 5.0 of the protocol, venetoclax was changed to start with Cycle 2.

12.2 Secondary Endpoints

The secondary objectives of this study include evaluation of ORR among treated patients; proportion of patients who achieve PR in induction and then CR with maintenance therapy; evaluation of PFS and OS among treated patients (ITT); and evaluation of compliance to therapy and toxicities of all patients.

Descriptive statistics will be used to compute proportion of ORR and the proportion of patients that achieve CR in maintenance therapy. A 90% exact binomial confidence interval (CI) around response rates will also be computed for descriptive purposes. Kaplan Meier method will be used to estimate the PFS and OS among all treated patients; the 90% CI will be provided for these estimates.

All enrolled patients who received treatment, irrespective of eligibility, will be evaluated for toxicities attributable to treatment during induction and maintenance therapy. Toxicity rates will be described using proportions and 90% exact binomial CI will be provided. If a total of 56 patients are treated, the maximum width of 90% CI on the proportion of treatment-related Grade 3 or higher toxicity will be no wider than 23%. The probability of observing at least one rare toxicity (true toxicity rate if 5%) is approximately 94.3%. We will also describe all toxicities, regardless of treatment attribution.

Descriptive statistics using mean and proportions will be used to describe compliance to induction and maintenance therapy.

12.2.1 Maintenance Therapy Suspension as of 9/16/2021

Due to a recent Grade 5 event of myocarditis in a patient on maintenance therapy, the study investigators are concerned about atypical infections that have been seen after induction therapy on study. There have been four events of atypical infections as listed below:

- Treatment related death due to cytomegalovirus encephalitis as well as *Pneumocystis jiroveci* Pneumonia (PJP) occurring after cycle 6 of induction but before maintenance therapy.
- BK virus nephropathy leading to end stage renal disease and chronic hemodialysis in a patient following 6 doses of maintenance obinutuzumab.
- Respiratory syncytial virus pneumonia 30 days after cycle 6 of induction and later, after 2 cycles of maintenance obinutuzumab, developed PJP.
- The recent fatal myocarditis which is suspected, but not proven, to be viral in etiology.

Given these adverse events we are suspending any additional maintenance therapy for those patients on study. These patients will not receive any further treatment and move on to the two year survival follow-up portion of the study. All study-required follow-up activities remain unchanged.

The PrECOG Data Safety and Monitoring Board has also reviewed and agree with the recommendation to stop additional maintenance therapy.

12.3 Exploratory Endpoints

As part of exploratory analyses, treatment outcome measures (ORR, PFS, and OS) will be correlated with potential prognostic factors and correlative measures. Fisher's exact or Chi-square test will be used to assess relationship between binary factors and outcome measures; logistic regression will be used for a combination of multiple factors with binary treatment outcome. Independent and paired t-tests (or Wilcoxon rank-sum and Signed Rank tests respectively) will be used to assess association between continuous correlative measures accordingly. For time-to-event treatment outcome measures, Kaplan-Meier and the logrank test, as well as Cox proportional hazards models, will be used to assess relationship with one or multiple factors.

13. Laboratory and Pathology Correlative Studies

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

13.1.1 Overview

Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery (if sufficient tissue is available, submission is mandatory): Formalin-fixed paraffin-embedded (FFPE) blocks and 7-10 FFPE tissue on unstained (4-5 um) slides or if blocks are not available, up to 25 FFPE tissue on unstained (4-5 um) slides plus H&E slide (if tissue is limited, then minimum of 13 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).

Analyses to be performed may include the following:

- Bcl-2 protein expression by immunohistochemistry (IHC) in pretreatment biopsies. Analysis will include assessment of Bcl-2 by IHC using the Ventana validated reagents, being developed as potential companion diagnostic for the venetoclax development program.
- Bcl-2 family expression by mRNA expression including ratios of Bcl-2/BIM, Bcl-2/Mcl-1 with response, PFS and OS and/or other analysis. Additional hypothesis from biomarker analysis from the CONTRALTO study, such as Bcl-2 alterations at the tumor DNA level, may be tested.
- *BCL2* rearrangement status by fluorescence in situ hybridization (FISH) in pretreatment biopsies.
- Mcl-1 and Bcl-X_L protein expression by IHC in pretreatment biopsies.
- Histologic features of pretreatment biopsies.

Seven to ten slides per patient will be sent to Ventana Medical Systems, Inc. within 4 months of slides being cut for Bcl-2, Mcl-1 and Bcl-X_L analysis.

Optional: Any tumor biopsy samples obtained during treatment or post-treatment (formalin-fixed paraffin-embedded (FFPE) blocks or up to 15 FFPE tissue on unstained (4-5 um) slides plus H&E slide) will be requested for research. Any leftover tissue (pre-treatment, during treatment or post-treatment) will be banked for future research.

All other samples will be sent to a central lab for storage. This will include up to 4 slides for mRNA/DNA analysis to test biomarker hypothesis from the CONTRALTO study. These samples will be stored at central lab until triggered at a testing lab. Additional testing will be batch-performed following receipt of all accrued samples by Vanderbilt University Medical Center.

13.1.2 Assay Methodology

13.1.2.1 To Compare Bcl-2 Protein Expression by IHC in Pretreatment Biopsies with Response, PFS, and OS.

In the rituximab era, the absence or presence of Bcl-2 protein expression and the intensity of expression are not significant prognostic indicators of PFS and OS in FL. We hypothesize that with the addition of the Bcl-2 inhibitor venetoclax to obinutuzumab and bendamustine therapy in FL, the presence of Bcl-2 protein expression and strong intensity of expression will be associated with favorable outcome compared to cases with lower or no Bcl-2 expression.

IHC for Bcl-2 protein will be performed on all pretreatment FFPE biopsy samples by Ventana Medical Systems. All samples with sufficiently abundant material will be included in triplicate on a tissue microarray (TMA) on which Bcl-2 IHC will be performed. Excisional lymph node or extranodal tissue biopsies are preferred over core needle biopsies. On any sample too small for inclusion on the TMA, Bcl-2 IHC will be performed on an unstained slide section in parallel with the TMA staining. If Bcl-2 IHC was performed on the case at the originating institution, these slides will also be reviewed and Bcl-2 expression and intensity assessed.

Additionally IHC assessment using the validated Ventana IHC test or rescoring of stained slides using the Ventana algorithm may be performed. Analysis will be performed within 4 months of slides being cut, to adhere to the IHC assay stability window.

The results will be compared with *IGH*/*BCL2* FISH status, treatment response, PFS, and OS.

13.1.2.2 To Compare BCL2 Rearrangement Status by FISH in Pretreatment Biopsies and Correlate with Response, PFS, and OS.

A majority of, but not all, FL harbor an isolated t(14;18) IgH/Bcl-2 translocation. Similarly, to Bcl-2 protein expression, we hypothesize that the presence of *BCL2* rearrangement may correlate with more favorable outcome compared to cases lacking a rearrangement.

Use of *BCL2* break-apart FISH probes is the most accurate qualitative method of capturing variant translocations[21] and cases with BCL2 mutations and/or extensive somatic hypermutation[22] that may prevent PCR primer binding. *IGH* and *BCL2* break-apart FISH probes will be applied to unstained slides of each pretreatment FFPE biopsy. Testing will be batch-performed following receipt of all accrued samples.

The reviewing molecular pathologist(s) will be blinded to the clinical outcome data and Bcl-2 expression status. The number of positive signals will be expressed as a percent of the total cells examined by clinically validated methods. The results will be compared with Bcl-2 protein expression status by IHC, treatment response, PFS, and OS.

13.1.2.3 To Compare Mcl-1 and Bcl-X_L Protein Expression by IHC in Pretreatment Biopsies with Response, PFS, and OS

Myeloid leukemia sequence 1 (Mcl-1) and B-cell lymphoma X_L (Bcl-X_L) are additional anti-apoptotic proteins closely related to Bcl-2. In pre-clinical studies, pharmacologic loss of Mcl-1 function is reported to sensitize B-cell lymphoma cell lines to Bcl-2 inhibition by ABT-199 and other agents.[23] Similarly, selective inhibition in vivo of BCL-X_L sensitizes zenograft models of carcinoma to standard cytotoxic chemotherapy.[24] We hypothesize that low expression levels of Mcl-1 and Bcl-X_L may correlate with more robust treatment response and longer PFS and OS compared with cases showing high Bcl-1 and Bcl-X_L expression.

IHC for Mcl-1 and Bcl-X_L protein expression will be performed and reviewed on all pretreatment FFPE biopsy samples on TMAs in the same manner as Bcl-2 IHC. Appropriate positive and negative control samples will be included from archival clinical tissue blocks, first assessed separately. As with Bcl-2 IHC, the reviewing pathologist(s) will be blinded to the clinical outcome data. Scoring of staining intensity for each antibody will be defined following initial stain review. Additional proteins in the Bcl-2 and related pathway may also be interrogated by IHC based on emerging literature. The results will be compared to Bcl-2 expression and intensity, histopathologic features, and treatment response, PFS, and OS.

13.1.2.4 To Compare Histologic Features of Pretreatment Biopsies with Response, PFS, and OS.

High histologic grade in FL, i.e. grade 3A, and diffuse architecture have been associated with relatively aggressive behavior and a greater likelihood of progression to DLBCL.[25] Similarly, tumor proliferative rate as estimated by Ki67 IHC in low-grade (grade 1-2) cases has been suggested as an adverse prognostic feature.[26] We hypothesize that in the setting of pharmacologic Bcl-2 inhibition, histologic grade, diffuse architecture, and Ki67 proliferation fraction may not be significantly associated with outcome.

All diagnostic pretreatment biopsies will be reviewed by the study pathologist(s). Histologic grade (grade 1-2 or grade 3A) will be assigned in a manner blinded to the original pathology report. Similarly, architectural pattern will be assigned in the following proportions as recommended by the WHO: follicular pattern=>75% follicular architecture, follicular and diffuse patterns=25-75% follicular architecture, focally follicular pattern=<25% follicular architecture, and diffuse=0%

follicular architecture. The Ki67 proliferation fraction will be estimated from Ki67 IHC on the TMA as follows: <10%, 10-20%, 20-30%, and >30% of tumor cells.

Each feature (grade, architecture, and Ki67 proliferation fraction) will be compared to treatment response, PFS, and OS. Statistical methods and inferences will be informed by relative sample sizes.

NOTE: Any tissue biopsies obtained during treatment or post-treatment (Formalin-Fixed Paraffin-Embedded (FFPE) blocks or up to 15 FFPE slides plus H&E slide), whether or not involved by lymphoma (persistent/recurrent/transformed), will also be centrally reviewed by the study pathologist(s). If deemed appropriate, additional immunohistochemistry (including but not limited to Bcl-2 and Mcl-1), *BCL2* FISH, and *IGH*/*BCL2* PCR may be performed for assessment of additional pathology objectives and/or for generation of additional histopathologic hypothesis generation.

13.1.3 Pathology Sample Processing and Shipment

13.1.3.1 Bcl-2 Samples to Ventana

Sites will submit 7-10 FFPE tissue slides per patient within 4 months of slides being cut to Ventana Medical Systems, Inc. Shipping kits, supplies and instructions will be provided.

13.1.3.2 Remaining Pathology Samples to Central Lab

Sites should submit FFPE diagnosis tumor tissue blocks or up to 15 FFPE (if tissue is limited, then minimum of 6 slides are required) unstained slides plus H&E slide from relevant tumor tissue block(s) within 12 months of patient registration. Thickness of the sections should be at 4-5 microns.

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 (4-5 microns) on unstained slides plus H&E slide) within 4 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.

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.

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

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics 2015, CA Cancer J Clin. 2015; 65:5-29.
2. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006; 107:265-276.
3. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med. 1984; 311:1471-1475.
4. Swenson WT, Wooldridge JE, Lynch CF, Forman-Hoffman VL, Chrischilles E, Link BK. Improved survival of follicular lymphoma patients in the United States. J Clin Oncol. 2005; 23:5019-5026.
5. Lai R, Arber DA, Chang KL, Wilson CS, Weiss LM. Frequency of bcl-2 expression in non-Hodgkin's lymphoma: a study of 7788 cases with comparison of marginal zone lymphoma and monocytoid B-cell hyperplasia. Mod Pathol 1998; 11:864-869.
6. Schraders M, de Jong D, Kluin P, Groenen P, van Krieken H. Lack of Bcl-2 expression in follicular lymphoma may be caused by mutations in the BCL2 gene of by absence of the t(14;18) translocation. J Pathol 2005; 205:329-335.
7. Rummel MJ, Niederle N, Maschmeyer G, Banat GA et al., Bendamustine plus rituximab versus CHOP plus rituximab as first line treatment for patients with indolent and mantle cell lymphomas: an open-label, multicenter, randomised, phase 3 non-inferiority trial. Lancet 2013; 381:1203-10.
8. Salles G, Seymour J, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a Phase 3, randomised controlled trial. Lancet 2011; 377:42–51.
9. F. Hoffman-La Roche, LTD. Obinutuzumab/GAZYVA Investigator's Brochure, Version 11; Date: September 2016.
10. Mössner E, Brünker B, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new Type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity. Blood 2010; 115:4393–402.
11. Niederfellner G,Lammens A, Mundigl O. et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. Blood 2011 Jul 14; 118(2):358-67.
12. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Ther. 2013 Oct; 12(10):2031-4.
13. Abbvie. Venetoclax/ABT-199 Investigator's Brochure, Version 8; Date: 15 February 2017.
14. Davids MS, Letai A. Targeting the B-cell lymphoma/leukemia 2 family in cancer. J Clin Oncol. 2012 Sep 1; 30(25):3127-35.
15. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013 Feb; 19(2):202-8.
16. Zinzani PL, Topp MS, Yuen SLS, et al. Phase 2 Study of Venetoclax Plus Rituximab or Randomized Ven Plus Bendamustine+Rituximab (BR) Versus BR in Patients with Relapsed/Refractory Follicular Lymphoma: Interim Data. Oral presentation at ASH 2016; Session: 623- Mantle Cell, Follicular, and Other Indolent B-Cell Lymphoma-Clinical Studies: Chemoimmunotherapy in Follicular Lymphoma; 05 December 2016.
17. Zelenetz AD, Gilles AS, Mason KD, et al. Results of a Phase Ib Study of Venetoclax Plus R- or G-CHOP in Patients with B-Cell Non-Hodgkin Lymphoma. Blood 2016: 128:3032.
18. Howard SC, Jones, DP and Pui CH. The Tumor Lysis Syndrome. N Engl J Med 2011; 364: 1844-54.

19. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister AT. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: the Lugano Classification JCO. 2014: 32' 3057-3067.
20. Bendamustine Package Insert. August 2008-2017.
21. Baro C, Espinet B, Salido M, et al. Cryptic IGH/BCL2 rearrangements with variant FISH patterns in follicular lymphoma. Leukemia Research 2011; 35(2):256-259.
22. Burkhard R, Bhagat G, Cogliatti SB, et al. BCL2 mutation spectrum in B-cell non-Hodgkin lymphomas and patterns associated with evolution of follicular lymphoma. Hematol Oncol 2015; 33(1):23-30.
23. Phillips DC, Xiao Y, Lam LT, et al. Loss in MCL-1 function sensitizes non-Hodgkin's lymphoma cell lines to the BCL-2-selective inhibitor venetoclax (ABT-199). Blood Cancer Journal 2015; 5:e368.
24. van Delft MF, Wei AH, Mason KD, et al. The BH3 mimetic ABT-737 targets selective Bcl-2 proteins and efficiently induces apoptosis via Bak/Bax if Mcl-1 is neutralized. Cancer Cell 2006; 10:389-99.
25. Martin AR, Weisenburger DD, Chan WC, et al. Prognostic value of cellular proliferation and histologic grade in follicular lymphoma. Blood 1995; 85:3671-3678.
26. Wang SA, Wang L, Hochberg EP, Muzikansky A, Harris NL, Hasserjian RP. Low histologic grade follicular lymphoma with high proliferation index: morphologic and clinical features. Am J Surg Pathol 2005; 29(11):1490-6.
27. Buske C, Hoster E, Dreyling M, Hasford J, Unterhalt M, Hiddemann W. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. Blood. 2006; 108:1504-1508.
28. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004; 104:1258-1265.
29. Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: A New Prognostic Index for Follicular Lymphoma Developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009 Sep 20; 27(27):4555-62.

Appendix I: Modified Ann Arbor Staging System

Stage I	Involvement of a single lymph node region.
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm.
Stage III_1	Involvement of lymph node regions on both sides of the diaphragm. Abdominal disease is limited to the upper abdomen: spleen, splenic hilar node, celiac node, porta hepatitis node.
Stage III_2	Involvement of lymph node regions on both sides of the diaphragm. Abdominal disease includes para-aortic, mesenteric, iliac, or inguinal involvement with or without disease in the upper abdomen.
Stage IV	Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

In Stage III_1, the subscript S may be used to denote splenic involvement. The subscript E (e.g., I_E or II_E) is used to denote involvement of an extra lymphatic site primarily or by direct extension, rather than hematogenous spread, as in the case of a mediastinal mass extending to involve the lung.

The presence of (B) or absence of (A) fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months prior to admission are denoted by the corresponding suffix letters B and A.

Appendix II: 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 housework, 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 III: 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 IV: Definitions of Tumor Lysis Syndrome[18]

All tumor lysis syndrome events should be graded per the NCI CTCAE, Version 5.0 criteria.

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	Potassium >6.0 mEq/L (6.0 mmol/liter) in adults.	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). This window applies to initiation of any study therapy. 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. (reused with permission)

Appendix V: Venetoclax Medication Diary

Patient Instructions:

1. Complete each form as instructed by your physician or study nurse. Please complete in ink.
2. Please complete this diary every day. Write the date of each dose of venetoclax you take.
3. Venetoclax should be administered with a meal and swallowed whole with an 8-ounce glass of water. Tablets should not be chewed, crushed or broken. You should take the tablets at approximately the same time each day.
4. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with food. There must be a minimum of 16 hours between the current dose and the next dose. Return to the normal schedule the following day.
5. Extra tablets should not be taken to make up for the missed dose. If you vomit within 15 minutes of taking venetoclax and all tablets are intact, you may take another dose otherwise, do not repeat the dose but resume dosing at the time of the next scheduled dose. Please mark dates of any missed tablet on your record.
6. You should not drink grapefruit juice, eat grapefruit, or eat Seville oranges (often used in marmalades) or starfruit while you are taking venetoclax. These products may increase the amount of venetoclax in your blood.
7. Store venetoclax at or below 86°F.
8. If you have any side effects or comments, please note in the comment section or on the back of the page. If you have questions or concerns, please call

   _____ at: (_____) _____ - _____.

Please bring your venetoclax bottle(s) (unused medication and empty bottles) and this form to every appointment with your study doctor.

INDUCTION Cycle 2-6 Venetoclax Medication Diary

Site #:_____	**Subject #:_____**	**Subject Initials:_____**
Cycle:_____	**Dose:_____**	**Number of Tablets: _____ mg: #_____**

DAY	DATE	DOSE	Aspirin (or any other blood thinning medication)	COMMENTS
1	____/____/____	_____mg		
2	____/____/____	_____mg		
3	____/____/____	_____mg		
4	____/____/____	_____mg		
5	____/____/____	_____mg		
6	____/____/____	_____mg		
7	____/____/____	_____mg		
8	____/____/____	_____mg		
9	____/____/____	_____mg		
10	____/____/____	_____mg		

Patient Signature: _____ Patient Initials: _____

MAINTENANCE Venetoclax Medication Diary

Site #:_____	**Subject #:_____**	**Subject Initials:_____**
Cycle:_____	**Dose:_____**	**Number of Tablets: _____ mg: #_____**

DAY	DATE	DOSE	Aspirin (or any other blood thinning medication)	COMMENTS
1	____/____/____	_____mg		
2	____/____/____	_____mg		
3	____/____/____	_____mg		
4	____/____/____	_____mg		
5	____/____/____	_____mg		
6	____/____/____	_____mg		
7	____/____/____	_____mg		
8	____/____/____	_____mg		
9	____/____/____	_____mg		
10	____/____/____	_____mg		
11	____/____/____	_____mg		
12	____/____/____	_____mg		
13	____/____/____	_____mg		
14	____/____/____	_____mg		
15	____/____/____	_____mg		
16	____/____/____	_____mg		
17	____/____/____	_____mg		
18	____/____/____	_____mg		
19	____/____/____	_____mg		
20	____/____/____	_____mg		
21	____/____/____	_____mg		
22	____/____/____	_____mg		
23	____/____/____	_____mg		
24	____/____/____	_____mg		
25	____/____/____	_____mg		
26	____/____/____	_____mg		
27	____/____/____	_____mg		
28	____/____/____	_____mg		

Patient Signature: _____ Patient Initials: _____

Appendix VI: 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

Co-administration with strong and moderate CYP3A inhibitors is not recommended. Consider alternative medications if necessary. If subject requires the use of these medications, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. If subject requires use of strong or moderate CYP3A inducers, use with caution and contact PrECOG for guidance. Co-administration with the use of weak CYP3A inducers and weak CYP3A4 inhibitors should be undertaken with caution.

INHIBITORS
STRONG INHIBITORS
boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, lopinavir, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, teleprevir, telithromycin, troleandamycin, voriconazole
MODERATE INHIBITORS
amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunovir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, nifedipine, seville oranges, star fruit, verapamil
INDUCERS
STRONG INDUCERS
avasimibe, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort
MODERATE INDUCERS
bosentan, efavirenz, etravirine, modafinil, nafcillin, oxcarbazepine

Cautionary Use

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
INDUCERS
WEAK INDUCERS
armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib
PgP
PgP SUBSTRATES
aliskiren, ambrisentan, colchicines, dabigatran etexilate, digoxin, everolimus, fexofenadine, indinavir, lapatinib, loperamide, maraviroc, nilotinib, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
PgP INHIBITORS
amiodarone, azithromycin, captopril, carvedilol, cyclosporine, elacridar, felodipine, ginkgo (ginkgo biloba), mibefradil, milk thistle (silybum marianum), nitrendipine, quercetin, quinidine, ronalzine, schisandra chinensis, telmisartan, ticagrelor, tipranavir, valspodar

Appendix VII: Follicular Lymphoma International Prognostic Index (FLIPI)-1

FLIPI-1[27,28]

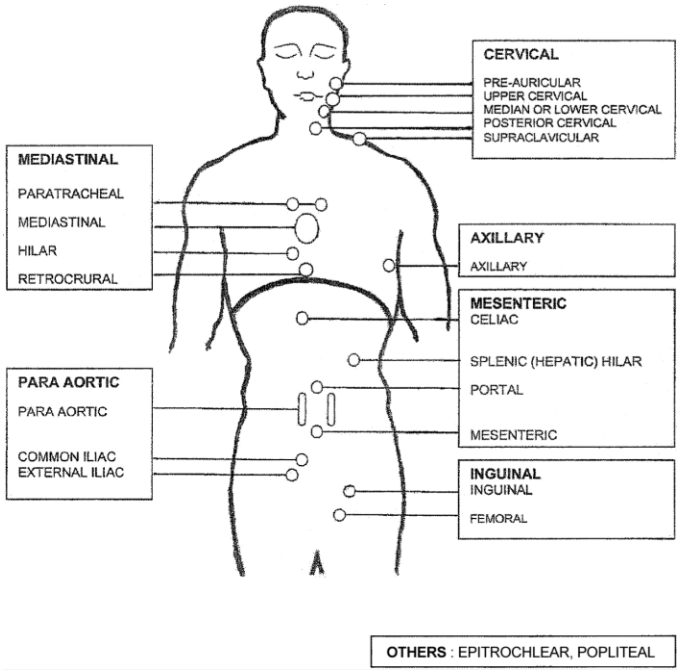
Each patient should be assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics): FLIPI 1

1) Age (*>60 years* vs. ≤ 60 years)
2) Ann Arbor stage (*III-IV* vs. I-II)
3) Hemoglobin level (*<120 g/L* vs. 120 g/L or higher)
4) Number of nodal areas (*>4* vs. 4 or less; see figure below)
5) Serum LDH level (*above normal* vs. normal or below)

Each patient should then be assigned into one of the following 3 risk groups:

- ☐ Low risk (0-1 adverse factor)
- ☐ Intermediate risk (2 factors) (Bilateral involvement = 2)
- ☐ High risk (3 or more adverse factors)

Figure. Nodal map according to FLIPI model.



Appendix VIII: Follicular Lymphoma International Prognostic Index (FLIPI)-2

FLIPI-2[29]

An updated analysis of the FLIPI was reported (FLIPI-2). This analysis was completed on 832 follicular lymphoma patients treated from 2003 through 2005, of who the majority received rituximab-based therapy. Five clinical factors were identified as being correlated with survival. Three of the parameters were different than the original FLIPI (FLIPI-1), while two were similar (i.e., anemia and older age).

Each patient treated should be further assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics):

1) Age (*>60 years* vs. 60 years or less)
2) Hemoglobin level (*<120 g/L* vs. 120 g/L or higher)
3) β2-microglobulin (*above normal* vs. normal or below)
4) Largest involved lymph node (*>6 cm* vs. 6 cm or lower)
5) Bone marrow (*involved* vs. not involved)

Appendix IX: Investigator's Statement

1. I have carefully read this protocol entitled **"Phase II Study of Venetoclax (ABT-199/GDC-0199) in Combination with Obinutuzumab and Bendamustine in Patients with High Tumor Burden Follicular Lymphoma as Front Line Therapy"**, **Version 8.0 dated 10/15/2021 (PrE0403)** 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