PROTOCOL

TITLE:	**A PHASE II EVALUATION OF BENDAMUSTINE, OBINUTUZUMAB AND VENETOCLAX IN PATIENTS WITH UNTREATED MANTLE CELL LYMPHOMA**
STUDY NUMBER:	ML40204
VERSION NUMBER:	4
TEST PRODUCTS:	Venetoclax (GDC-0199, ABT-199, RO5537382) Obinutuzumab (GA-101, RO5072759, Gazyva®)
INDICATION:	Mantle Cell Lymphoma – previously untreated
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SUPPORT PROVIDED BY:	Genentech, Inc.
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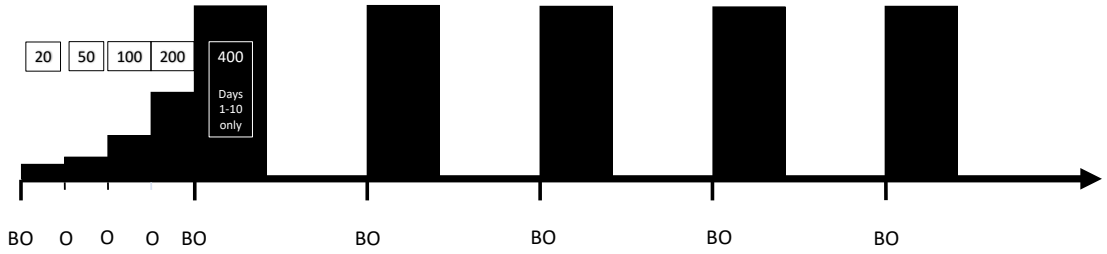
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	activated B-cell like
ABT-199	venetoclax (GDC-0199)
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AML	acute myeloid leukemia
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
AUC	area under the time-concentration curve
Bcl-2	B-cell lymphoma-2
BR	bendamustine plus rituximab
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
Clb	chlorambucil
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CVP	cyclophosphamide, vincristine, prednisone
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
FC	fludarabine, cyclophosphamide
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
G	obinutuzumab (GA101)
G-benda	obinutuzumab, bendamustine
GCB	germinal center B-cell like
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
G-CHOP	obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Abbreviation	Definition
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HPW	highly purified water
HR	hazard ratio
IB	Investigator's Brochure
IBM	ideal body mass
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IND	Investigational New Drug
iNHL	indolent non-Hodgkin's lymphoma
IMP	investigational medicinal product
IRC	Independent Review Committee
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IWWM	International Workshop-Waldenstrom's macroglobulinemia (criteria)
JC virus	John Cunningham virus
LPLV	last patient, last visit
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin's lymphoma
NK	natural killer (cell)
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy

Abbreviation	Definition
PR	partial response
PRO	patient-reported outcome
PTT	partial thromboplastin time
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R/R	relapsed or refractory
SLL	small lymphocytic leukemia
TGI	tumor-growth inhibition
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
USPI	United States Package Insert
WM	Waldenstrom's macroglobulinemia

Study Schema (First patient cohort with venetoclax initiation on C1D1 prior to amendment)



B: Bendamustine 90mg/m2 on days 1 & 2
O: Obinutuzumab 1000mg
--Cycle 1: Days 1, 8 and 15
--Cycles 2 – 6: Day 1 only
Venetoclax
--Ramp up dosing over 28 days in C1
--400mg D1-10 on C2-6

Study Schema (Revised post-amendment dosing schedule with venetoclax start on C1D8)

B: Bendamustine 90mg/m2 on days 1 & 2
O: Obinutuzumab 1000mg
--Cycle 1: Days 1, 8 and 15
--Cycles 2 – 6: Day 1 only
Venetoclax
- Ramp up dosing over 21 days in C1
  - Days 1-7: No venetoclax administered
  - Days 8-10: Venetoclax 20mg
  - Days 11-14: Venetoclax 50mg
  - Days 15-21: Venetoclax 100mg
  - Days 22-28: Venetoclax 200mg
- 400mg D1-10 on C2-6

Dosing Table (First patient cohort with venetoclax initiation on C1D1 prior to amendment)

Cycle	Cycle 1						Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2					90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg	1000mg		1000mg			1000mg		
Venetoclax (Days administered)	20mg daily (D1-7)			50mg daily (D8-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg						6mg			6mg
Allopurinol**	300mg/daily during cycle 1						300mg daily through C2D7					
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs												
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1												

Dosing Table (Revised post-amendment dosing schedule with venetoclax start on C1D8)

Cycle	Cycle 1							Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	11	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2						90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg		1000mg		1000mg			1000mg		
Venetoclax (Days administered)				20mg daily (D8-10)	50mg daily (D11-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg							6mg			6mg
Allopurinol**	300mg/daily during cycle 1							300mg daily through C2D7					
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs													
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1													

Dosing Table (Revised to include PJP prophylaxis recommendations)

Cycle	Cycle 1							Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	11	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2						90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg		1000mg		1000mg			1000mg		
Venetoclax (Days administered)				20mg daily (D8-10)	50mg daily (D11-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg							6mg			6mg
Allopurinol**	300mg/daily during cycle 1							300mg daily through C2D7					
Antiviral and PJP ppx***	Required during therapy. Suggested continuation until immune reconstitution (eg CD4 >200 or ALC >1000)												
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs													
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1													
***Antiviral and PJP ppx per institutional protocol. If patients are to receive trimethoprim-sulfamethoxazole, this may be deferred to the beginning of cycle 2 in order to limit the risk of dermatologic complications associated with allopurinol and bendamustine. All patients should receive some form of PJP prophylaxis no later than Cycle 2, Day 8.													

Table of Assessments

			CYCLE 1								CYCLE 2			CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X				
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1[#]	X				
Clonoseq MRD monitoring (Optional)	X[@]														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X[$]														X[$$]				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X
*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine																			
**Hematology/Chemistry: CBC with differential, Platelets, CMP																			
***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen																			
~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures																			
^Lab checked twice during a given day, with at least 6 hours between blood draws.																			
[#]C5D1 PET/CT may be performed up to 7 days prior to C5D1																			
[$]Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy																			
[$$]Therapy Completion BMBx/Aspirate only required if screening BMBx was positive																			
[@]Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up																			

Table of Assessments (Revised to Include CMV monitoring recommendations)

			CYCLE 1								CYCLE 2			CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X				
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1[#]	X				
Clonoseq MRD monitoring (Optional)	X[@]														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
CMV viremia by PCR	X										X			C4D1, C6D1	X				
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X[$]														X[$$]				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X

*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine

**Hematology/Chemistry: CBC with differential, Platelets, CMP

***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen

~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures

^Lab checked twice during a given day, with at least 6 hours between blood draws.

[#]C5D1 PET/CT may be performed up to 7 days prior to C5D1

[$]Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy

[$$]Therapy Completion BMBx/Aspirate only required if screening BMBx was positive

[@]Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up

1. BACKGROUND

Management of Mantle Cell Lymphoma Patients Ineligible for Autologous Stem Cell Transplantation

A significant number of individuals diagnosed with mantle cell lymphoma will not be candidates for high-intensity induction therapy followed by autologous stem cell transplantation. For these individuals, the combination of bendamustine and rituximab is commonly used to balance disease control and treatment toxicity. R-CHOP was a standard of care until StIL trial demonstrated decreased toxicity and improved survival with a median progression-free survival (PFS) for the BR combination of 35 months, and the complete remission rate of MCL and indolent lymphoma subtypes of 40%[1]. This was further supported by the BRIGHT trial in which a higher CR rate of 50% was seen with BR vs 27% with R-CHOP/R-CVP[2]. Bortezomib in addition to R-CAP (VR-CAP) was also compared to R-CHOP, with an improved median PFS of 24.7 months in the VR-CAP arm, but significantly worse hematologic toxicity with grade 3+ neutropenia in 85% and thrombocytopenia in 57% of patients on the VR-CAP arm[3]. A 38 patient phase II study evaluating the combination of lenalidomide and rituximab (R^2) in upfront mantle cell lymphoma also reported CR rate of 64% and 2-yr PFS of 84%, making it a viable combination, although the small number of patients, single-arm design, and incomplete follow-up make it difficult to compare to BR. Recently the US Intergroup has completed accrual to a study evaluating bendamustine-based induction therapies in MCL (E1411), and the results of this study should be reported soon. As a result of this work, many providers consider bendamustine to be the chemotherapy backbone of choice for patients with MCL deemed ineligible for ASCT.

While most prior regimens evaluated in MCL have included rituximab, its addition to induction therapy in MCL has not previously been associated with improved PFS or overall survival (OS)[4]. As a result, evaluation of novel CD-20 antibodies is indicated given their importance in multiple B-cell malignancies. Obinutuzumab is a humanized anti-CD20 monoclonal antibody that is FDA-approved for management of untreated chronic lymphocytic leukemia in combination with chlorambucil and for relapsed follicular lymphoma. While its activity in aggressive NHL appears similar to rituximab, its efficacy in other lymphoma subtypes suggests an improvement over rituximab. In the phase 2 GAUGUIN study evaluating obinutuzumab as a single agent in relapsed/refractory DLBCL or MCL, the ORR for MCL patients was 27% among a variety of dose levels[5]. It has been safely combined with bendamustine in several prior studies including the GADOLIN and GALLIUM studies in follicular lymphoma, and the GREEN study in chronic lymphocytic leukemia. In GALLIUM, the PFS compares favorably to bendamustine-rituximab, although this study incorporated a maintenance component. Across all studies, toxicities are typically predictable and include infusion-related reactions, neutropenia, and thrombocytopenia.

Venetoclax (ABT-199) is a BCL2 inhibitor with efficacy in multiple lymphoid malignancies and FDA approved for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). In a phase I trial,

single-agent venetoclax was efficacious in multiple relapsed/refractory NHL subtypes with an ORR in patients with MCL of 75% and an estimated median PFS of 14 months[6]. It has been combined with bendamustine and rituximab in a phase 1 dose escalation study and the recently reported CONTRALTO study in follicular lymphoma. In the phase 1 study, the combination was well tolerated with the most common grade 3+ toxicities being neutropenia (32%), lymphopenia (26%), thrombocytopenia (21%), anemia (15%), and leukopenia (13%). There was 9% febrile neutropenia and no drug-related deaths. 38 patients were evaluable for disease response with 29/38 with an objective response (10CR, 19PR, 4 stable disease) through a range of venetoclax doses in a heavily pretreated population[7]. The CONTRALTO evaluated B-R+ venetoclax in follicular lymphoma. The regimen was associated with expected hematologic and GI toxicities, and the ORR and CR rates in the venetoclax-containing arms were somewhat increased compared to B-R alone although more mature follow-up is needed regarding long-term benefits of adding venetoclax. Venetoclax has also been associated with life-threatening tumor lysis syndrome, encountered primarily in CLL but also in other lymphoma subtypes including MCL. As a result, a "ramp up" has been developed for both venetoclax monotherapy and combination studies.

1.1 BACKGROUND ON VENETOCLAX AND OBINUTUZUMAB

Venetoclax (GDC-0199, ABT-199, A-1195425.0, or RO5537382) is a selective, orally bioavailable, small-molecule Bcl-2 family protein inhibitor being developed by AbbVie and Roche/Genentech for oncology indications. Venetoclax (Venclexta™) was first approved in the United States (U.S.) on 11 April 2016 for the treatment of patients with chronic lymphocytic leukemia (CLL) with del(17p). Subsequent approvals in 2018 and 2019 have included CD20 monoclonal antibody-containing combinations in the relapsed/refractory and frontline settings in CLL, and venetoclax is also utilized in acute myelogenous leukemia in combination with azacytidine, decitabine, or low-dose cytarabine.

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.

Obinutuzumab (GA101, RO5072759, Gazyva®, Gazyvaro®) is a humanized glycoengineered type II anti-CD20 monoclonal antibody being developed by Roche/Genentech for the treatment of various hematologic malignancies. Obinutuzumab (Gazyva®) was approved in the U.S. on 1 November 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated CLL. In Europe, obinutuzumab (Gazyvaro®) was approved on 25 July 2014 for use in combination with chlorambucil for the treatment of adult patients with previously untreated CLL and comorbidities making them unsuitable for full-dose fludarabine-based therapy.

For further details on each individual agent, please refer to the current United States Package Insert (USPI) for obinutuzumab and the obinutuzumab or venetoclax Investigator's Brochures (IBs).

1.1.1 Mechanism of Action

Venetoclax and obinutuzumab target proteins that are overexpressed by B-cell lymphoid malignancies, Bcl-2 and CD20, respectively. Their different yet complementary mechanisms of action, the promising nonclinical data for the combination, and their current safety profiles make them appropriate agents to combine for clinical investigation for treatment of malignancies expressing CD20 and Bcl-2, such as CLL and NHL, including MCL.

In vitro, venetoclax demonstrated cell-killing activity against patient-derived CLL and acute myeloid leukemia (AML) cells and a variety of lymphoma and leukemia cell lines, including B-cell FL, mantle cell lymphoma (MCL), DLBCL, and multiple myeloma (MM). Venetoclax was especially potent against NHL cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than non-mutated lines.

Venetoclax is currently undergoing evaluation in CLL/small lymphocytic lymphoma (SLL), NHL, AML, and MM. Rapid reductions of peripheral lymphocytes and lymphoid masses observed after initial dosing with venetoclax has provided support for evaluation of a non-chemotherapy combination treatment regimen as well as for future combinations with myelosuppressive chemotherapy as part of the overall clinical development plan. .

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody 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. 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.

1.2 CLINICAL STUDIES OF VENETOCLAX AND OBINUTUZUMAB

There are multiple ongoing studies of the combination of venetoclax and obinutuzumab. GP28331 is an ongoing phase 1b dose finding and safety study of the combination of venetoclax and obinutuzumab in CLL. In this study, the majority (97.5%) of subjects in experienced at least 1 treatment-emergent adverse event. The most common adverse events were diarrhoea and infusion related reaction (54.3% each), nausea (51.9%), neutropenia (49.4%), fatigue (43.2%), pyrexia (39.5%), anaemia (34.6%), cough and chills (33.3% each), headache (30.9%), and vomiting and thrombocytopenia (27.2% each). Fifty-seven (70.4%) subjects experienced adverse events grade 3 or above. The most common adverse events grade 3 and above were neutropenia

(43.2%) and thrombocytopenia (14.8%). Serious adverse events were reported for 36 (44.4%) subjects and included the following: febrile neutropenia (8 subjects), pneumonia (5 subjects), cellulitis, lower respiratory tract infection, urinary tract infection, hyperphosphataemia, and pyrexia (3 subjects each), and acute sinusitis, rhinovirus infection, neutropenia, tumour lysis syndrome, and pleural effusion (2 subjects each). All other events were reported for 1 subject each. Adverse events leading to discontinuation of any treatment, including 1 fatal event of acute respiratory failure, 2 events of diarrhoea, 1 event of pneumocystis jirovecii pneumonia, and 1 event of oesophageal cancer, were reported for 5 (6.2%) subjects, all with R/R CLL. An overview of all adverse events, grade ≥ 3 adverse events, and serious adverse events reported in Study GP28331 is presented in Table 30 (Section 8.3.1.2.6) of the venetoclax investigator brochure.

GO28440 is a phase 1b study evaluating the combination of venetoclax in combination with bendamustine and rituximab or bendamustine and obinutuzumab in CLL. Nearly all (97.1%) R/R and frontline CLL subjects in Study GO28440 experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade 3 adverse events, and SAEs reported in Study GO28440 is presented in Table 30 (Section 8.3.1.2.6). The most common adverse events for R/R CLL subjects were neutropenia (63.6%), nausea (54.5%), thrombocytopenia and anaemia (42.4% each), and diarrhoea (39.4%). The most common adverse events for previously untreated CLL subjects were nausea (65.7%), neutropenia (60.0%), thrombocytopenia (48.6%) and diarrhoea (37.1%). The majority of subjects (78.8% R/R and 82.9% previously untreated) experienced adverse events grade 3 or above. The most common adverse events grade 3 and above for R/R CLL and previously untreated subjects, respectively, were neutropenia (63.6% and 57.1%), thrombocytopenia (24.2% and 31.4%), and anaemia (21.2% and 22.9%). Serious adverse events were reported for 17 (51.5%) R/R CLL subjects and 12 (34.3%) previously untreated CLL subjects. Febrile neutropenia and pyrexia were reported in 2 subjects in each group and thrombocytopenia in 2 subjects in previously untreated CLL subjects; all other serious events occurred in 1 subject each. Three (4.4%) subjects experienced adverse events that led to study discontinuation; the events were chronic lymphocytic leukaemia transformation, myelodysplastic syndrome, and neutropenia (1 subject each). Two subjects experienced adverse events that led to death.

Overall for NHL, when treated with venetoclax as a single agent or in combination with other therapies, most subjects experience at least 1 adverse event with the most common being nausea, diarrhoea, and neutropenia in both monotherapy and combination studies. Approximately two-thirds to three-quarters of subjects in NHL clinical trials experience ≥ grade 3 adverse events with most common being neutropenia, anaemia and thrombocytopenia. Of the fatal events in the NHL program, the majority are the adverse events of malignant neoplasm progression. Many of the adverse events reported in the current NHL studies are consistent with underlying disease or concomitant medical conditions, as well as other combination agents used to treat NHL patients. TLS, neutropenia, and infections are consistent with the expected safety profile of venetoclax based on expected on-target effects of Bcl-2 inhibition; the important identified and potential risks for venetoclax in NHL program remain the same as in CLL population and are described

below, as well as in Section 9.2 (Guidance for the Investigator). The incidence of TLS in NHL studies is low with reports of 2 cases (1.9%) of TLS in monotherapy Study M12-175 (Arm B), 4 cases of TLS (2.5%) in combination. Study BO29337 (1 subject venetoclax + R, 3 subjects venetoclax + BR), and 3 cases of TLS (1.2%) in combination Study GO27878 (venetoclax + R-CHOP or G-CHOP). Tumor lysis syndrome remains as important identified risk for NHL program. The guidance for TLS prophylaxis can be found in Section 9.2.2.1 (Guidance for the Investigator) and in NHL study protocols. Neutropenia has a similar frequency in NHL clinical program as in CLL with higher frequency in NHL combination studies. Serious adverse events of neutropenia and febrile neutropenia, albeit in small numbers, occurred in higher frequency in combination studies and remains as an important identified risk. Infections, including serious, were observed in NHL clinical program, with similar incidence in monotherapy and combination studies. One death reported in the NHL program was due to infection (sepsis; not related to venetoclax). Infections remain as a potential risk for the NHL clinical program.

Clinical experience using the combination of venetoclax and obinutuzumab in MCL has been limited. Although not as frequent as in CLL, there is a significant risk of TLS with the use of venetoclax in MCL, most prominent during treatment initiation and ramp-up. In the M12-175, phase I, first in human study of single agent Venetoclax in R/R CLL and NHL, subjects with MCL enrolled in the NHL arm appear to be at a greater risk of experiencing TLS-associated laboratory changes with venetoclax than subjects with other NHL subtypes. MCL cell line data indicates that venetoclax enhances the efficacy of bendamustine plus rituximab (BR).

Obinutuzumab use in MCL may be associated with acute thrombocytopenia occurring immediately after infusion. Preclinical studies have demonstrated a dose-dependent anti-tumor activity of obinutuzumab in a panel of aggressive NHL xenograft mouse models, including MCL models, mediating increased overall and median survival in the Z138 model when compared to rituximab. The combination of obinutuzumab and chemotherapeutic agents, including bendamustine, is superior to combinations of rituximab and chemotherapeutic agents in these models. In the Phase I study of BO21003, one MCL patient was included.

1.2.1 Clinical Pharmacokinetics and Pharmacodynamics of Venetoclax

Venetoclax pharmacokinetic results were available from Study GO28440, a Phase 1b, open-label study evaluating the safety and pharmacokinetics of venetoclax in combination with BR and BG in subjects with R/R or previously untreated CLL. Pharmacokinetic results from 12 subjects demonstrate that dose-normalized venetoclax Cmax and AUC0-24 after administration of venetoclax alone (20 mg venetoclax, ramp-up Day 1) were comparable with that obtained in combination with BR (100, 200, 400 mg venetoclax, Cycle 1 Day 3). Based on the limited data available, there was no evidence to suggest a marked effect of co-administration of bendamustine and rituximab, on the pharmacokinetics of venetoclax.

1.2.2 Clinical Efficacy of Venetoclax

Preliminary efficacy data for Study M12-630 (venetoclax in addition to bendamustine and rituximab) are available for 60 subjects with R/R NHL as of 20 October 2016.6 The ORR was 65.0% (39 of 60 evaluable subjects), with CR in 17 subjects (28.3%) and PR in 22 subjects (36.7%). Six additional subjects (10.0%) experienced stable disease.

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1.2.3 Clinical Safety of Venetoclax

TLS is an important identified risk for venetoclax. Risk of TLS is highest in CLL and mantle cell lymphoma. Serious infections and neutropenia are also identified risks for venetoclax. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including aneamia, thrombocytopenia, and lymphopenia). Decreased spermatogenesis has been observed in nonclinical studies with dogs and could present a risk to male infertility. Embryofetal toxicity has also been observed in mice at the highest dosage administered. Venetoclax is not advised in pregnancy or lactation.

In the M12-175 study, the most common adverse events in Arm B (NHL subjects) were nausea (48.1%), diarrhea (45.3%), fatigue (42.5%, and vomiting and decreased appetite (21.7% each). The most common events grade 3 or above were anemia (17%) and neutropenia (11.3%). Serious adverse events were reported in 34.9% of subjects. The most common serious adverse events were malignant neoplasm progression (9.4%), and influenza, lower respiratory tract infection, pneumonia, and hyponatremia (2.8% each).

A total of 18 (17.0%) subjects experienced adverse events that led to discontinuation of venetoclax. The most common adverse events leading to discontinuation were malignant neoplasm progress (6 [5.7%] subjects), and thrombocytopenia and nausea (2 [1.9%] subjects each). All other events leading to discontinuation were reported in 1 subject each. A total of 10 (9.4%) subjects experienced adverse events that led to death, including 9 events of malignant neoplasm progression and 1 event each of disease progression and respiratory failure. All fatal events were considered to have no reasonable possibility of being related to venetoclax.

As of 10 June 2016, a total of 106 subjects with R/R NHL (Arm B) were enrolled in Arm B (70 in the Dose-Escalation Cohorts and 36 in the Safety Expansion Cohort) and evaluated for objective response following the International Working Group criteria (subjects with Waldenstrom's Macroglobulinemia [WM] were evaluated using the International Workshop [IW]-WM criteria). The investigator-assessed ORR for all FL subjects and DBLBCL subjects excluding DLBCL-Richter's transformation subjects (across dose-escalation and safety expansion) was 37.9% and 17.6%, respectively; CR was achieved by 4 subjects in each group (13.8% and 11.8%, respectively).

In the study M12-630, venetoclax was dose escalated and evaluated for safety in combination with bendamustine and rituximab. The most common adverse events were nausea (68.3%), neutropenia (68.3%), diarrhoea (55.0%), thrombocytopenia (51.7%), vomiting (46.7%), fatigue

(43.3%), constipation (40.0%), lymphocyte count decreased and anaemia (38.3% each), and hyperglycaemia (33.3%). Fifty (83.3%) subjects experienced adverse events grade 3 or above. The most common adverse events grade 3 and above were neutropenia (60.0%), lymphocyte count decreased (38.3%), and thrombocytopenia (28.3%). Serious adverse events were reported for 24 (40.0%) subjects and included the following: febrile neutropenia and malignant neoplasm progression (5 subjects, 8.3% each), and diarrhoea, nausea, vomiting, malignant melanoma, syncope, dyspnoea and respiratory failure (2 subjects, 3.3% each). All other events were reported for 1 subject each. Adverse events leading to discontinuation were reported for 13 (21.7%) subjects. Five subjects experienced fatal events: 4 events of malignant neoplasm progression and 1 event of respiratory failure. None of these events were considered to have a reasonable possibility of being related to venetoclax.

1.2.4 Clinical Pharmacology of obinutuzumab

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies in patients with CLL or NHL. These studies include two Phase I/II monotherapy studies (BO20999 and BO21003); two Phase I monotherapy studies in Japanese patients with NHL (JO21900) and Chinese patients with FL, DLBCL, or CLL (YP25623); two Phase Ib combination studies (BO21000 and GAO4779g); two Phase II studies (a combination Study GAO4915g and a monotherapy Study GAO4768g at 1000 mg and 2000 mg); and two Phase III combination studies (BO21004/CLL11 and GAO4753g). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis, which demonstrated that a two-compartment PK model comprising both a linear clearance pathway and a non-linear time-varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was $> 2 \times$ higher than the steady-state clearance, which is consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition such that, at the start of treatment when there is a large quantity of CD20-positive cells, it binds obinutuzumab. With repeated dosing of obinutuzumab, the pool of CD20-positive cells is saturated, thereby reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies and is therefore independent of CD20-positive cells. Analysis further supports the need to minimize the time-varying clearance component quickly and has led to the proposed dose and regimen of 1000 mg in both induction and extended treatment.

Consistent with the mechanism of action of obinutuzumab, extensive B-cell depletion was observed both in patients with NHL and CLL. In most patients receiving obinutuzumab monotherapy, there was no notable increase in complement levels during or following an infusion. Changes in the levels of interleukin (IL)-6 and IL-8 were observed, i.e., increases during the course of the first infusion followed by a decrease to pre-infusion levels 7 days later.

1.2.5 Clinical Efficacy of obinutuzumab

In the monotherapy setting (i.e., studies, BO20999, BO21003, YP25623 and JO21900), the proportion of patients who had a response (complete 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 [R/R]) 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% in FL and 55% in DLBCL) than in the monotherapy studies.

In the pivotal chemotherapy combination Phase III study GAO4753g, which was unblinded and analysed at a pre-planned interim analysis, treatment with obinutuzumab + bendamustine (G-benda) followed by 2-year monotherapy with obinutuzumab resulted in a clinically meaningful and statistically significant increase in PFS compared with bendamustine alone in patients with relapsed/refractory iNHL. Independent Review Committee (IRC)-assessed median PFS was 14.9 months for benda and not reached for G-benda (hazard ratio [HR] 0.55, 95% confidence interval (CI): 0.40–0.74; p ∃ 0.0001). The median investigator assessed PFS was 14.0 months for benda and 29.2 months for G-benda (HR 0.52, 95% CI: 0.39–0.70; p ∋ 0.0001). IRC-assessed best overall response up to 12 months from the start of treatment was 78.6% in the G-benda arm and 76.6% in the benda arm. Overall response rates at end of induction as assessed by IRC were numerically higher in the G-benda arm than in the benda arm (69.1% G-benda vs. 63.0% benda). An updated overall survival (OS) analysis performed at a median observation time of 24M showed that 48 patients (28.1%) in the B arm and 30 patients (18.3%) in the G-benda arm had died (stratified HR for OS of 0.62 (95% CI:0.39, 0.98)). The PFS results in the updated analysis are consistent with the primary analysis and its significance is unchanged (median PFS in the updated analysis was 29.2 months (95% CI: 20.5, NE) in the G-benda arm, (13.8 months [95% CI: 11.5, 15.8])). The safety profile in the updated analysis is consistent with the primary analysis.

1.2.6 Clinical Safety of obinutuzumab

As of 04 July 2016 (the safety data cutoff date for all studies except MO28543), obinutuzumab has been administered to 36361 patients (see Table 19) comprising patients with CLL (1496) or NHL (2140), with doses of 50 mg to 2000 mg, as monotherapy or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), bendamustine, chlorambucil, fludarabine and cyclophosphamide (FC), cyclophosphamide, vincristine and prednisone (CVP) or atezolizumab (Atezo). The most frequent causes of death were disease progression and adverse events (AEs) describing infectious diseases. This is consistent with the study populations and diseases being treated. Overall, the safety of monotherapy obinutuzumab, or obinutuzumab combination therapy, was manageable.

Thrombocytopenia is very commonly seen with obinutuzumab. Acute thrombocytopenia has been described with mantle cell lymphoma being a histology described as a risk factor for this. Other risk factors include high tumor burden, bone marro winvolvment and splenomegaly.

1.2.7 Rationale for Clinical Development of the Combination of Venetoclax and Obinutuzumab

The triplet of obinutuzumab, bendamustine, and venetoclax has not been evaluated to date in MCL. Recently reported preliminary results in CLL identified a high ORR (100%) although therapy was limited by neutropenia and thrombocytopenia resulting in a median of 4 of 6 planned cycles of bendamustine being completed throughout the study. Additional studies are planned in follicular lymphoma (PrE0403) which will further describe the toxicities and potential benefits of this regimen in indolent NHL. In this study, we aim to evaluate the combination of obinutuzumab, bendamustine, and venetoclax in MCL using a target venetoclax dose of 400mg in an attempt to improve upon the historical CR rate for bendamustine-rituximab.

Both obinutuzumab and venetoclax show first-dose toxicity due to rapid cell killing, which requires special consideration related to the administration of the first dose. Venetoclax has been associated with laboratory and clinical TLS, and obinutuzumab has been associated with severe IRRs and, rarely, TLS. Such first-dose effects are familiar to oncologists, and intensive management measures have been incorporated into the combination studies, including prophylactic treatment to prevent or reduce the severity of effects, adjustment of initial dose and schedule, and careful monitoring.

1.2.8 Amendment delaying venetoclax initiation until cycle 1 day 8

In the cohort of the first 5 patients enrolled, there were found to be a high number of infusional toxicities related to obinutuzumab on the first two days of the first cycle. This included a case of cardiac arrhythmia in an elderly individual requiring hospitalization, from which she recovered without lasting morbidity from the arrhythmia and was able to continue study therapy. Although infusion reactions are common with obinutuzimab.. In order to minimize risk of future toxicities on days 1 and 2 of the first cycle and to limit the challenges associated with managing venetoclax treatment initiation concurrently, future patients will delay initiation of venetoclax to cycle 1 day 8.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE(S)

The primary objective will be to evaluate the efficacy of the combination of bendamustine, obinutuzumab and venetoclax in patients with untreated mantle cell lymphoma.

2.1.1 PRIMARY ENDPOINT

The primary endpoint is the rate of complete response at completion of induction therapy with this combination.

2.2 SECONDARY OBJECTIVE(S)

1) To evaluate the safety and dose intensity of the combination of bendamustine, obinutuzumab and venetoclax in untreated mantle cell lymphoma.

2) To explore methods of determining molecular remission for patients with untreated MCL.

3) To evaluate long-term outcomes including progression-free and overall survival for patients with untreated MCL who receive the combination.

2.2.1 SECONDARY ENDPOINTS

2.2.1.1 SECONDARY EFFICACY ENDPOINTS

- Rate of minimal residual disease negative complete response by ClonoSEQ MCL assay (in patients and institutions who have access to this assay)
- Overall response rate
- Time to tumor progression
- Progression free survival
- Overall survival

2.2.1.2 SECONDARY SAFETY ENDPOINTS

- Grade 3+ adverse events
- All grade adverse events
- Rate of treatment discontinuation and frequency of completion of study therapy
- Rate of maximum venetoclax dose achievement without clinical tumor lysis syndrome

2.2.1.3 OPTIONAL SECONDARY TRANSLATIONAL ENDPOINTS

- Rate of minimal residual disease negativity assessed by CAPP-SEQ at end of induction with BOV (in patients and institutions who have access to this assay)
- Rate of MRD positivity by CAPP-Seq at 3, 6, and 12 months prior to clinical relapse (in patients and institutions who have access to this assay

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a phase II, open-label, single-arm, non-randomized study of the combination of bendamustine, obinutuzumab and venetoclax in untreated mantle cell lymphoma. Patients will receive up to 6 cycles bendamustine, obinutuzumab and venetoclax delivered on a 28-day cycle. Therapy will be dosed as described in the Table 1 and Figure 1, with bendamustine administered on days 1 and 2 of each cycle; obinutuzumab administered weekly during cycle 1, then day 1 of cycles 2-6, and venetoclax administered daily during a dose escalation phase in cycle 1 days 8-28 followed by days 1-10 for each subsequent cycle.

Patients will receive supportive care with allopurinol TLS prophylaxis, and growth factor prophylaxis. Patients considered high-risk (as described in Appendix 7) for TLS will be admitted for initiation of therapy with cycle 1 as outlined in hospitalization procedures in section 5.2.3. Antimicrobial prophylaxis should be provided as per institutional protocol. Antiviral prophylaxis

with acyclovir and *Pneumocystis jirovecii (*PJP) prophylaxis are both required, and patients will also be monitored for CMV reactivation during and immediately after completion of therapy.

Table 1: BOV Dosing

Dosing Table (Patients with venetoclax initiation on C1D1 prior to amendment)

Cycle	Cycle 1						Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2					90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg	1000mg		1000mg			1000mg		
Venetoclax (Days administered)	20mg daily (D1-7)			50mg daily (D8-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg						6mg			6mg
Allopurinol**	300mg/daily during cycle 1						300mg daily through C2D7					
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs												
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1												

Dosing Table (Revised post-amendment dosing schedule with venetoclax start on C1D8)

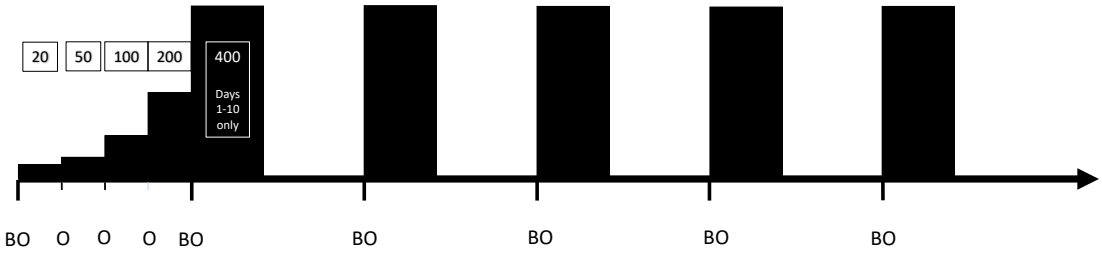
Cycle	Cycle 1							Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	11	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2						90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg		1000mg		1000mg			1000mg		
Venetoclax (Days administered)				20mg daily (D8-10)	50mg daily (D11-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg							6mg			6mg
Allopurinol**	300mg/daily during cycle 1							300mg daily through C2D7					
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs													
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1													

Dosing Table (Revised to include PJP prophylaxis recommendations)

Cycle	Cycle 1							Cycle 2			Cycles 3-6		
Day	1	2	3 or 4	8	11	15	22	1	2	3 or 4	1	2	3 or 4
Bendamustine	90mg/m2	90mg/m2						90mg/m2	90mg/m2		90mg/m2	90mg/2	
Obinutuzumab*	1000mg			1000mg		1000mg		1000mg			1000mg		
Venetoclax (Days administered)				20mg daily (D8-10)	50mg daily (D11-14)	100mg daily (D15-21)	200mg daily (D22-28)	400mg (D1-10 only)			400mg (D1-10 only)		
Pegfilgrastim			6mg							6mg			6mg
Allopurinol**	300mg/daily during cycle 1							300mg daily through C2D7					
Antiviral and PJP ppx***	Required during therapy. Suggested continuation until immune reconstitution (eg CD4 >200 or ALC >1000)												
*Obinutuzumab may be given as split dosing over a 2-day period if needed for infusion reactions of logistical needs													
**Allopurinol should be started at least 3 days prior to Cycle 1 Day 1													
***Antiviral and PJP ppx per institutional protocol. If patients are to receive trimethoprim-sulfamethoxazole, this may be deferred to the beginning of cycle 2 in order to limit the risk of dermatologic complications associated with allopurinol and bendamustine. All patients should receive some form of PJP prophylaxis no later than Cycle 2, Day 8.													

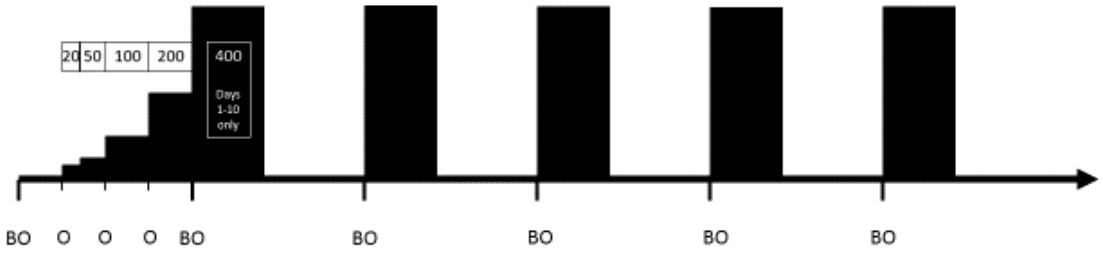
Figure 1: Dosing schema

Study Schema (First patient cohort with venetoclax initiation on C1D1 prior to amendment)



B: Bendamustine 90mg/m2 on days 1 & 2
O: Obinutuzumab 1000mg
--Cycle 1: Days 1, 8 and 15
--Cycles 2 – 6: Day 1 only
Venetoclax
--Ramp up dosing over 28 days in C1
--400mg D1-10 on C2-6

Study Schema (Revised post-amendment dosing schedule with venetoclax start on C1D8; Accrued after Version 2.0 activation)



B: Bendamustine 90mg/m2 on days 1 & 2
O: Obinutuzumab 1000mg
--Cycle 1: Days 1, 8 and 15
--Cycles 2 – 6: Day 1 only
Venetoclax

- Ramp up dosing over 21 days in C1
  - Days 1-7: No venetoclax administered
  - Days 8-10: Venetoclax 20mg
  - Days 11-14: Venetoclax 50mg
  - Days 15-21: Venetoclax 100mg
  - Days 22-28: Venetoclax 200mg
- 400mg D1-10 on C2-6

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date 5 years after the last patient completes the therapy completion evaluation that occurs 45-60 days after cycle 6. However, no treatment will be administered after cycle 6, and subsequent follow-ups will be completed solely for the purposes of determining duration of response, progression-free, and overall survival. The primary endpoint will be calculated and reported after the final patient completes their end of treatment evaluation. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2.5 years (30 months) for the primary endpoint, but 7 years for study close-out to allow for survival analysis.

3.3 RATIONALE FOR STUDY DESIGN

Bendamustine and rituximab is a current standard of care for patients with newly diagnosed mantle cell lymphoma who are not eligible for high-intensity cytarabine containing induction and consolidative ASCT. However, the combination of BR provides a mPFS of less than 3 years, and maintenance rituximab may not be beneficial in this subset of patients. We seek to improve on the bendamustine based backbone by using the Type II anti-CD20 monoclonal antibody obinutuzumab in place of rituximab, and add the BCL-2 targeting agent venetoclax to the regimen.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability and willingness to comply with the requirements of the study protocol
- Age $\geq$ 18 years
- Histologic diagnosis of mantle cell lymphoma. This diagnosis must be confirmed at the treating center and patients must have this diagnosis confirmed by at least one of the following criteria:
    - A) FISH or conventional cytogenetics positive for t(11;14)
    - B) Cyclin D1 positive by immunohistochemistry
    - C) Documentation by a hematopathologist at the treating institution that there is pathologic evidence of mantle cell lymphoma if neither criteria above are met
- No previous therapy for diagnosis of lymphoma *(note that in patients deemed to be high-risk for tumor lysis syndrome or for rapid clinical deterioration due to symptomatic disease by the investigator, a short course of steroids designed to decrease tumor burden is permitted).*
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Adequate hematologic function (unless caused by underlying disease, as established by bone marrow involvement or as a result of hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:

    Hemoglobin ≥ 9 g/dL

    Absolute neutrophil count $\geq 1.5 \times 10^9$/L

    Platelet count $\geq 75 \times 10^9$/L

- Adequate renal and liver function, as indicated by:

    Serum creatinine $\leq$2.0 mg/dL or creatinine clearance $\geq$ 40mL/min.

    AST or ALT $\leq 2.5 \times$ ULN

    Total bilirubin $< 1.5 \times$ ULN (or $\leq 3 \times$ ULN for patients with documented Gilbert syndrome)

    NOTE: Patients with renal or hepatic impairment that is disease-related (ie, hydronephrosis, hepatic involvement) in the opinion of the investigator but who meet all other eligibility criteria may be considered for enrollment in consultation with the study chair and consideration of the impact of such impairment on risk for TLS. Documentation of prior adequate renal/hepatic function and clear association with the disease will be required.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<$ 1% per year

during the treatment period and for at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of other malignancy that could affect compliance with the protocol or interpretation of results

  Patients with a history of curatively treated basal or squamous cell carcinoma or Stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible.

  Individuals in documented remission without treatment for ≥ 2 years prior to enrollment may be included at the discretion of the investigator. Patients with more recently treated low risk prostate cancer, thyroid cancer, or DCIS who are felt to be at low risk for progression and who are not currently taking any chemotherapy, hormonal therapy or other anti-cancer therapy are eligible. Patients who have been treated and been in remission for < 2 years must be cleared with the study chair prior to initiating study therapy.

- 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, including renal disease that would preclude chemotherapy administration.
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment.
- Requires the use of warfarin (because of potential drug-drug interactions that may potentially increase the exposure of warfarin)
- Received strong or moderate CYP3A inhibitors or inducers within 7 days of initiating venetoclax. Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to first dose of venetoclax.
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of a positive/detectable CMV pcr. This is a screening criterion and *any* result other than "undetectable" would be an exclusion criterion.
- Presence of positive test results for hepatitis B virus (HBV), hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) antibody

  Patients who are positive for HCV antibody must be negative for HCV RNA by polymerase chain reaction (PCR) to be eligible for study participation

  Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing and to remain on Hepatitis B prophylaxis during therapy.
- Patients with HIV are eligible if they have a CD4 Count > 400 and an undetectable viral load. They must be under the care of an infectious disease physician and have no history of an AIDS-defining illness (except lymphoma).
- Receipt of live-virus vaccines within 28 days prior to the initiation of study treatment or need for live-virus vaccines at any time during study treatment
- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 21 days prior to initiation of study drug.
- Recent major surgery (within 6 weeks prior to the start of Cycle 1, Day 1) other than for diagnosis or line placement.
- Malabsorption syndrome or other condition that precludes enteral route of administration, including inability to swallow a large number of tablets
- Known allergy to both xanthine oxidase inhibitors (ie, allopurinol) and rasburicase
- Known hypersensitivity to any of the study medications or to any of their excipients. Note: Patients previously exposed to a CD20-directed monoclonal antibody who experienced an infusion reaction but were subsequently able to complete the infusion with supportive care would be eligible if deemed appropriate by the treating investigator.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a phase II, open-label, single-arm, non-randomized study of the combination of bendamustine, obinutuzumab and venetoclax in untreated mantle cell lymphoma. Enrolled patients with untreated MCL will receive induction therapy with the regimen as detailed. There will be no blinding, randomization, or cohort assignment.

4.2.1 Registration of Patients at Collaborating Sites.

Participating site(s): After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form.

Registration: Participating site(s): The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator (MSC) or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days from scheduled treatment visit. Eligibility will be confirmed by the site investigator co-investigator and the MSC or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria.

OnCore: The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and assigned dose cohort. All data must be entered no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The MSC will provide OnCore training and request access to the appropriate staff at the participating sites.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are venetoclax and obinutuzumab. Bendamustine will be administered as a standard of care medication per institutional guidelines.

Induction with bendamustine, obinutuzumab and venetoclax will be administered as follows. Criteria for dose delay, modification, and de-escalation will be detailed in Sections 5.2 – Section 5.6.

4.3.1 Bendamustine

90mg/m2 IV as described by package insert on days 1 and 2 of each cycle. This will be given after venetoclax oral dosing, and before obinutuzumab dosing (if obinutuzumab scheduled for that day). The specific formulation of bendamustine administered (Bendeka, Treanda, or other formulation) will be determined by the institutional practice and formulary.

4.3.2 Obinutuzumab

Dosing will be administered per package insert:

- Cycle 1: 1000mg will be administered on days 1, 8, and 15 for cycle 1. Split dosing may be used as detailed below.

    - If the circulating lymphocyte count is above the normal reference range for the laboratory, it is recommended that cycle 1 obinutuzumab be administered at 100mg on day 1 and 900mg on day 2 in order to reduce the risk of an infusion reaction.

- Cycles 2 – 6: 1000mg will be administered only on day 1 of each cycle (unless split dosing used as detailed below).

- Patients with high circulating lymphocyte count as detailed above should be considered for split dosing with 100mg on Cycle 1, day 1 and 900mg on cycle 1, day 2. In all other circumstances, the dose may be split if needed for medical and/or logistic reasons with the dosing for each day determined by the needs of the patient and available time. However, at the conclusion of day 2, no further obinutuzumab may be administered and every attempt should be made to give the full dose within the two days.

- Patients may be premedicated with glucocorticoid, acetaminophen, and anti-histamine at the preference of the investigator in accordance with the package insert and/or institutional guidelines/practice.

4.3.3 Venetoclax

Venetoclax will be dose escalated as follows:

- Cycle 1: Dose escalated from 20mg to 200mg over 21 days as follows (See Table 1):
    - Days 1- 7: No venetoclax to be administered
    - Days 8-10: 20mg/day
    - Days 11-14: 50mg/day
    - Days 15-21: 100mg/day
    - Days 22-28: 200mg/day
- During cycles 2 – 6, Venetoclax will be dosed at 400mg/day on days 1 – 10 only
- NOTE: Patients who experience delays in venetoclax dose escalation for any reason may continue dose escalation through cycle 2, day 28 as needed. NO further dose escalation shall occur after the conclusion of cycle 2, and patients shall receive venetoclax on days 1-10 on cycles 3-6 at the maximum dose achieved and tolerated during dose escalation through the end of cycle 2.

Note for the first cohort of patients prior to the amendment delaying venetoclax initiation until day 8, the following dosing escalation was used:

- Cycle 1: Dose escalated from 20mg to 200mg over 21 days as follows (See Table 1):
    - Days 1- 7: 20mg/day
    - Days 8-14: 50mg/day
    - Days 15-21: 100mg/day
    - Days 22-28: 200mg/day

During cycles 2 – 6, Venetoclax will be dosed at 400mg/day on days 1 – 10 only.

4.3.4 Supportive Care Medications

Allopurinol 300mg/day should be started at least 3 days prior to cycle 1 day 1 and continued until cycle 2 day 7. Patients with an allergy to allopurinol should receive an alternative TLS prophylaxis regimen such as febuxostat or rasburicase. Growth-factor will be administered within 72 hours of the completion of bendamustine at the beginning of each cycle. Pegfilgrastim administered by single injection or by self-injecting device (OnPro) will be acceptable.

Patients considered high-risk for TLS will be admitted the day/evening prior to cycle 1 day 8 for hydration and TLS management. Definition of risk level for TLS and hospitalization is detailed in the safety protocols in section 5.2.2.

Antimicrobial prophylaxis should be provided as per institutional protocol. Antiviral prophylaxis with acyclovir and *Pneumocystis jirovecii* (PJP) prophylaxis should be utilized. Patients may complete the prophylaxis per their institutional standards. If patients are to receive trimethoprim-sulfamethoxazole, this *may* be deferred to the beginning of cycle 2 in order to limit the risk of dermatologic complications associated with allopurinol and bendamustine. All patients should receive some form of PJP prophylaxis no later than Cycle 2, Day 8.

Prior to proceeding with the next dose escalation or next cycle, safety criteria must be met. Criteria for proceeding with treatment will differ between cycle 1 (dose escalation cycle) vs cycles 2-6 (flat dose cycles), as detailed in section 5.6.

4.3.5 Formulation, Packaging, and Handling

4.3.5.1 Venetoclax

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. The tablets must be stored at 15°C–25°C (59°F–77°F). If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal.

For details regarding venetoclax formulation, see the Venetoclax IB.

Venetoclax will be provided to the patient at the beginning of each cycle, with the exception of cycle 1, where patients will receive enough treatment for one dose level at a time due to the planned dose escalation. Patients will be required to return the pill bottle and any remaining pills to the study team at each planned study visit so that dosing and compliance can be monitored. Patients will be provided with a pill diary to document compliance with this medication.

4.3.5.2 Obinutuzumab

Obinutuzumab is provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50-mL glass vials containing 40 mL of the 25-mg/mL liquid

concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water (HPW). HPW meets the specified limits of HPW according to Pharm. Eur. and for water for injections (WFI) according to USP.

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For further instructions as well as information on in-use stability, see the packaging label.

For details regarding obinutuzumab formulation, see the Obinutuzumab IB.

4.3.5.3 Bendamustine

Bendamustine may be used as either the Treanda or Bendeka formulations per institutional formulary. It should be stored, handled, and administered per package insert. For details regarding bendamustine formulation, see the bendamustine package insert.

Bendamustine will be obtained commercially for each patient and will not be provided by the study.

4.3.6 Dosage, Administration, and Compliance

4.3.6.1 Venetoclax

The target dose of venetoclax in MCL for this protocol is 400mg/day. Venetoclax will dose escalated from 20mg to 200mg over 21 days (was originally 28 days prior to amendment) during the first cycle in order to decrease the risk of tumor lysis syndrome and evaluate toxicities at several dose levels. During cycles 2 – 6, venetoclax will be dosed on days 1 – 10 only with a planned dose of 400mg/day for patients who are able to tolerate full dose therapy (Note the only exception would be patients who experience a delay for any reason in dose escalation of venetoclax who *may* continue dose escalation per the guidelines through the completion of cycle 2. No dose escalation shall occur prior to the conclusion of cycle 2 and patients will receive the maximum dose achieved and tolerated for cycles 3-6).

Risk assessment for tumor lysis and hospitalization procedures for high-risk patients are described in section 5.2 and appendix 7.

Guidelines for venetoclax dosage modification and treatment interruption or discontinuation are provided in sections 5.2 – 5.6.

Venetoclax Administration

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.

On days when venetoclax is given with additional agents, venetoclax should be given first. When patients are returning to the clinic for a study-specified follow-up appointment, venetoclax should not be taken until they have been evaluated by the study team.

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.

All doses, including those taken as prescribed, missed/forgotten, vomited, or otherwise consumed should be documented in the pill diary which will be reviewed by study staff at study-specified visits.

All patients must receive prophylaxis for TLS prior to the initiation of venetoclax.

Any overdose or incorrect administration of study drug should be noted in the medical chart. Adverse events associated with an overdose or incorrect administration of study drug should be reported.

4.3.6.2 Obinutuzumab

Both 1000mg/day single day dosing, as well as 2-day-split dosing will be allowed (if needed due to disease burden, infusion reactions or logistical needs). Dosing will be administered per package insert.

Premedication to reduce the risk of IRRs is outlined below.

Hypotension may occur during obinutuzumab IV infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion, and for the first hour after administration.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Tables 3-4.

Any overdose or incorrect administration of study drug should be noted in the medical chart. Adverse events associated with an overdose or incorrect administration of study drug should be reported.

4.3.6.3 Bendamustine

Bendamustine may be used as either the Treanda or Bendeka formulations per institutional formulary. It will be dosed at 90mg/m^2 on days 1 and 2 of each cycle.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards. Pegfilgrastim will be administered at the beginning of each cycle within 72 hours of completion of bendamustine. Although pegfilgrastim is preferred, patients may receive filgrastim if required due to hospitalization (i.e., during cycle 1) or other reason which prevents use of pegfilgrastim. In this case, filgrastim should be administered as directed by the patient's treating physician and its use should be documented. Patients who do not received required growth factor and subsequently develop a complication related to neutropenia may be treated with growth factor as clinically indicated.

Antiemetic therapy may be instituted for any patient if clinically indicated. It is recommended that chemotherapy infusions be administered following premedication with a serotonin (5-HT3) antagonist (i.e., dolasteron, ondansetron, etc.) or per institutional practice.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment or at any time during study treatment. Systemic steroid therapy should not be administered while on study. However, short-course (less than 4 days per cycle) steroids given for anti-emetic purposes, inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease, single infusions of hydrocortisone prior to obinutuzumab infusions (for hypersensitivity reactions), topical steroids, or replacement corticosteroid therapy for an inherited or acquired deficiency are permitted. Patients may have received a brief (< 7 days) course of systemic steroids (≤ 100 mg/day prednisone equivalent) prior to initiation of study therapy for control of lymphoma-related symptoms.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Insulin and levothyroxine are both permitted to manage chronic conditions.

Central Nervous System Prophylaxis

CNS prophylaxis with intrathecal chemotherapy may be given according to institutional practice and its use documented. CNS prophylaxis with systemic chemotherapy is not allowed during this study.

Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and hepatitis B core antibody (anti-HBc) positive may be included in studies with venetoclax. 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. Patients who have a positive Hepatitis B Core antibody but no evidence of active disease, including a negative Hepatitis B surface antigen and undetectable HBV DNA should receive prophylaxis against hepatitis B reactivation as close to the beginning of therapy as possible and this should continue for at least 6 months after completion of study therapy.

If the HBV DNA assay becomes positive and is above the World Health Organization's 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 patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, treatment with immunochemotherapy must be permanently discontinued.

Monitoring of CMV Reactivation

All patients should be screened at study entry for CMV viremia using pcr. CMV PCR should then be checked on day 1 of cycles 2, 4, and 6, and at the end of study visit. Any patient experiencing CMV reactivation should be treated appropriately and will be removed from study therapy.

4.4.2 Excluded Therapy

Patients who require the use of any of the excluded therapies listed below will be discontinued from study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of venetoclax (or 90 days following the patient's last dose of obinutuzumab, whichever is later) or until the patient receives another anti-cancer therapy, whichever occurs first.

Use of the following therapies is prohibited during the study:

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

The following concomitant medications are not allowed from 7 days prior to the first dose of study drugs and during venetoclax ramp-up. If any of these therapies are required after achieving the full venetoclax dose, they should be administered with caution and a dose reduction of venetoclax (See US Package Insert) should be considered in collaboration with the study chair:

- Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids. Steroids may be used as needed prior

to initiation of study therapy with no required washout for patients at risk of rapid clinical deterioration.

- Strong or moderate CYP3A4 or P-gp inhibitors such as fluconazole, ketoconazole, and clarithromycin. Note: P-gp substrates with a narrow therapeutic index should be avoided.
- Strong or moderate CYP3A4 inducers such as rifampin and carbamazepine

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:

- Moderate/weak CYP3A inducers such as efavirenz and oxcarbazepine
- 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.

A sample list of excluded medications and cautionary medications that fall into the categories within this section can be found in Appendix 8. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

4.5 STUDY ASSESSMENTS

4.5.1 Clinical and Laboratory Evaluations

Clinical and laboratory evaluations will occur as outlined in Table 2 with details of each test outlined in this section.

Table 2: Clinical and laboratory evaluations

Version 1.0 - See next page for updated table that includes CMV monitoring

			CYCLE 1								CYCLE 2			CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X				
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1[#]	X				
Clonoseq MRD monitoring (Optional)	X[@]														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X[$]														X[$$]				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X

*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine

**Hematology/Chemistry: CBC with differential, Platelets, CMP

***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen

~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures

^Lab checked twice during a given day, with at least 6 hours between blood draws.

[#]C5D1 PET/CT may be performed up to 7 days prior to C5D1

[$]Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy

[$$]Therapy Completion BMBx/Aspirate only required if screening BMBx was positive

[@]Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up

Table of Assessments (Revised to Include CMV monitoring recommendations)

			CYCLE 1								CYCLE 2			CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X				
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1[#]	X				
Clonoseq MRD monitoring (Optional)	X[@]														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
CMV viremia by PCR	X										X			C4D1, C6D1	X				
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X[$]														X[$$]				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X

*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine

**Hematology/Chemistry: CBC with differential, Platelets, CMP

***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen

~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures

^Lab checked twice during a given day, with at least 6 hours between blood draws.

[#]C5D1 PET/CT may be performed up to 7 days prior to C5D1

[$]Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy

[$$]Therapy Completion BMBx/Aspirate only required if screening BMBx was positive

[@]Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up

See Appendix 1 for larger table format

For patients who cannot undergo imaging with PET, alternate imaging with MRI is acceptable. Any non-PET, non-MRI imaging must be discussed with the principle investigator.

Cardiac evaluation with MUGA or echocardiogram is not required, but should be considered in patients with a history of heart failure or other cardiac pathology.

4.5.1.1 Minimal Residual Disease Monitoring (Optional)

Minimal residual disease will be measured with the Clonoseq assay for description of MRD negativity. Samples should be collected for Clonoseq if able but may not be feasible at all sites. Additionally, the CAPP-Seq peripheral blood circulating tumor DNA samples will be collected at the same time as the Clonoseq assay. Details regarding the collection and processing of CAPP-Seq specimens are detailed in Appendix 9.

Optimally, the CAPP-Seq correlative specimens will consist of 3 separate types of patient samples:

1) Patient plasma cell free DNA, obtained from plasma samples.
2) Patient germline DNA, obtained from plasma depleted whole blood
3) Patient tumor DNA, obtained from archived FFPE samples, fresh tumor biopsies from the time of enrollment in study, or tumor DNA provided by the treating institution

While 1 & 2 above (plasma cell free DNA and germline DNA from peripheral blood) are strongly encouraged, sample 3 is not required if there is not enough tissue available from diagnosis.

CAPP-Seq samples are intended to be collected on all patients enrolled on the study for correlative analysis. However, an institution is not able to participate in the CAPP-Seq correlative studies, they may forgo CAPP-Seq sample collection, and proceed with the protocol, including commercially available Clonoseq MRD monitoring.

4.5.1.2 Tumor Lysis Monitoring

For low risk patients (procedures for high-risk patients is outlined in section 5.2.2), outpatient tumor lysis testing should occur as follows, with respect to venetoclax dosing:

Cycle 1 first dose:

- Within 7 days prior to cycle 1 day 8
- 0-2 hours pre-dose (on morning of cycle 1 day 8)
- 6-8 hours post-dose (prior to leaving infusion center on day 8)
- 18-28 hours post-dose (cycle 1 day 9)

Cycle 1 dose escalations (days 11, 15, 22) and Cycle 2 Day 1:

- Pre-dose
- 6-8 hours post-dose

Cycles 3 – 6: Days 1 and 2 prior to bendamustine

On days of planned dose escalation during cycle 1, and on day 1 of all subsequent cycles, the treating investigator must document review of TLS labs, chemistry, hematologic labs, and, if applicable, pregnancy test, prior to administration of study therapy. This should occur even on days when a study visit/physical exam is not required.

4.5.2 Windows for Study Assessments:

- All screening procedures to establish eligibility must occur within 30 days of cycle 1, day 1.
- Screening BMBx/Aspirate does not have to be completed if they have previously documented involvement OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy
- There is no permitted treatment "window" for cycle 1 days 1 and 2. Patients may not initiate therapy if they are unable to be evaluated per study on days 1 and 2. Patients may not receive bendamustine or obinutuzumab on day 3 or afterwards.
- Study procedures and administration of study therapy for cycle 1, days 8, 11, 15, and 22 may occur +/- 1 day from the designated day. For dose levels 20mg at day 8 and 50mg at day 11, the patient must have received at least 3 doses prior to increasing to the subsequent dose level. For dose levels 100mg at day 15 and 200mg at day 22, patients must receive AT LEAST 5 doses of venetoclax at one dose level prior to increasing to another dose level.
- Cycle 2, Day 1 may occur +/- 1 day from the designated day, but cycle 2, day 2 MUST occur on the calendar day following cycle 2, day 1. *Note that if there is a venetoclax ramp-up delay due to holding for toxicity during cycle 1, C2D1 may be at a lower venetoclax dose, but*

bendamustine and obinutuzumab should still be administered as scheduled.

- If a patient receives day 1 of therapy for any cycle and is unable to receive day 2 for any reason (toxicity, non-compliance, holiday, etc) the day 2 dose will be skipped and they will proceed with remaining study therapy as scheduled assuming it is safe to do so.
- Additional study-specified on therapy visits (Cycle 2, day 15, and C3-6, Day 1) may occur +/- 5 days from the designated day.
- The post-treatment visit shall occur between 45-60 days after cycle 1, day 1.
- Subsequent follow-up visits may occur +/- 28 calendar days from the designated day but every event should be made to try to complete the scheduled follow-up as close to the designated day as possible.

4.5.3 Evaluation of Response

Response assessment in all patients will consist of PET/CT imaging and peripheral blood minimal residual disease (MRD) monitoring. If the bone marrow was involved at diagnosis, it will be assessed at completion of 6 cycles of induction therapy.

Response assessment will occur at the following times:

1. Cycle 5, Day 1: PET/CT imaging. PET/CT may be performed up to 7 days prior to C5D1.
2. Post-treatment eval: PET/CT imaging and MRD. Marrow assessment if involved at diagnosis. Post-treatment staging evaluation should occur between 45 and 60 days after cycle 6, day 1.

MRD will be assessed by peripheral blood using the Clonoseq assay available by Adaptive Biotechnologies when able. It is acceptable to store samples if needed for future Clonoseq assessment if the assay is not able to be completed in real time. In addition, if a site is unable to collect samples due to institutional or other restrictions, it is acceptable to forego some or all of the MRD assessment. Patients who develop symptomatic progressive disease at any time (not including by MRD assessment) and those who have PD that is felt to be clinically significant will be removed from study therapy. Patients with radiographic PD after cycle 4 will be removed from study therapy.

There will be no study required imaging assessments after the completion of the post-treatment study visit. Imaging shall be completed per standard of care at the discretion of the treating investigator.

4.6 PATIENT, TREATMENT, AND STUDY DISCONTINUATION

4.6.1 Patient Discontinuation

Patients who meet the following criteria should be discontinued from the study:

- Symptomatic or clinically significant disease progression. Patients with asymptomatic progressive disease who are felt to be clinically benefitting from the treatment may continue therapy.
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Tumor Lysis Syndrome that prevents administration of venetoclax despite appropriate supportive care measures
- Patient withdrawal of consent at any time
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient noncompliance
- Pregnancy
- Investigator determines it is in the best interest of the patient
- Determination by the investigator that it is no longer safe for the patient to continue therapy

4.6.2 Study Discontinuation

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- The pharmaceutical company decides to stop development of study drug

5. SAFETY PLAN

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events, including all events of death, pregnancy, and any study-specific issue of concern.

The safety plan for obinutuzumab is based on clinical experience in completed and ongoing clinical studies and from postmarketing experience. Please refer to the obinutuzumab USPI and IB for a complete summary of safety information.

The safety plan for venetoclax is based on clinical experience in completed and ongoing studies. The anticipated important safety risks for venetoclax are outlined below. Please refer to the Venetoclax USPI and IB for a complete summary of safety information.

In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1 RISKS ASSOCIATED WITH THE COMBINATION OF VENETOCLAX AND OBINUTUZUMAB

Based on nonclinical and clinical findings, the potential overlapping toxicities include B-cell depletion, neutropenia, and TLS. Given that venetoclax and obinutuzumab target different B-cell subsets and result in an additive pharmacological effect in disease models when combined, it is possible that the rapid, marked depletion of B cells (and total lymphocytes for venetoclax) could lead to increased cases of TLS and infection, and that full reversibility of normal B cells may require a prolonged period without treatment. Additional risks on this protocol include infusion

related reactions (most common with Gazyva), thrombocytopenia (including acute thrombocytopenia), infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions and GI perforation. See the Obinutuzumab and Venetoclax IB for additional details.

5.2 TUMOR LYSIS SYNDROME PREVENTION AND MANAGEMENT

TLS is a risk for patients with MCL who are treated with high cell-killing agents, including venetoclax. 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 venetoclax. 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 PET/CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing clinically significant chemistry abnormalities prior to initiation of treatment with venetoclax.

All patients must receive prophylaxis for TLS before the initiation of the first dose of venetoclax. Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours before the start of treatment
- Allopurinol 300 mg/day orally beginning 3 days prior to C1D1 and continued through C2D7 (or 7 days after last venetoclax dose increase, whichever is later). Patients with an allergy to allopurinol should receive an alternative TLS prophylaxis regimen such as febuxostat. Rasburicase IV (for those high risk patients with elevated uric acid levels before treatment) may be given as judged to be appropriate by the investigator. Allopurinol may be held for up to 1 day prior through 1 day after bendamustine infusion at the investigator's discretion if concerned for acute skin reactions such as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.
- Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration before the initiation of dosing.

Per the Cairo-Bishop definition, Laboratory Tumor Lysis Syndrome is defined as having ≥2 of the following criteria within 24 hours:

- Potassium > 6mmol/L
- Uric acid > 8gm/dL
- Phosphorus > 4.5 mg/dL
- Corrected Calcium < 7mg/dL

Clinical Tumor Lysis Syndrome is defined as Laboratory Tumor Lysis Syndrome PLUS one or more of the following thought to be attributable treatment:

- Increased serum creatinine of 0.3mg/dL attributed to elevated uric acid
- Cardiac arrhythmia/sudden death attributed to hyperkalemia or hypercalcemia
- Seizure, neuromuscular irritability, hypotension, or heart failure attributed to hypocalcemia

Patient TLS lab samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly (prior to any dosing for that day, if applicable). Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Prior to administration of C1D1 therapy, the first set of C1D1 pre-dose TLS labs must have resulted and been reviewed by the investigator with no evidence of TLS as defined above. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 6: (Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome).

If TLS is observed in a patient, they will subsequently be admitted for all future dose escalations until they have tolerated a dose escalation without clinically significant TLS.

5.2.1 Management of Tumor Lysis Syndrome

The following algorithm will be utilized for management of laboratory or clinical TLS ONLY. Management of non-TLS toxicities is described in section 5.5 for non-hematologic toxicities, and section 5.6 for hematologic toxicities..

1. 1st occurrence of laboratory TLS at a given dose level: Patient will hold venetoclax until resolution of TLS. If this occurs within 48 hours, the patient may resume venetoclax at the same dose level. They MUST receive a total of at least 5 doses before escalating to the next dose level. If TLS occurs at the 20mg level (where 3 doses are planned per protocol) or the 50mg level (where 4 doses are planned per protocol), then those dose levels will be extended to 5 days as well before escalating to the next dose. If this results in a delay in the uptitration schedule to the next dose, all doses uptitrations will be delayed so that there will be at least 5 and no more than 7 venetoclax doses at each dose level prior to full dosing at 400mg. *This may result in cycle 2 day 1 venetoclax dosing being less than 400mg, but patients should still receive bendamustine and obinutuzumab on cycle 2 day 1 (eg C2D1 consists of bendamustine and obinutuzumab as scheduled with a venetoclax dose of 200mg)*. Patients developing clinical or laboratory TLS must receive and tolerate venetoclax for at least the three consecutive days without subsequent tumor lysis (and five total days of treatment at a dose level) at a given dose level preceding dose escalation.

2. 2nd occurrence at the same dose, failure to resolve within 48 hours, or *clinical* TLS: Patients receiving 20mg will be removed from study therapy and will not receive further venetoclax. Patients who are at a higher dose level may, at the discretion of the treating investigator in collaboration with the study chair, resume venetoclax at the next lower dose level (see table below) after resolution of TLS. If the patient tolerates venetoclax at the lower dose level for at least 5 days, they can resume dose escalation per protocol. In this case, patients would require hospitalization for each dose increase and would require TLS monitoring per protocol for each dose increase. Patients who experience a second episode of TLS after re-escalation, must follow the prescribed procedures for holding of venetoclax and management of laboratory and clinical abnormalities. Upon recovery, the patient may, if deemed to be clinically benefitting, resume venetoclax therapy at the highest tolerated dose that does not cause TLS, and may administer venetoclax at that dose on days 1-10 of all subsequent cycles. If dose re-escalation is tolerated, patients may escalate to the next highest dose after at least 5 consecutive days of venetoclax, with a maximum dose of 400mg.

   Note: If TLS or other toxicity results in a delay of dose escalation during cycle 1, the patient may continue dose escalation as indicated into cycle 2, taking at least 5 consecutive days of venetoclax prior to each successive dose increase up to a maximum of 400mg. During cycle 2, the patient should discontinue venetoclax after the day 10 dose or after 7 days of venetoclax 400mg/day, whichever occurs later.

   No venetoclax dose escalation shall occur after cycle 2, regardless of the reason for delay (ie, TLS or other toxicity). The dose determined to be safe for the patient after cycle 2 shall be the dose utilized for the remainder of the trial.

These rules will apply to all patients initiating therapy as well as patients who are starting a new dose.

Any patients that cannot proceed with treatment as outlined above will be removed from the study.

Venetoclax dose levels for TLS associated toxicity

Dose Level	***Venetoclax dose***
Level 1 (Initial dose)	20mg daily
Level 2	50mg daily
Level 3	100mg daily

Level 4	200mg daily
Level 5 (Target Dose)	400mg daily

5.2.2 Guidelines for Hospitalization Due to TLS Risk

Patients exhibiting specific characteristics at screening or initiation of venetoclax treatment are considered to be at high risk of developing TLS and must be hospitalized for more intensive prophylaxis and monitoring for the initial dose of venetoclax at 20mg through the dose escalation at 50mg. These patients are identified by the presence of any of the following:

- Any lymph mass ≥ 10 cm on the screening CT scan
- ALC ≥ $25x10^9$/L AND any lymph mass ≥ 5cm

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include, but are not limited to, the following:

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Compromised renal function, creatinine clearance < 80 mL/min
- Extensive bone marrow involvement
- Dehydration or concern about patients inability to meet oral hydration requirements (approximately 2–3 L/day starting 24–48 hours before the start of treatment, with continued intake during therapy)

Hospitalization is not mandatory for patients exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the patient's state and their risk of TLS. Investigators should use their judgment in assessing TLS risk for their patients and may optionally hospitalize any patient they consider to be at risk for TLS for the first dose of venetoclax.

5.2.3 Hospitalization Procedures

For patients requiring hospitalization, hospitalization will begin the evening before the first dose of venetoclax and continue for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of 150–200 cc/hr or as clinically appropriate. Patients who have already had a hematology and chemistry obtained as an outpatient on the day of admission do not require repeat labs as long as there are no clinically significant abnormalities that need to be addressed. Laboratory results should be reviewed, and electrolyte values should not demonstrate clinically significant abnormalities before the first dose of venetoclax; otherwise, the patient should receive additional prophylactic treatment and hydration before the initiation of dosing. Dosing should not be initiated until the laboratory abnormalities resolve. Telemetry should also be considered.

Serial vital signs and TLS laboratory samples will be drawn on the following schedule:

- Less than 4 hours pre-dose (on morning of cycle 1 day 8)
- 3 - 4 hours post-dose
- 7 - 8 hours post-dose
- 10 - 12 hours post-dose
- 20 - 24 hours post dose

These samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour post-dose must be reviewed before receiving the dose of venetoclax for that day and before the patient is discharged. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 6 (Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome).

5.3 NEUTROPENIA AND SERIOUS INFECTIONS

Neutropenia is an important identified risk for venetoclax and bendamustine. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Tables 3 & 4. Granulocyte colony stimulating factors are mandatory as part of this protocol.

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 CMV reactivations, have been reported in patients treated with venetoclax in combination with other agents, including obinutuzumab. Any patient experiencing detectable CMV viremia will be removed from study therapy.

It is required that patients receive prophylaxis against pneumocystis jiroveci pneumonia as well as antiviral prophylaxis per institutional guidelines, unless contraindicated and discussed with

primary investigator. PJP prophylaxis may be initiated during cycle 2. Additional anti-infective prophylaxis (i.e, bacteria and fungus) are permitted per investigator discretion but not required.

Management of Infections

Toxicities such as infection seen in venetoclax studies are detailed above. The following guidance is provided for infections that occur during the study:

- Patients with uncontrolled systemic infection are excluded from the trial.
- Blood counts should be closely monitored for evidence of infection throughout the trial.
- All patients should be monitored closely for infection and treated aggressively according to institutional guidelines, including growth factor and transfusion support. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion and per institutional protocol. Antiviral and PJP prophylaxis are required as detailed in the dosing tables. Antibacterial and antifungal prophylaxis are at the discretion of the investigator.
- If Grade 3−4 (CTCAE v4) infection occurs, treatment (any or all study treatments) must be held and may be delayed for a maximum of 4 weeks after last dose, regardless of presence or absence of neutropenia. Patients with grade 2 infection may have study therapy held at the discretion of the investigator. If the infection has not resolved after 3 weeks, study treatment must be discontinued.
- Patients should be advised to report fever and signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.

5.4 DOSE MODIFICATIONS TO REDUCE RISK OF ADVERSE EVENTS

Sample guidelines for non-hematologic toxicity are in section 5.5. Guidelines for hematologic toxicity associated with dose delay and modification of venetoclax are in section 5.6. These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Dose delays and dose modifications as a result of adverse events not specified should proceed on the basis of the principle of maintaining the dose intensity of immunochemotherapy. The determination of all dose and schedule modifications will be made on the basis of the investigator’s assessment of ongoing clinical benefit with continuing study treatment.

No dose modifications of obinutuzumab are allowed. If a patient is unable to tolerate obinutuzumab in the assessment of the investigator, further doses may be held and the patient may continue to receive bendamustine and venetoclax. Bendamustine should not be dose reduced while patients remain on venetoclax unless a toxicity develops which is clearly related to bendamustine, in which case it may be reduced at the discretion of the investigator. If reduced,

bendamustine dose should not be re-escalated. Venetoclax dose re-escalation due to toxicity for TLS should occur as outlined in section 5.2.

If administration of chemotherapy is delayed, the administration of obinutuzumab should be delayed for the same timeframe; for example, if chemotherapy is delayed, administration of obinutuzumab should also be delayed so that they are given together beginning on Day 1 of the same cycle.

A dose delay of 14 days is permitted for immunochemotherapy to allow recovery of hematologic toxicities to Grade ≤2 or non-hematologic toxicities to Grade ≤1 or baseline status for the first episode. Actions for recurrent hematologic adverse events are described Tables 3 & 4. If treatment is delayed for more than 2 weeks (except for hepatitis B reactivation), the patient should be withdrawn from study treatment except in exceptional circumstances. (Note that lymphopenia is not considered a cytopenic toxicity, as it is an expected outcome of therapy.) Patients who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments through progression and standard follow-up.

5.5 MANAGEMENT OF NON-HEMATOLOGIC TOXICITIES

For non-hematologic toxicities deemed to be at least possibly related to study therapy (with the exception of asymptomatic electrolyte abnormalities -not meeting TLS criteria- that are correctible and alopecia), *dosing of immunochemotherapy should be held until resolution to Grade ≤1 or baseline status*. Resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the benefits and risks with the patient and discussion with the principal investigator. *If treatment is delayed for more than 2 weeks (except for hepatitis B reactivation), the patient should be withdrawn from study treatment except in exceptional circumstances. Any patient experiencing CMV viremia will be removed from the study.*

Note: Dose delay/interruption is only required for non-hematologic toxicities which are felt to be at least possible related to study therapy. However, in the event an adverse event occurs that is not related to study therapy but which would make treatment unsafe, the investigator may hold study therapy for up to 14 days and resume treatment at full dose when it is felt to be safe. Delays of greater than 14 days should be discussed with the study chair.

Non-hematologic toxicities including infections that are felt to be at least possibly related to study therapy should be managed as follows with dose adjustments according to Table 5:

Grade 1	Continue all therapy on schedule
Grade 2 (except asymptomatic electrolyte abnormalities that are not felt to be TLS and alopecia)	Hold all therapy until resolution to grade ≤ 1. For first occurrence, may resume at same dose level. For second and subsequent occurrences, reduce venetoclax one dose level unless *clearly* related to bendamustine in which case, document as such and reduce bendamustine at discretion of investigator per institutional practice.
Grade 3 (Except infusion-related reactions to obinutuzumab)	Hold all therapy until resolution to grade ≤ 1 First occurrence: May resume venetoclax at same dose level Second and subsequent occurrences: Reduce venetoclax by one dose level unless *clearly* related to bendamustine in which case, document as such and reduce bendamustine at discretion of investigator per institutional practice.
Grade 4 (Except infusion-related reactions to obinutuzumab)	Hold all therapy until resolution to grade ≤ 1 First occurrence: May resume venetoclax at one lower dose level if deemed safe by investigator Second and subsequent occurrences: Permanently discontinue study therapy.

5.6 GUIDELINES FOR HEMATOLOGIC TOXICITY AND INITIATION OF A NEW CYCLE

5.6.1 Criteria to start a new cycle at full dose:

1) ANC ≥ 1000/mm^3 (unless due to disease infiltration of bone marrow)

2) Plts ≥ 50,000/mm^3 (unless due to disease infiltration of bone marrow)

3) Non-hematologic toxicities deemed to be potentially related to study therapy must be resolved to grade ≤ 1 or baseline, with the exception of asymptomatic glucose/electrolyte abnormalities that are felt to be non-clinically significant and can be corrected. Alopecia is also not a cause for study drug delay/modification.

5.6.2 Criteria to escalate venetoclax dose:

1) No clinically evident TLS

2) Non-hematologic toxicities deemed to be potentially related to venetoclax must be resolved to grade ≤ 1 or baseline, with the exception of asymptomatic glucose/electrolyte abnormalities that are felt to be non-clinically significant and can be corrected. Alopecia is also not a cause for study drug delay/modification

5.6.3 Dose Delays or Modifications during Cycle 1 Venetoclax Dose Escalation based on hematologic toxicities (Table 3)

Event	Dose Delay or Modification
Grade 3 febrile neutropenia or Grade 3 neutropenia with infection	• Hold all study treatments. Reminder that all patients should receive pegfilgrastim as part of standard supportive care. If this was not administered for any reason, GCSF may be administered to patients experiencing clinically significant neutropenia. • Once resolved to grade 1 or baseline, may resume venetoclax. Each subsequent occurrence will result in a dose reduction of venetoclax to the next lowest dose level. • Resume obinutuzumab as follows: o If Cycle 1, Day 8 is delayed to within 72 hours days of Day 15 then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if infection or neutropenic fever has resolved). o If Cycle 1, Day 15 is delayed to within 72 hours of Cycle 2, Day 1 then omit the Day 15 dose and administer the Cycle 2, Day 1 dose as scheduled (if infection or neutropenic fever has resolved).
Grade 4 febrile neutropenia or Grade 4 neutropenia with infection	• Patient will be removed from study. Reminder that all patients should receive pegfilgrastim as part of standard supportive care. If this was not administered for any reason, GCSF may be administered to patients experiencing clinically significant neutropenia.
Grade 3 neutropenia without fevers or infection	• No modifications needed. Reminder that all patients should receive pegfilgrastim as part of standard supportive care. If this was not administered for any reason, GCSF may be administered to patients experiencing clinically significant neutropenia.

Grade 4 neutropenia without fevers or infection	• Hold venetoclax until resolution to grade ≤ 2 neutropenia. Labs to be rechecked as frequently as clinically feasible but no less frequently than twice weekly until recovery. • Upon recovery of neutropenia, patient may resume venetoclax at the same dose. • Patient may resume venetoclax dose escalation after at least 5 days (and no more than 7 days) of treatment at dose level at which toxicity was experienced, and should resume dose escalation as previously scheduled, with at least 5 days of venetoclax administered at each dose level (this may require additional doses beyond the planned 3 doses at 20mg or 4 doses at 50mg). As discussed previously in the TLS management section, dose escalation may continue, if needed through cycle 2 but no dose escalation is permitted after cycle 2. • Give obinutuzumab as scheduled • If venetoclax dose increase has to be held twice, the patient may continue on study at the highest tolerated dose of venetoclax. • 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 the Medical Monitor.
Grade 3 Thrombocytopenia	• No modifications needed
Grade 4 Thrombocytopenia (for platelet counts below 20,000/μL, see below)	• Hold venetoclax until resolution to grade ≤ 2 thrombocytopenia. Labs to be rechecked as frequently as clinically feasible but no less frequently than twice weekly until recovery. • Upon recovery of thrombocytopenia, patient may resume venetoclax at the same dose. • Patient may resume venetoclax dose escalation after at least 5 days (and no more than 7 days) of treatment at dose level at which toxicity was experienced, and should resume dose escalation as previously scheduled, with at least 5 days of venetoclax administered at each dose level (this may require additional doses beyond the planned 3 doses at 20mg or 4 doses at 50mg). As discussed previously in the TLS management section, dose escalation may continue, if needed through cycle 2 but no dose escalation is permitted after cycle 2. • Give obinutuzumab as scheduled • If venetoclax dose increase has to be held twice, the patient may continue on study at the highest tolerated dose of venetoclax. • If 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. Decisions must be made in consultation with and with approval of the Medical Monitor.
Severe thrombocytopenia (platelets < 10,000/μL) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet inhibitors during Cycle 1	• Hold obinutuzumab in case of severe thrombocytopenia (platelets < 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves. • If the Cycle 1, Day 8 dose is delayed then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the Cycle 1, Day 15 dose is delayed then omit the Day 15 dose and administer the Cycle 2 Day 1 dose as scheduled (if symptomatic bleeding has resolved).
Thrombocytopenia	• Hold obinutuzumab in case of platelets < 20,000/μL or symptomatic bleeding

with platelets < 20,000/μL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors during Cycle 1 [b, c]	(irrespective of platelet count) until it resolves. • If the Cycle 1, Day 8 dose is delayed then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the Cycle 1, Day 15 dose is delayed, then omit the Day 15 dose and administer the Cycle 2, Day 1 dose as scheduled (if symptomatic bleeding has resolved). • For patients who are receiving concomitant anticoagulant when thrombocytopenia with platelets < 20,000/μL develops, adjust the dose or hold the drug per investigator discretion. • For patients who are on platelet inhibitors when thrombocytopenia with platelets < 20,000/μL develops, consider temporarily holding their use. [c]

NOTE: Dose delay/modifications are not required for hematologic toxicities other than neutropenia or thrombocytopenia.

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

[b] If the patient's clinical condition requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when thrombocytopenia with platelets < 20,000/μL develops. When possible, replace prior therapy with vitamin K antagonists with low-molecular-weight heparin before Cycle 1, Day 1.

[c] Clinical decision-making may be adjusted depending on the patient-specific assessment of benefit and risk.

5.6.4 Cycles occurring after completion of venetoclax dose escalation Dose Delay or Modification of Venetoclax, Obinutuzumab, and Bendamustine (Table 4)

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Day 1 of cycle with or without infection or fever [a] First delay	• **FIRST EPISODE** • Delay doses of all study treatment. • If ANC recovers to ≥ 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment. In this case, day 1 of the cycle will be considered the day the patient receives obinutuzumab/bendamustine and starts venetoclax. • If ANC fails to recover to ≥ 1000/μL within 7 days, but within 14 days of the scheduled cycle 1, venetoclax should be dose reduced by one dose level (as specified in Table 5) for this and all future cycles. • If ANC fails to recover to ≥ 1000/μL by day 14, discontinue venetoclax. • 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 the Medical Monitor.
Recurrent Grade 3 neutropenia on Cycle Day 1	• Delay doses of all study treatment. • If ANC recovers to > 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to > 1000/μL on or after Day 8 of the scheduled date for the next cycle, then decrease venetoclax dose by one dose

Event(s)	Dose Delay or Modification
	level (as specified in Table 5).
Recurrent Grade 4 neutropenia on Cycle Day 1	• If patient develops recurrent Grade 4 neutropenia (after at least one prior episode of grade 4 neutropenia) requiring dose delay despite growth factor support and following venetoclax dose reductions, discontinue all study treatment permanently.
Grade 3 or 4 thrombocytopenia on Cycle Day 1 First episode	• Delay doses of all study treatment. • If platelet count recovers to > 50,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. In this case, day 1 of the cycle will be considered the day the patient receives obinutuzumab/bendamustine and starts venetoclax. • If platelet count fails to recover to ≥ 50,000/μL within 7 days, but within 14 days of the scheduled cycle 1, venetoclax should be dose reduced by one dose level (as specified in Table 5) for this and all future cycles. • If platelet count fails to recover to ≥ 50,000/μL by day 14, discontinue venetoclax. • 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 > 50,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to > 50,000/μL on or after Day 8 of the scheduled date of the next cycle, then decrease venetoclax dose by one dose level (as specified in Table 5). • If patient develops Grade 4 thrombocytopenia following venetoclax, reduction, consider further reduction to the next lowest dose level.
Grade 1 or 2 neutropenia and/or thrombocytopenia	• No dose reduction or delay.

Event(s)	Dose Delay or Modification

After completion of dose escalation of venetoclax, hematologic toxicity encountered within a cycle will not require dose delay or modification unless it is felt to be clinically warranted by the treating investigator.

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

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

[b] If the patient's clinical condition requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when thrombocytopenia with platelets < 20,000/μL develops. When possible, replace prior therapy with vitamin K antagonists with low-molecular-weight heparin before Cycle 1, Day 1.

[c] Clinical decision-making may be adjusted depending on the patient-specific assessment of benefit and risk.

5.6.5 Dosing levels for dose reduction due to hematologic toxicities (Table 5)

The following table are dose levels as needed for patients who experience hematologic toxicity. This table does not apply to patients who have not achieved target dosing during cycle 1 ramp up.

Dose Level	Dose
1	200mg daily on days 1-5
2	200mg daily on days 1-7
3	400mg daily on days 1-5
4	400mg daily on days 1-7
5	400mg daily on days 1-10

Hematologic toxicity encountered during the cycle 1 ramp-up dosing of venetoclax should not result in a dose reduction for cycle 2. However, patients must still meet criteria to initiate therapy on cycle 2, day 1 (See Section 5.6.1). Patients who do not meet criteria to start therapy on cycle 2, day 1, shall be delayed until recovery but do NOT require a dose reduction.

5.7 REPRODUCTIVE SYSTEM EFFECTS

Based on nonclinical studies, there is a potential for decreased spermatogenesis. Non-reversible depletion of testicular germ cells has been observed in dogs at all doses tested after 4 weeks of dosing.

Male patients should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

Embryofetal toxicity has also been observed in mice at the highest dosage administered. Venetoclax is not advised in pregnancy or lactation.

5.8 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.

5.9 TREATMENT-EMERGENT MALIGNANCIES (SECOND PRIMARY MALIGNANCIES)

Events of second primary malignancies have been reported across the venetoclax oncology program. No pattern has been observed. As venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

5.10 HEPATITIS B REACTIVATION

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 HBsAg positive and also in patients who are HBsAg negative but are 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 by measuring HBsAg and anti-HBc 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 consideration for 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.

5.11 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

JC virus infection resulting in 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 preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging, and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.12 CYTOMEGALOVIRUS REACTIVATION

CMV reactivation (and fatal encephalitis) have been identified in patients treated with this combination. All patients will be monitored by CMV pcr at study entry, at the beginning of cycles 2, 4, and 6, and at the end of study visit. Any patient with detectable CMV viremia (any reading other than "undetectable") shall discontinue study therapy.

5.13 INFUSION 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). Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Management of patients with IRRs includes the following:

- Premedicate 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 IRR, stop the obinutuzumab infusion and 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 IRRs and manage symptoms.
- For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because 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 administration, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding antihypertensive medication as suggested above.

NOTE: Patients who experience severe IRR's and are not felt to be able to continue obinutuzumab despite maximal supportive care may continue to receive bendamustine and venetoclax on study if felt to be medically appropriate.

5.14 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.

5.2 Study-wide Stopping Rules for Safety

In addition to monitoring for expected hematologic toxicities and tumor lysis syndrome, we will have study-wide rules for stopping should excessive toxicity be identified.

5.2.1 The study chair, may at his discretion temporarily hold accrual to the study at any time should there be concern for excessive toxicity, unexpected adverse events, or new information available to the study chair suggesting that the current treatment is no longer safe. In this event, the study chair will communicate this with all participating investigators and accrual shall cease until an appropriate amendment addressing this concern is developed. Continuation of treatment for patients on study therapy at that time would be determined based on the severity and frequency of the toxicity.

5.2.2 Any death that occurs to a patient while on study that is at least possibly related to study therapy shall trigger an immediate accrual hold while additional information is obtained regarding the details of the event and to determine what amendments to the protocol are necessary to ensure the safety of subsequent patients. Patients who are currently on treatment at that time may continue therapy at the discretion of the study chair depending on the circumstances surrounding the death (ie, a death during cycle 1 from tumor lysis syndrome would not necessarily require that patients on active therapy who are receiving subsequent cycles of treatment without incident discontinue treatment).

5.2.3 If at least 5 patients (> 15% of planned accrual) experience a grade 4 non-hematologic toxicity that is at least possibly related to study therapy at any time during the treatment, further accrual shall cease until additional information is obtained regarding the details of these events and a determination is made regarding appropriate changes to the protocol. In this setting, the study chair will determine whether patients currently on active treatment must discontinue therapy.

6. SAFETY DEFINITIONS AND REPORTING

6.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

6.1.1 Adverse Events

An adverse event is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution. This includes the following:

- adverse events not previously observed in the subject that emerge during the protocol-specified adverse event reporting period, including signs or symptoms associated with MCL that were not present prior to the adverse event reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, adverse events that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified adverse event reporting period.

6.1.2 Serious Adverse Events

An adverse event should be classified as a serious adverse event if the following criteria are met:

- It results in death (i.e., the adverse event actually causes or leads to death)
- It is life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It 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).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

6.1.3 Adverse Events of Special Interest

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

Adverse events of special interest for this study include the following:

- 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:
- * Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 ´ ULN
- * Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
-

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- In addition, venetoclax events of special interest are:

  -Tumor lysis syndrome (irrespective of seriousness)

- In addition, obinutuzumab events of special interest are:
  - TLS (irrespective of seriousness, causality or severity)
  - Second malignancies

6.1.4 Selected Adverse Events

Selected events (in clinical trials, these are 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/mm3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia - defined as neutrophil count < 1000 cells/mm3, which does not resolve after 28 days (without obinutuzumab treatment)
- Thrombocytopenia (including acute thrombocytopenia - events occurring during and within 24 hours post obinutuzumab infusion)
- TLS
- Hepatitis B reactivation
- Cardiac events
- GI perforation
- Richter's transformation

6.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The sponsor-investigator is responsible for ensuring that all adverse events and serious adverse events that are observed or reported during the study, are collected and reported to the FDA, appropriate Institutional Review Boards (IRBs), and Genentech in accordance with instructions provided in this section and in sections 6.2 and 6.3, as well as in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

6.2.1 Adverse Event Reporting Period

The study period during which all adverse events and serious adverse events must be reported begins after informed consent is obtained and initiation of study treatment and ends at the time of the therapy completion evaluation at 45-60 days after cycle 6 day 1 except for patients who discontinue study therapy in order to proceed with autologous stem cell transplantation. Patients who move to autologous stem cell transplantation without an intervening relapse (ie, a planned consolidative transplant) shall be monitored for AE's through day 100 post-transplant. After this period, investigators should only report serious adverse events that are attributed to prior study treatment.

6.2.2 Assessment of Adverse Events

All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported adverse event or serious adverse event will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to venetoclax and/or obinutuzumab (see following guidance), and actions taken.

To ensure consistency of adverse event and serious adverse event causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the adverse event and administration of the therapy, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to venetoclax and/or obinutuzumab; and/or the adverse event abates or resolves upon discontinuation of venetoclax and/or obinutuzumab dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the therapy (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to venetoclax and/or obinutuzumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the USPI or current IB.

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

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

6.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.3.1 Eliciting Adverse Event Information

A consistent methodology for eliciting adverse events at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?"

6.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting adverse events or serious adverse events. Avoid colloquialisms and abbreviations.

6.3.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.3.2.2 Deaths

All deaths that occur during the protocol-specified adverse event reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

6.3.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an adverse event or serious adverse event only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

6.3.2.4 Hospitalizations for Medical or Surgical Procedures

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an adverse event, the event responsible for the procedure, not the procedure itself, should be reported as the serious adverse event. For example,

if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the serious adverse event.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study. This includes planned hospitalization to monitor for tumor lysis syndrome during administration of the study therapy.

6.3.2.5 Pregnancies

Pregnancies in Female Patients

If a female patient becomes pregnant while receiving venetoclax and/or obinutuzumab or within 18 months after the last dose of obinutuzumab or 30 days after the last dose of venetoclax, whichever is longer, a report should be completed and expeditiously submitted to Genentech.

Follow-up to obtain the outcome of the pregnancy should also occur.

Pregnancies in Female Partners of Male Patients

If the female partner of male patients become pregnant while receiving the study drug or within 3 months after the last dose of obinutuzumab or 30 days after the last dose of venetoclax, whichever is longer, a report should be completed and expeditiously submitted to Genentech. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Pregnancy Report when updated information on the course and outcome of the pregnancy becomes available.

6.3.2.6 Congenital Anomalies/Birth Defects and Abortions

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as a serious adverse event. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event.

6.3.2.7 Post-Study Adverse Events

For studies involving collection of survival data/ follow up until progression free period/ Extended follow up period (5 years) the investigator after the end of the adverse event reporting period (as defined in section 6.2.1) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject or in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug.

Patients who have subsequently initiated additional anti-cancer therapy (whether or not there's been an intervening progression/relapse) should only have SAE's or deaths reported that are clearly related to the study treatment.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

6.3.2.8 Reconciliation

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Sponsor-investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by Sponsor-investigator to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Sponsor/Investigator to Genentech within five (5) calendar days from request by Genentech

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

6.4 ADVERSE EVENT REPORTING

The Sponsor-investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all above mentioned single case reports to Genentech within the timelines described below. The completed MedWatch/case report should be faxed/emailed immediately upon completion to Genentech Drug Safety .

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:
Email: kaiseraugst.global_impcomplaint_management@roche.com

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.
Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Serious adverse events, pregnancy reports(including pregnancy occurring in the partner of a male study subject, adverse event SIs, other Special Situation Reports and Product Complaints (with or without an AE) where the patient has been exposed to venetoclax and/or obinutuzumab will be sent on a MedWatch or CIOMS I form to Genentech Drug Safety . Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below.

For participating subsites, adverse events collected at weekly treatment visits is to be entered into OnCore no later than 14 calendar days after data collection.

Site investigators must also report all SAEs and unanticipated problems to the sponsor-investigator within 24 hours of the participating site becoming aware of the event. The participating site will submit the MedWatch Form 3500A to the Winship regulatory staff and will also enter the data into OnCore within the specified timelines above. The Emory sponsor must review and sign off on the event and return to the Winship regulatory staff. Regulatory will review the assessment to determine IRB and/or FDA reporting requirements.

Serious Adverse Drug Reactions

Serious adverse event reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

Other Serious Adverse Events

Serious adverse event reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

Pregnancy Reports

While such reports are not serious adverse events or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of obinutuzumab or 30 days after the last dose of venetoclax . A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

Adverse Events of Special Interest

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

6.4.1 Special Situation Reports

In addition to all adverse events, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with a adverse event/serious adverse event unless otherwise specified in the protocol
- Lack of therapeutic efficacy

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

6.4.2 Aggregate Reports

The principal investigator will forward a copy of the Publication to Roche upon completion of the Study.

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

The Investigator as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. Sponsor-Investigator agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion. Genentech agrees to forward to Sponsor- Investigator an executive summary of the Genentech/Roche DSUR upon request. Furthermore, Genentech/Roche agrees that Sponsor- Investigator may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable

Note: Investigators should also report events to their IRB as required.

6.4.3 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the event description of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

6.4.4 Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A form and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter, including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number (if assigned), brief adverse event description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally, Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding serious adverse event reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (mandatory reporting) form is available at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

6.5 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study: venetoclax-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

The Sponsor-investigator of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations

The Sponsor-investigator of the Study will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The Sponsor-investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The Sponsor-investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Additional Reporting Requirements for IND Holders

For investigator-initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The sponsor-investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of venetoclax or obinutuzumab. An unexpected adverse event is one that is not already described in the Venetoclax and Obinutuzumab IBs. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The sponsor-investigator is also required to notify the FDA and all participating investigators in a written IND Safety Report of any serious, unexpected adverse event that is considered reasonably or possibly related to the use of venetoclax or obinutuzumab. An unexpected adverse event is one that is not already described in the Venetoclax and Obinutuzumab IBs.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed, and the significance of the new report in light of the previous, similar reports should be commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

And the sponsor-investigator will be responsible for the distribution of safety information **to the Site IRB:**

Emory University Institutional Review Board
1599 Clifton Road NE, 5th Floor
Atlanta, GA 30322

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

QUERIES

Queries related to the Study will be answered by Sponsor-Investigator However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Sponsor-Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. Sponsor-Investigator agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

7. STATISTICAL CONSIDERATIONS

7.1 DETERMINATION OF SAMPLE SIZE

The primary endpoint will be rate of CR in patients with MCL who receive the combination. The study will have 80% power to detect an improvement in CR rate over historical control, with an alpha of 0.05. Based on historical data, we will assume a baseline CR rate of 60% with a goal CR rate of 85% in this study. Simon's two-stage design will be utilized using the Optimal design.[10] The null hypothesis that the true response rate is 60% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued. If there are 6 or fewer responses in these 9 patients, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 23. The null hypothesis will be rejected if 18 or more responses are observed in 23 patients. This design yields a type I error rate of 0.05 and a power of 80% when the true response rate is 85%. This will require 23 patients to be evaluated. Assuming 4 patients (~10%) ultimately cannot be evaluated, we will plan to enroll 27 patients total.

7.2 PLANNED EFFICACY EVALUATIONS

Response will be evaluated after cycle 4 (prior to cycle 5) and at end of treatment. Following is the schedule for efficacy evaluation:

Cycle 2 Day 1 Efficacy evaluation

- Clinical disease assessment

Cycle 5 Day 1 Efficacy Evaluation

- PET/CT imaging (can occur up to 7 days prior to C5D1)
- Clinical disease assessment

6-week post-induction restaging

- PET/CT imaging (can occur up to 7 days prior to 6 week visit)

- Bone marrow aspirate and biopsy if positive at screening
- MRD testing with Clonoseq assay (if available)
- Clinical disease assessment

All efficacy evaluations will occur (but do not have to be resulted) prior to treatment for the associated cycle (eg C5D1 efficacy evaluations should be complete prior to any C5D1 treatment).

Efficacy evaluations during cycle 2 will not be used to remove any patient from therapy. Evidence of progressive disease on cycle 5 efficacy evaluation will result in discontinuation of therapy and removal of the patient from the trial.

7.3 PRIMARY ENDPOINT

The primary endpoint is the rate of complete response at completion of therapy.

Response will be assessed according to the *Lugano Classification* for response assessment in lymphoma, developed at the 2014 International Conference on Malignant Lymphoma (IMCL '14).[8]

The following are excerpts from the classification:

Complete Response

- PET/CT imaging with a score of 1-3 out of 5 using the Deauville Criteria[9]. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within the spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No FDG-avid disease in bone marrow and bone marrow normal by morphology if involved at diagnosis.

Partial Response

- Score of 4 or 5 using the Deauville Criteria, but reduced uptake compared with baseline and residual mass(es) of any size.
- Residual uptake higher than uptake in normal marrow but reduced compared to baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.

Stable Disease

- Score of 4 or 5 using the Deauville Criteria, with no significant change in FDG uptake from baseline at interim or end of treatment

- No change in baseline marrow avidity

Progressive Disease

- Score of 4 or 5 using the Deauville Criteria with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma.

7.4 SECONDARY ENDPOINTS

1. Grade 3+ adverse events
2. All grade adverse events
3. Rate of treatment discontinuation and frequency of completion of study therapy
4. Rate of minimal residual disease negative complete response
5. Overall response rate
6. Time to tumor progression
7. Progression free survival
8. Overall survival
9. **Rate of maximum venetoclax dose achievement without clinical TLS**

7.5 METHOD OF ANALYSIS

Response rates will be calculated, and a 95% confidence interval will be estimated using the Clopper-Pearson method[11-13]. Overall survival and progression free survival will be described using the Kaplan-Meier methodology. Some patients may undergo consolidative autologous stem cell transplant without evidence of disease progression. This will not be counted against PFS, and will be reported and described. Remaining endpoints will be summarized descriptively, using frequency and percentage for categorical variables and mean, median, range, and standard deviation for numeric variables. Safety endpoints will include the safety-evaluable population which will include any patient who received any amount of study therapy.

8. RETENTION OF RECORDS

FDA regulations (21 CFR § 312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

8.1 THE WINSHIP CANCER INSTITUTE DATA SAFETY MONITORING COMMITTEE

The study will also be followed by the Winship Cancer Institute Data Safety Monitoring Committee to allow for local review and confirmation of proper study execution and safety measures.

Patient safety, study efficacy and compliance will be reviewed at the Winship Cancer Institute Lymphoma Working Group meeting. The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study (every 6 months or annually – depending on the risk level of the protocol). This committee will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. Initial study monitoring will occur within 6 months from date of 1st subject accrued to study. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. The Committee reserves the right to conduct additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI or designee will also notify the DSMC of study status within 2 months before the next scheduled review is due.

8.1.1 Procedures to assure data integrity and protocol adherence

Imaging and clinical data will be analyzed in a quarterly meeting of investigators, clinical research coordinators and regulatory personnel.

Adverse event reporting will utilize NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and is detailed in section 6 above.

Study Team Oversight: The study progress in terms of enrollment, activity of current patients under active treatment, observed toxicities will be reviewed in the weekly Emory Lymphoma Working Group. Here there will be random and selected case report form and chart review. Special and problematic items requiring additional attention will be addressed in separate sessions of the Lymphoma Working Group occurring up to weekly including selected study investigators, clinical research coordinators and regulatory personnel.

Training of investigators, clinical research coordinators and regulatory personnel at all sites will be performed by one of the site investigators utilizing the written protocol and a summary of pertinent treatment activities. Completion of the training of investigators, clinical research coordinators and regulatory personnel will be documented on a study training log.

8.1.2 On-site Audits

Regulatory authorities, the IRB and Genentech's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support given reasonable notice at all times for these activities.

8.1.3 Monitoring plan of Subsite(s):

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spread sheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spread sheet will be shared with the Emory PI via e-mail. Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). Once all subjects have completed study therapy the frequency of teleconferences will be determined by the PI and study team. The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site. Chart reviews will be performed on selected cases by the participating site staff to confirm that the data collection is accurate.

Winship's Multi- Site Coordinator will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (annually once onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

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10. APPENDIX 1: STUDY FLOWCHART

See next page for updated table

			CYCLE 1						CYCLE 2				CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X	X			
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1#	X				
Clonoseq MRD monitoring (Optional)	X@														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X$														X$$				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X

*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine

**Hematology/Chemistry: CBC with differential, Platelets, CMP

***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen

~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures

^Lab checked twice during a given day, with at least 6 hours between blood draws.

#C5D1 PET/CT may be performed up to 7 days prior to C5D1

$Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy

$$Therapy Completion BMBx/Aspirate only required if screening BMBx was positive

@Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up

Table of Assessments (Revised to Include CMV monitoring recommendations)

			CYCLE 1								CYCLE 2			CYCLE 3-6					
Activity	Screen	≤ 7 days prior to C1	C1D1	C1D2	C1D3 (if needed per clinician discretion)	C1D8	C1D9	C1D11	C1D15	C1D22	C2D1	C2D2	C2D15	D1 of cycles 3-6	Therapy completion eval at 45-60 days after C6D1	3 month post Tx Completion Eval	6 month post Tx Completion Eval	1 year post Tx Completion Eval	2 year post Tx Completion Eval
Venetoclax dose change						20mg		50mg	100 mg	200 mg	400 mg								
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Outpatient Tumor lysis labs~*	X	X	X	X	X	XX^	X	XX^	XX^	XX^	XX^	X	X	X	X	X		X	X
Hematology/Chemistry**	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Combined PET/CT scan	X													C5D1[#]	X				
Clonoseq MRD monitoring (Optional)	X[@]														X				
CAPP-Seq MRD monitoring (Optional)	X														X	X	X	X	X
ECOG performance status	X		X						X		X			X	X	X	X	X	X
Physical examination (including weight)	X		X						X		X			X	X	X	X	X	X
Medical/Oncology History	X																		
Pregnancy test	X	X									X			X					
Informed Consent	X																		
TLS risk categorization	X	X																	
CMV viremia by PCR	X										X			C4D1, C6D1	X				
Viral Serologies***	X																		
12-lead ECG	X																		
BM Aspirate and Biopsy	X[$]														X[$$]				
Dispense/Collect Study Drug and Subject Diary			X								X			X	X				
Survival Assessment															X	X	X	X	X
AE/Conmed Assessment	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X	X

*Tumor Lysis Labs: Uric acid, LDH, Phosphorus, Calcium, Potassium, Creatinine

**Hematology/Chemistry: CBC with differential, Platelets, CMP

***Viral Serologies: HIV Ab screen; Hepatitis B (HBsAg, anti-HBc, anti-HBsAb), Hepatitis C screen

~TLS labs must have resulted and pt must not have laboratory evidence of TLS prior to administration of any dose increases. See section 5.1.2.1.2.3 for inpatient procedures

^Lab checked twice during a given day, with at least 6 hours between blood draws.

[#]C5D1 PET/CT may be performed up to 7 days prior to C5D1

[$]Screening BMBx/Aspirate does not have to be completed if they have previously documented involvment OR if a negative biopsy has been obtained within 6 weeks prior to starting therapy

[$$]Therapy Completion BMBx/Aspirate only required if screening BMBx was positive

[@]Screening sample for clonoseq must be a high disease load sample (blood, bone marrow or tissue) from the initial diagnostic work-up

11. APPENDIX 2
CALCULATION OF CREATININE CLEARANCE USING THE COCKCROFT-GAULT FORMULA

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

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

12. APPENDIX 3
SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

ROCHE/GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

Page 1 of ___

Roche/Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/___/___ dd / mm / yyyy
Follow-up Report Date	_____/___/___ dd / mm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

Serious adverse event or Safety Reporting questions, contact Roche/Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

13. APPENDIX 4
FDA MEDWATCH 3500 FORM

This form is included in the study start-up zip file to be sent to sites via email.

14. APPENDIX 5 CURRENT NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

15. APPENDIX 6 RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME

1. FIRST DOSE OF VENETOCLAX OR DOSE INCREASE

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not < 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform immediate ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform immediate ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. – If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour.

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Administer rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus > 10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours.

IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.

2. ONGOING DOSING OF VENETOCLAX

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as below. Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.

  Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of TLS prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

16. APPENDIX 7 TUMOR LYSIS SYNDROME RISK ASSESSMENT FORM FOR SCREENING

At screening (as in the study table outlining the schedule of assessments), patients must be categorized into risk categories for development of TLS using this form.

High risk criteria – Requires hospitalization for Venetoclax initation

Criteria	***High-risk criteria***
Largest lymph node mass	Any mass ≥ 10 cm
Absolute lymphocyte count	ALC ≥ $25x10^9$/L AND any lymph mass ≥ 5cm

Moderate-risk criteria – Consider hospitalization for Venetoclax initation, especially if multiple factors present

Criteria	***Moderate risk criteria***
Serum LDH	Elevated
Creatinine clearance	<80 mL/min
Number of lymph node masses ≥ 5cm	Two or more
Concern about ability of patient to maintain adequate PO intake (~2-3L per day)	Concern present

17. APPENDIX 8: SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Use of the following therapies is prohibited during the study:

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

The following concomitant medications are not allowed from 7 days prior to the first dose of study drugs and during venetoclax administration:

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

This is not an exhaustive list. If there are questions, please contact the medical monitor.

Appendix 9: CAPP-Seq sample collection process

Emory Specific Collection Process and Workflow

Peripheral blood sample collection description

1. Study coordinator to leave 4 K2EDTA 10ml size (smaller example pictured below, we will use 10mL size) tubes and collection information/phlebotomy instructions form in plastic bag at lab prior to patient arrival. *Note that any heparin in the collection tube of the line used to draw the blood will make it unusable for our assay.*

2. Phlebotomy to draw 4 K2EDTA 10mL tubes from peripheral blood and call study coordinator within 10 minutes of drawing blood.
3. If sample is not to be processed immediately, sample is to be immediately stored in cold room (3rd floor WCI space in Dr. Bernal's section of the cold room. Cold room is diagonal to the Tissue bank freezer). Samples stored in the 4-degree Celsius cold room must be processed within 24 hours.

Peripheral blood sample processing description

1. Samples should be processed immediately (i.e., within 6 hours) if possible. Processing can occur at room temperature if samples are being processed immediately. If there is any delay in processing samples, they should be stored at 4 degrees Celsius until processing, which then can occur at room temperature.
2. Sample will be centrifuged at 1800g (RPM will be machine dependent) for 10min. This can be performed on the 3rd floor WCI until a centrifuge is obtained for the 5th floor B-building lab.
3. Remove the tubes from the centrifuge without disturbing the cellular layer.
4. Plasma should be pipetted/removed from the cellular layer and transferred to Eppendorf tubes in 1-2mL aliquots. Do not fill the tubes beyond 70% capacity. *Do not disturb the buffy coat while pipetting plasma; leave ~3-4mL of plasma behind to ensure the buffy coat is undisturbed. (Shown below is a 1.5 mL Eppendorf tube; 2.0mL varieties are also available).*

5. Store the above collected aliquots of isolated plasma at -80 degrees (3rd floor WCI space in Dr. Bernal's/ tissue bank section) to be shipped to the Alizadeh lab in batches at a later date. *Note that samples should be clearly labeled as CAPP-Seq samples and the patient ID, so they can be easily identified at a later date for shipping.*
6. The remaining plasma depleted whole blood (PDWB) should be mixed and frozen at -80°C also in 1-2mL aliquots, also in the Eppendorf tubes; this will serve as our germline DNA.

Samples will be shipped to the Alizadeh frozen on dry-ice at a later date where the CAPP-Seq protocol will be performed.

As an alternative to EDTA tubes (purple top, above), blood can also be collected in Streck tubes (below). If blood is collected in Streck tubes, it should be processed identically to blood draw in EDTA tubes. The only difference is that blood can be stored at room temperature until processing (rather than at 4 degrees Celsius). Processing should still occur withing 24 hours.