Bendamustine + obinutuzumab induction chemoimmunotherapy with risk-adapted obinutuzumab maintenance therapy in previously untreated mantle cell lymphoma

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INVESTIGATOR SIGNATURE PAGE

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The signature below confirms that I have read this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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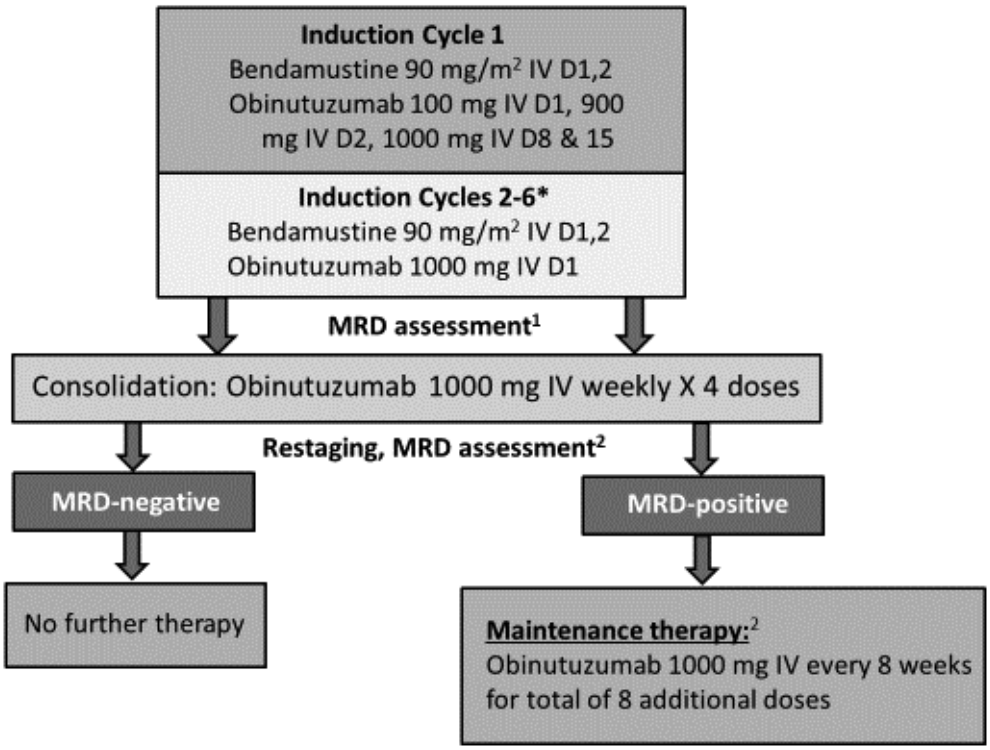
1 Schema



*Subjects achieving an objective response to induction therapy but with toxicities that may limit ability to receive 6 cycles of bendamustine + obinutuzumab (BO) may proceed to consolidation therapy as early as after 4 cycles of induction BO. Subjects formally meeting criteria for stable disease (SD) and evidence of objective response may continue to consolidation and maintenance at investigator discretion.

[1] Minimal residual disease (MRD) assessment on peripheral blood will be performed after cycle 2 of induction BO.

[2]Restaging and MRD assessments with marrow aspirates and peripheral blood will be performed after completion of consolidation therapy. In patients going on to maintenance therapy, an additional MRD assessment on peripheral blood only will be performed after completion of maintenance therapy or end of treatment (EOT).

2 Protocol Synopsis

PROTOCOL TITLE: Bendamustine + obinutuzumab induction chemoimmunotherapy with risk-adapted obinutuzumab consolidation and maintenance therapy in previously untreated mantle cell lymphoma	
UWCCC PROTOCOL NUMBER:	UW16086
DATE PROTOCOL FINAL:	3/17/2017
INDICATION:	Mantle cell lymphoma, previously untreated with cytotoxic chemotherapy.
STUDY PHASE:	Phase II

Background and rationale

Non-intensive chemotherapy-based therapy remains the standard for older and less fit mantle cell lymphoma (MCL) patients unable to tolerate consolidative autologous stem cell transplant (ASCT). Bendamustine + rituximab (BR) was established as a reasonable induction standard by the German StiL trial,[1] with MCL patients having 2-year progression-free survival (PFS) of approximately 60-70% (after 6 cycles of BR and no maintenance therapy).[2] Various other induction regimens such as rituximab + modified hyper-CVAD and VcR-CVAD (bortezomib, rituximab and modified hyper-CVAD) followed by maintenance rituximab have shown 3-year PFS >60-70%.[3,4] These cited trials involved previously untreated MCL patients conducted within the Wisconsin Oncology Network (WON). These data have been the basis for cooperative group trial E1411, which is investigating an induction regimen of BR versus BVR (BR + bortezomib) X 6 cycles and a 2nd randomization to rituximab versus rituximab + lenalidomide. This trial is scheduled to meet accrual by fall 2016. At present, there are no predecessor studies for non-intensive therapy of previously untreated MCL planned for roll-out from the U.S. cooperative groups (personal communication, Dr. Brad Kahl, Washington University, ECOG Lymphoma Committee Chair). In the interim, induction chemotherapy with BR with or without maintenance rituximab is the most common first-line non-intensive regimen used for older or less fit adults with MCL.

There are emerging data in MCL showing a strong correlation between achieving minimal residual disease (MRD) after induction therapy and PFS. For example, the results of S1106 (BR versus rituximab + hyper-CVAD induction followed by ASCT) included MRD evaluation using next-generation sequencing (NGS) in 10 patients treated with BR induction therapy.[5] Eight patients achieved MRD-negative status post-induction, and 2-year PFS was 100% among these MRD-negative patients post-induction. In another lymphoid malignancy, diffuse large B-cell lymphoma (DLBCL), there was a strong correlation between MRD status after 2 cycles of EPOCH ± rituximab and 5-year time-to-progression (TTP) with use of NGS on peripheral blood (PB) samples; patients who were MRD-negative after 2 cycles of chemotherapy had 5-year TTP of 80.2% compared with 41.7% for MRD+ patients.[6]

Prior to the availability of NGS technology, MRD evaluation with polymerase chain repeat (PCR)-based techniques was explored in MCL, and confirmed to have prognostic value.[7,8] A retrospective analysis of 27 patients evaluable for MRD after ASCT for consolidation of initial cytoreductive chemotherapy showed a significant association between MRD status in the first year post-ASCT and PFS and overall survival (OS).[7] Another retrospective review of outcomes based on MRD status prior to ASCT in MCL (n=75) reported from the Fred Hutchison Cancer Center found that MRD-positive patients had significantly worse outcomes, with a median PFS of 2.38 years (median PFS not reached for MRD-negative patients and median OS of 3.01 years (median OS not reached for MRD-negative patients; 5-year OS 82% for MRD-negative patients).

Pott et al described the relationship of MRD status to clinical outcomes in 2 large international phase III trials of the European MCL Network in which MRD was a secondary endpoint.[8] The 2 trials included both younger patients treated with a more intensive induction and ASCT (MCL Younger) and older patients (MCL Elderly) treated with a less intensive induction (R-FC versus R-CHOP) followed by rituximab or interferon maintenance. Patients in clinical remission who achieved an MRD-negative status after induction had an 87% chance of ongoing remission at 2 years compared with 61% of patients with residual MRD-positivity despite clinical remission (p=.004).[9] Sustained MRD negativity during maintenance therapy was also predictive of outcome. In the MCL Elderly trial, the response duration at 2 years was 76% in those with sustained MRD-negative status, compared with 36% of those with persistent residual disease by MRD analysis (p=.015).[9]

In addition, MCL has a variable disease course, with up to one-third of patients experiencing a more indolent disease course.[10-12] There are limited clinical or histologic markers that can prospectively identify patients with more favorable disease course. MRD status may prove to be a means of identifying patients with more favorable disease for which prolonged durations of remission may be achieved with less therapy.

Obinutuzumab, a novel glycoengineered anti-CD20 monoclonal antibody, offers additional benefits when combined with bendamustine in induction and continued as consolidation and maintenance therapy. Although direct comparisons of obinutuzumab versus rituximab activity in previously untreated MCL are not available, inference from available data show an advantage in terms of higher rates of response, and could offer the possibility of higher rates of MRD negativity after a course of induction chemotherapy with bendamustine-based treatment. Obinutuzumab is a glycoengineered type II antibody, with increased affinity on the Fc-receptors of effector cells that confers greater antibody-dependent cell-mediated cytotoxicity compared with non-glycoengineered antibodies (i.e., rituximab). Obinutuzumab has demonstrated superiority to rituximab in preclinical studies using whole-blood depletion assays and human DLBCL and MCL xenograft models.[13] The GAUGUIN study investigated differing dose levels of single-agent obinutuzumab in previously treated DLBCL and MCL. Overall response rates were 24% (for 400 mg treatment arms) and 37% (for 1600/800 mg treatment arms) in this pretreated population, including a 20% response rate in rituximab-refractory patients.[14] The GADOLIN trial of bendamustine + obinutuzumab (BO) + versus bendamustine alone in relapsed and rituximab-refractory indolent NHL (not including MCL patients) showed significant improvement in PFS with the combination of BO. The study was closed after a pre-planned interim analysis determined a statistically significant improvement in the primary endpoint of PFS after a median follow-up of 21.0 months (BO arm) and 20.3 months (B-alone arm). PFS was not reached in the BO arm versus 14.9 months in the B-alone arm (hazard ratio 0.55, p=.0001).[15]

The activity of obinutuzumab in up-front therapy of lymphoma may be superior to rituximab as suggested by results of the CLL11 trial.[16] In CLL11, the activity of obinutuzumab + chlorambucil was compared with rituximab + chlorambucil and chlorambucil alone in older adults with previously untreated chronic lymphocytic leukemia (CLL). PFS was significantly improved with the combination of obinutuzumab + chlorambucil (26.7 months) compared with chlorambucil alone (11.1 months), and a trend toward improved PFS compared with rituximab + chlorambucil (16.3 months).[16] It is of considerable interest as to whether this same benefit with use of obinutuzumab as front-line therapy can be extrapolated to other non-Hodgkin lymphoma (NHL) histologies, including MCL.

This proposed study would build on the known activity of bendamustine, with the addition of obinutuzumab as a more potent anti-CD20 monoclonal antibody alternative agent to rituximab. This study will investigate the impact obinutuzumab will have on the depth and duration of remission in previously untreated MCL. The other novel aspect of this trial includes MRD evaluation after 2 cycles of induction BO (evaluating correlation with PFS at this time point as previously described in DLBCL[6]) and following consolidation obinutuzumab, with omission of post-consolidation therapy in subjects

achieving MRD-negativity at the time of post-consolidation restaging. This approach will allow for minimizing treatment-related toxicity in an older and less fit population that has achieved a very high level of remission by MRD testing following induction and consolidation therapy.

STUDY DESIGN:

This is a phase II single-arm, open-label, multicenter study evaluating the efficacy and safety of the combination of induction chemoimmunotherapy with bendamustine and obinutuzumab (BO) followed by consolidation therapy and maintenance therapy with obinutuzumab in subjects who have not received prior cytotoxic chemotherapy for their MCL (i.e., prior single-agent rituximab is permitted, prior involved-field radiotherapy is permitted). Therapy for individual subjects will be risk-adapted based on results of minimal residual disease (MRD) testing performed after the consolidation phase. The study will be carried out at the University of Wisconsin Carbone Cancer Center (UWCCC) and participating community and academic practice sites within the Wisconsin Oncology Network (WON). There will be 6-10 sites participating in this study.

The subject participation will include a screening period, treatment period, and a follow-up period. The induction chemoimmunotherapy regimen consists of bendamustine and obinutuzumab for 4-6 cycles, followed by consolidation and maintenance therapy with obinutuzumab in subjects achieving an objective response to induction therapy (i.e., complete or partial response; stable disease with objective evidence of tumor shrinkage. Subjects who are MRD-negative (determined by MRD testing on bone marrow and PB) after consolidation therapy will omit maintenance therapy.

Subjects will undergo disease reassessment after C4 of induction BO chemoimmunotherapy, after obinutuzumab consolidation therapy, and after C4 and C8 of maintenance obinutuzumab. See schedule of assessments for details. MRD testing will be done after C2 of induction (PB only), after consolidation (BMA and PB), and post-maintenance or EOT (PB only).

STUDY ENDPOINTS

Primary Objective:

- The primary objective is progression-free survival (PFS).

Secondary Objectives:

- To estimate the MRD status (MRD defined as reduction to $\geq 10^{-6}$ fold reduction in the IgV_H unique clone of MCL by NGS).
- To estimate the concordance rate between peripheral blood and bone marrow aspirates in predicting MRD-negative status.
- To determine objective response rates (CR + PR) with induction BO in previously untreated MCL using the International Working Group Criteria[17] for response in lymphoma.
- To determine overall survival.

To determine toxicities observed with induction BO and consolidation and maintenance obinutuzumab.

STUDY DURATION: Anticipated accrual period of 30 months, with a follow-up period of at least 2 years after completion of therapy or until death or profession, or until the last subject has been followed for at least 1 year following completion of therapy.	**TOTAL SAMPLE SIZE**: Approximately 32 subjects are planned for enrollment.

DOSING REGIMEN(S):	**STUDY DRUG SUPPLIES:**
Induction chemoimmunotherapy (28 day cycles): • Bendamustine 90 mg/m^2 IV days 1 & 2 every 28 days X 4-6 cycles • Obinutuzumab: Cycle 1: 100 mg IV day 1, 900 mg IV day 2, 1000 mg IV days 8 & 15 Cycles 2-6: 1000 mg IV day 1 Consolidation phase: Obinutuzumab 1000 mg IV weekly X 4 doses Maintenance phase (8 week cycles): Obinutuzumab 1000 mg IV on day 1 of cycles 1-8	Bendamustine is commercially available. For study participants, obinutuzumab will be provided by Genentech, Inc. at no charge.

3 Schedule of Study Assessments

	Baseline[1]	C1-6 Induction chemotherapy D1 (±7 days)[1]	Consolidation therapy[19] (±3 days)	Post Consolidation therapy[20]	Maintenance therapy (every 8 weeks ±14 days)	EOT[17]	Follow-up phase[2] Every 3 months for 2 years (±3 weeks)
Informed consent	X						
Medical history & medications	X						
Physical exam, vital signs, weight, height[3], ECOG performance status	X	X	X[4]	X	X[4]	X	X
MIPI score (Appendix D)[1]	X						
Bone marrow aspirate (BMA) & biopsy and flow cytometry[5]	X		X[7]	X[7]	X		
MRD assessment	X[6]	X[7]	X[7]	X[7]	X[7]	X[7]	
P53 mutation analysis	X[22]						
Hematology profile	X	X[8]	X[8]	X	X[8]	X	X
Chemistry profile	X[9]	X[9,10]	X[9]	X[10]	X[10]	X[10]	X[10]
Creatinine clearance[18]	X						
Beta-2 microglobulin level	X						
Immunoglobulin levels[11]	X	X	X	X		X	
Hepatitis screening[12]	X						
Pregnancy testing[13]	X	X	X		X		
CT of the chest & abdomen/pelvis[14,23]	X	X	X	X	X	X	X
PET imaging[15,23]	X	X	X		X		X
Formal Disease assessment (CT scans, palpated disease, and other assessable disease)[16]	X	X	X	X	X	X	X
Record adverse events	X	X	X	X	X	X	X
Bendamustine infusion		X					
Obinutuzumab infusion		X[21]	X		X		

[1]Baseline assessments to be done within 28 days of enrollment, unless otherwise noted. If baseline assessments were done within 7 days of C1D1, they do not need to be repeated on C1D1. Baseline disease assessments (i.e. CT scans and bone marrow biopsy/aspirate) may be performed within 6 weeks of enrolment. The parameters used for calculating MIPI score (i.e., ECOG performance status, LDH, white blood cell count) must be collected from the baseline assessment values.

[2]The follow-up phase of therapy will begin after confirmation of MRD-negative status, after treatment completion (last cycle of treatment completed), or after stopping treatment early for reasons other than PD. The follow-up phase will continue for up to 2 years or until: death, progression of disease, start of a new anti-cancer therapy, or withdrawal. After the follow-up phase is completed, subjects will be followed annually for 5 years after treatment completion for survival and disease progression. See section 7.5.

[3]Required as baseline only.

[4]Required to be performed on D1 of consolidation, and on D1 of each maintenance dose.

[5]Bone marrow aspirate **(BMA) and biopsy and flow cytometry** to be done at baseline and after completion of consolidation therapy as part of restaging and MRD assessment of marrow. Subjects with possible CR during maintenance therapy will require a BMA and biopsy to confirm a CR as best treatment response at scheduled disease assessments. Refer to section 12.0. Response criteria for additional guidance of when BMA and biopsy are required.

[6]Confirm that baseline MRD sample available on enrollment or pre-enrollment samples. Pre-enrollment samples must be from within 12 months of enrollment. Additional details, including sample types, outlined in section 7.1.1.

[7]**MRD assessments** will include: PB only after C2 of induction (up to 7 days before C3D1); both (peripheral blood) PB and BMA post consolidation therapy; PB only after completion of maintenance (4-6 weeks after final dose of maintenance); PB only at EOT. Required at EOT visit in subjects discontinuing protocol therapy due to toxicity or patient preference. Not required at EOT in subjects stopping protocol treatment due to progression. Not required at EOT visit in subjects with MRD negative status in both marrow and blood after consolidation who proceed to clinical observation.

[8]**Hematology profile** (CBC, differential) is required within 48 hours prior to D1 of: induction C2-6, consolidation, and each maintenance dose.

[9]**Chemistry profile during baseline, C1D1 of induction and D1 of consolidation:** sodium, potassium, chloride, CO_2 (bicarbonate) calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, lactate dehydrogenase (LDH), and uric acid. To be obtained within 48 hours of: induction C1D1 and D1 of consolidation.

[10]**Chemistry profile during C2-6 of induction, post consolidation, maintenance, EOT and follow-up phase:** sodium, potassium, chloride, CO_2 (bicarbonate), BUN, creatinine, and LDH. To be obtained within 48 hours of visit.

[11]**Immunoglobulin levels** (quantitative serum levels of IgA, IgG, IgM) should be evaluated at baseline, at the end of induction chemotherapy (at least 4 weeks after last induction dose and/or prior to C1D1 of consolidation), post consolidation therapy, at completion of maintenance therapy, and/or at the EOT.

[12]**Hepatitis screening** to include hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody

[13]**Pregnancy tests for females of childbearing potential**: A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy testing must be performed with a method of serum or urine testing with a sensitivity of at least 50 mIU/mL. Pregnancy testing in FCBP will occur at baseline and within 48 hours of each induction, consolidation, and maintenance therapy.

[14]**CT imaging of chest, abdomen, pelvis (and neck if clinically indicated)** to be performed at baseline, after C4 of induction, post consolidation therapy, and after C4 and C8 of maintenance**.** The post C8 scans should be done at the same time as the EOT visit, approximately 30 (+/-5) days post last dose. CT imaging is required after treatment completion or at the EOT visit for all subjects, regardless of reason for treatment discontinuation. During the follow-up phase, CT imaging will occur approximately every 6 months for up to 2 years. Thereafter, follow-up imaging will be at physician discretion. See section 7.5. CT imaging of the neck, abdomen, and pelvis should be performed with IV contrast; chest CT imaging may be performed without IV contrast.

[15]**PET imaging** is required as part of disease assessments only for subjects who require re-assessment to determine CR status or if clinically indicated as part of disease assessment (i.e., disease sites not adequately visualized/assessed by CT imaging).

[16]Formal disease assessments (palpable disease, imaging assessment, other clinically evaluable disease) to be performed at baseline, after C4 of induction, post consolidation therapy, and after C4 and C8 of maintenance. The post C8 disease evaluation should be done at the same time as the EOT visit, approximately 30 (+/-5) days post last dose. During the follow-up phase, disease assessment with clinical evaluation will occur every 3 months for up to 2 years. After 2 years of follow-up, subjects will be followed annually for up to 5 years for survival and disease progression. See section 7.5.

[17]EOT visit will be performed at 30 days (±5 days) following the last dose of study drug, including post C8 of maintenance.

[18]Creatinine clearance to be calculated using Cockcroft-Gault formula (Appendix C). Baseline creatinine clearance may be verified by 24-hour urine collection.

[19]To be obtained pre-consolidation, unless otherwise noted.

[20]Post consolidation therapy visit will be performed at 30 days (+5 days) following the final dose of consolidation therapy.

[21]Obinutuzumab infusions C1D8 and C1D15 may be given in a treatment window of ±3 days.

[22]Baseline p53 mutation analysis is strongly recommended, although not required for study enrollment. In subjects already enrolled, p53 mutation analysis can be performed retrospectively or prospectively on diagnostic specimens. For ALL UW subjects, additional, but separate p53 testing will be performed on existing tissue samples as part of Dr. Yang's research study, UW16068.Acceptable methods of p53 mutation testing include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and/or molecular sequencing.

[23]Spleen craniocaudal dimension of 13 cm is the upper limits of normal for response assessment.

4 Glossary of Abbreviations

Abbreviation	*Term*
5-HT_3	5-hydroxytryptamine (serotonin)
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse events of special interest
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BM	Bone marrow
BMA	Bone marrow aspirate
BO	Bendamustine + obinutuzumab
BR	Bendamustine + rituximab
BSA	Body surface area
BVR	Bendamustine, bortezomib, rituximab
C	Cycle
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRC	Clinical Research Committee
CrCl	Creatinine clearance
CRF	Case report form
CRCO	Central Research Coordinating Office
Cri	Complete response with incomplete count recovery
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
D	Day

DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DOT	Disease Oriented Team
DSMB	Data Safety Monitoring Board
EC	Ethics committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FCBP	Females of childbearing potential
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony stimulating factor
GCP	Good clinical practice
IB	Investigational Brochure
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion related reactions
IV	Intravenous/intravenously
IWCLL	International Working Group on Chronic Lymphocytic Leukemia
L O D	Limit of Detection
LOQ	Limit of quantification
MCL	Mantle cell lymphoma
mAb	Monoclonal antibody
MIPI	Mantle cell lymphoma International Prognostic Index
MRD	Minimal residual disease
NK	Natural killer
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse
Events NGS	Next generation sequencing
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate

OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
PFS	Progression-free survival
PD	Progressive disease
PET	Positron-emission tomography
PI	Principal investigator
PR	Partial response
PSR	Protocol Summary Report
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-FC	Rituximab, fludarabine, cyclophosphamide
SAE	Serious adverse events
SD	Stable disease
SPM	Second primary malignancy
TLS	Tumor lysis syndrome
TTP	Time to progression
ULN	Upper limit of laboratory normal
UWCCC	University of Wisconsin Carbone Cancer Center
VcR-CVAD	Bortezomib, rituximab, cyclophosphamide, vincristine, doxorubin, dexamethasone
WBC	White blood cell count
WON	Wisconsin Oncology Network

5 Background and Rationale

5.1 Diagnosis and natural history of mantle cell lymphoma

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma (NHL) with a disease history and prognosis that tends to be intermediate between that of indolent and aggressive NHLs.[18,19] Patients with MCL tend to present with advanced stage disease and extranodal sites of involvement.[19] Therapy can result in disease remission, but ultimately any therapy administered is not curative. The median age of diagnosis is above the age of 60 years, and many patients diagnosed in this typical age range have pre-existing medical co-morbidities.[19] The natural history and prognosis of MCL can be quite variable, with up to one-third of MCL patients exhibiting a more indolent disease progression pattern.[10-12] The variability in disease behavior and diversity in patients; ages and co-morbidities can greatly affect the choice and tolerability of first-line therapy.

Based on current prognostic indices, it remains difficult to predict patients who may experience more indolent disease behavior at the time of diagnosis. The MCL International Prognostic Index (MIPI) is based on the 4 independent prognostic factors of age, ECOG performance status, LDH, and WBC, and is of value for pretreatment risk-assessment in patients with advanced stage MCL.[20] However, additional indicators of longer-term outcomes based on early response assessment and other means of individual risk assignment remain insufficient. Minimal residual disease (MRD) testing is proposed as a means of identifying patients who may experience durable remissions with initial non-intensive therapy approaches, and offers the possibility of individually tailoring therapy based on early response, thereby minimizing treatment-related toxicities while preserving efficacy of therapy.

5.2 Initial treatment of MCL

In younger and fitter adults with MCL, more intensive induction therapy with consolidative ASCT is considered a standard therapy approach. This is based on compelling data from the NORDIC lymphoma group reporting impressive 6 year event-free and progression-free survivals of 56% and 66%, respectively, in patients younger than age 66 with newly diagnosed MCL treated with dose-intensive induction chemotherapy (R-maxi-CHOP alternating with R-cytarabine) followed by consolidative ASCT.[21] Similarly, several studies using dose-intensive regimens in younger MCL patients have demonstrated excellent long term outcomes, with 5-year progression-free survival (PFS) rates of 50-60% and 5-year overall survival (OS) rates of 65-75%.[21-24] As anticipated, toxicities (primary hematologic and infectious) are substantial with these intensive up-front treatment approaches, making them not feasible for older adults. However, it is still somewhat unclear as to whether intensive strategies improve OS in MCL relative to non- intensive strategies. One randomized clinical trial showed improved PFS using an intensive strategy, while one observational study reveals similar outcomes using non-intensive strategies.[25,26] In addition, moderate intensity induction regimens with bortezomib combined with rituximab and a modified hyper-CVAD regimen have demonstrated 3-year PFS of 63% and 72%, with an enrolled population that included older and less fit adult patients.[3,4]

However, a majority of patients with MCL will not be eligible for these high- or moderate- intensity regimens based on age and co-morbidities. In these patients, a

bendamustine + rituximab (BR) induction regimen has been a standard based on the data reported by the German StiL trial,[1] with MCL patients having an overall response rate of 93% (CR rate of 40%) and 2-year PFS of approximately 60-70% after receiving 6 cycles of BR and no maintenance therapy).[2] In the StiL trial, patients were randomized between 6 cycles of BR or R-CHOP, and toxicity was more favorable with BR, with significantly less neutropenia with BR (rates of grade 3-4 neutropenia 29% versus 69%) and infections (37% versus 50%).[1] Confirmation of these high rates of objective responses with an initial BR induction in MCL and other indolent NHLs was reported in the BRIGHT trial.[27] These data have been the basis for cooperative group trial E1411, which is investigating an induction regimen of BR versus BVR (BR + bortezomib) X 6 cycles and a 2nd randomization to rituximab versus rituximab + lenalidomide. This trial is scheduled to meet accrual by fall 2016. At present, there are no predecessor studies for non- intensive therapy of previously untreated MCL planned for roll-out from the U.S. cooperative groups (personal communication, Dr. Brad Kahl, Washington University, ECOG Lymphoma Committee Chair). In the interim, induction chemotherapy with BR with or without maintenance rituximab is the most common first-line non-intensive regimen used for older or less fit adults with MCL.

5.3 Bendamustine in MCL

Bendamustine is a chemotherapeutic agent that has dual functional properties of both an alkylating agent and a nitrogen mustard.[28] Through these unique cytostatic properties, bendamustine is able to inhibit DNA transcription, replication, and repair. In addition, some data have suggested that bendamustine's improved chemical stability compared with other nitrogen mustards may enable the compound to have more efficient DNA alkylating properties. These unique properties of bendamustine also enable it to exhibit only partial cross-resistance with other alkylating agents.[28,29] Bendamustine is approved in the U.S. for treatment of CLL and for indolent B cell NHLs progressing during or within 6 months of rituximab or a rituximab - containing regimen.

Bendamustine is frequently administered as a front-line chemotherapy agent in multiple subtypes of indolent NHL, including CLL and MCL, based on its known efficacy and acceptable toxicity profile.[1,30,31] Overall response rates of 75-92% and complete response (CR) rates of 33- 50% were reported in three separate phase II studies of BR in subgroup analyses of relapsed, indolent NHL populations with MCL.[32-34] BR was established as a reasonable induction standard by the German StiL trial (R-CHOP versus BR in previously untreated indolent NHL and MCL), with MCL patients (n=94) having 2-year PFS of approximately 60-70% (after 6 cycles of BR and no maintenance therapy).[1] The BRIGHT trial investigated the activity of R-CHOP/R-CVP versus BR as initial therapy for indolent NHL and MCL.[27] In this international, randomized, non- inferiority study (n=447), BR was determined to be non-inferior to R-CHOP/R-CVP with overall response rate (ORR) 97% versus 91% and CR rate of 31% versus 25%. There was more GI toxicity (i.e., nausea and vomiting) and hypersensitivity reactions with bendamustine, but less neutropenia, alopecia, and neuropathy.[27] Among the subgroup of patients with previously untreated MCL, ORR was 94% and CR was 50%, consistent with other reports.[27] However, data regarding PFS with front-line therapy with BR in MCL was not reported.

Additional reports have shown activity of bendamustine in relapsed and previously untreated MCL. Rummel et al reported outcomes of a subgroup of patients with relapsed/refractory NHL treated with BR, including 16 patients with MCL (7 refractory to their last therapy).

Among these MCL patients, 12/16 (75%) responses were observed, including 50% with a CR.[33] Robinson et al reported an ORR of 92% and complete or unconfirmed CR rate of 59% among a subgroup of NHL patients with MCL.[32] PFS was 23 months in the entire cohort of relapsed indolent NHL treated with bendamustine.[32] Toxicity was manageable in this report of patients with relapsed indolent NHL or MCL treated with BR (n=66). While 36% of patient experienced grade 3-4 neutropenia, only 10% of patients experienced grade 3-4 infections; only 9% of patients experienced grade 3-4 thrombocytopenia.[32] Warsch et al reported a multicenter experience with bendamustine for treatment of MCL. The ORR of 83% and CR rate of 50% was consistent with objective response in other reports, and the observed time-to-treatment failure was 16.2 months in this predominantly relapsed MCL population.[35] Grade 3-4 infections were observed in 10% of treated patients, and neutropenic fever occurred in only 7% of patients. Thrombocytopenia is common with bendamustine, and 20% of patients experienced grade 3-4 thrombocytopenia, although notably without significant bleeding complications observed.[35]

Based on these data of efficacy and tolerability of bendamustine in MCL, the combination of bendamustine + monoclonal antibody therapy (primarily rituximab) is considered a standard induction therapy for previously untreated ML, particularly in older adults with co-morbidities and toxicity concerns with more intensive induction approaches. BR is a listed as a standard therapy option in elderly MCL in the NCCN guidelines: (https://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf).

5.4 Monoclonal antibody therapy in MCL

The majority of data with monoclonal antibody (mAb) therapy in treatment of MCL has been with the anti-CD20 mAb rituximab. Rituximab has limited durable benefit as a single-agent in MCL, but rituximab combinations with cytotoxic chemotherapy are standard induction therapy approaches in both newly diagnosed and relapsed MCL. In addition, there has been experience with maintenance rituximab in MCL, utilizing the same approach to improve PFS demonstrated with maintenance rituximab in follicular lymphoma and other indolent NHL histologies.[36-40]

Two small, randomized controlled trials observed conflicting results about the benefit of maintenance rituximab following induction chemotherapy in MCL. The German Low Grade Lymphoma Study Group treated patients with relapsed NHL with induction rituximab + chemotherapy, then randomized patients to rituximab maintenance for 9 months or observation.[38] Of the 47 patients analyzed in the MCL cohort, a statistically significant improvement in response duration was observed in favor of maintenance rituximab (remission beyond 2 years, 45% vs. 9%, p = 0.049).[38] In comparison, the Swiss Group for Clinical Cancer Research (SAKK) randomized104 patients with a mixture of untreated and relapsed MCL to a single 4-week rituximab treatment or a prolonged rituximab schedule of a 4-week treatment followed by a single dose every 8 weeks for 4 doses. The extended schedule did not improve response rates, response duration, or event-free survival (EFS).[41] The reasons for these discrepant results are unclear, but the quality of the response to induction therapy may affect the likelihood of benefit from maintenance rituximab.

A phase II study from the Wisconsin Oncology Network (WON) in 30 patients with previously untreated MCL observed a 3-year PFS of 63% and OS of 86% following treatment with an induction regimen of bortezomib, rituximab, and modified hyper-CVAD chemotherapy (VcR-CVAD) followed by maintenance rituximab as a single dose every 3 months for 5 years.[42]

E1405 further evaluated the efficacy of VcR-CVAD X 6 cycles in previously untreated MCL, followed by 2 years of maintenance rituximab or ASCT. Three-year PFS and OS were 77% and 88%, respectively, and did not differ between those patients who received maintenance rituximab (n=44) and ASCT (n=22).[43] Similarly, a recent report by the European Mantle Cell Lymphoma Network reported an excellent 3- year overall survival of 86% among elderly patients with newly diagnosed MCL treated with 8 cycles of R-CHOP chemotherapy followed by rituximab maintenance administered until disease progression.[44] The observed PFS and OS in these studies compares favorably with some reports of more intensive induction regimens with or without consolidative ASCT in front-line therapy of MCL.[22,24] Incorporation of novel mAbs such as obinutuzumab may improve upon these established outcomes with rituximab maintenance without significantly altering the toxicity profile.

5.5 Obinutuzumab

5.5.1 Structure and mechanism of action of obinutuzumab

Obinutuzumab (GA101, RO5072759), is a glycoengineered, humanized, type II anti-CD20 mAb. Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high antibody-dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement- dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction.[13,45] Obinutuzumab has demonstrated superiority to rituximab in preclinical studies using whole-blood depletion assays and human diffuse DLBCL and MCL xenograft models.[13] Given the direct cell death-inducing properties of obinutuzumab and the significantly enhanced ADCC in preclinical assays, it is possible that obinutuzumab may have greater efficacy than the widely used anti-CD20-mAb rituximab (Rituxan).

5.5.2 Clinical experience with obinutuzumab in CD20+ NHLs

For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure. Summaries of the clinical experience in CD20+ NHLs are included in the following section.

Study BO20999 (GAUGUIN; NCT00517530) (Phase I)

BO20999 is an open-label, multicenter, phase I/II study to explore obinutuzumab safety and activity in relapsed/refractory NHL and CLL.[46] Thirteen CLL patients have received obinutuzumab at doses with a range of 400–2000 mg (given as a flat dose) across four cohorts.[47] There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL patients and were characterized predominantly by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two patients experienced four NCI- CTCAE grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis. Although the safety profile appears otherwise similar between NHL and CLL, there was an increase in NCI-CTCAE v3.0 grade 3/4 neutropenia noted in CLL patients, which were observed in 9 patients across the four dose levels administered. Five patients experienced NCI-CTCAE grade 4 neutropenia and 4 patients experienced NCI-CTCAE grade 3

neutropenia as the maximum severity. Of the 9 patients, 7 had one NCI-CTCAE grade 3/4 event and 2 patients experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 patients, and these patients responded quickly to G-CSF support. For the 3 patients who did not receive G-CSF, neutrophil counts normalized spontaneously.

Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL.

As assessed by the International Working Group on CLL (IWCLL) criteria, the end-of-treatment response rate with obinutuzumab monotherapy was 62% (8 of 13 patients with partial response (PR)).[47]

Study BO20999 (GAUGUIN; NCT00517530) (Phase II)

Twenty patients with relapsed/refractory CLL have received 1000 mg of obinutuzumab. The most commonly reported adverse event (AE) during the treatment period was IRR, reported in 19 (95%) of 20 patients. Fifteen patients experienced grade 3/4 AEs, of whom 14 patients had treatment-related grade 3/4 AEs (investigator assessment). Treatment-related grade 3/4 AEs were IRR (6 patients), neutropenia (4 patients), lymphopenia (2 patients), thrombocytopenia (2 patients), and anemia, pure red cell aplasia, pancytopenia, febrile neutropenia, herpes zoster, and interstitial lung disease (1 patient each). Eleven serious adverse events (SAEs) in 9 patients were reported during treatment, 9 of which were assessed by the investigator as related to obinutuzumab: IRR (4 patients) and febrile neutropenia, pancytopenia, pure red cell aplasia, interstitial lung disease and pyrexia (1 patient each). Three patients withdrew from further study treatment after the first infusion due to IRR. One death has been reported during follow-up from colon cancer. The most common AE in follow-up was nasopharyngitis, reported in 2 patients. End-of-treatment response assessment showed that four patients (20%) achieved a clinical response, with a best ORR of 25% in evaluable patients.[48]

A separate randomized phase II portion of the GAUGUIN trial evaluated the efficacy and safety of two doses of obinutuzumab in patients with heavily pretreated diffuse large B-cell lymphoma (DBLCL) and MCL.[14] The GAUGUIN study investigated differing dose levels of single-agent obinutuzumab in previously treated DLBCL and MCL. Patients were randomized to receive either 8 cycles of a 400 mg flat dose (n=21, 10 DLBCL, 11 MCL) or 8 cycles of obinutuzumab at an initial dose of 1600 mg for cycle 1 followed by 800 mg dosing for cycles 2-8 (n=19, 15 DLBCL, 4 MCL). Overall response rates were 24% (for 400 mg treatment arm) and 37% (for 1600/800 mg treatment arm) in this pretreated population, including a 20% response rate in rituximab-refractory patients.[14] Infusion-related reactions (IRR) were the most common treatment-related AEs, which were primarily grade 1-2 with the exception of 3 patients experiencing grade 3-4 IRRs. Hematologic toxicity was manageable, with only 1 patient experiencing grade 3-4 neutropenia.[14]

Study BO21003 (GAUSS; NCT00576758) (Phase I)

BO21003 is an open-label, dose-escalating, multicenter phase I/randomized phase II study in patients with relapsed/refractory CD20+ malignant disease. In study BO21003, 22 patients have been administered obinutuzumab (10 follicular, 5 CLL, 2 small lymphocytic lymphoma, 3 DLBCL, 1 MCL, 1 transformed lymphoma). Patients were heavily pretreated

with a median of 4 prior therapies, and 50% of patients were rituximab-refractory. Infusion related events were the most common toxicity, with 16 events during the first infusion and only 8 events with all subsequent infusions. Most IRR were grade ≤2, although 4 grade 3 IRR were observed and 1 grade 4 IRR (associated hypoxia which led to permanent discontinuation of study treatment in this patient). Five events of grade 3/4 neutropenia were observed, and 1 event of grade 3 thrombocytopenia was reported. Six minor infections and 1 event of febrile neutropenia were reported. The ORR was 25% (5 patients, all partial responses), with 13 additional patients demonstrating SD.[49]

Study GAO4768g / GAGE / NCT01414205 (Phase II)

GAO4768g is an open-label, randomized, multicenter, phase II study evaluating the efficacy and safety of obinutuzumab administered at 1000 mg versus 2000 mg doses in patients with previously untreated CLL.[50] Eighty patients were randomized and stratified based on Rai stage and tumor mass. For patients who received the 1000-mg doses, obinutuzumab was administered with three 1000-mg doses in the first 21-day cycle (the first 1000-mg dose was administered over 2 days: 100 mg administered on day 1, 900 mg administered on day 2; 1000 mg was administered on both days 8 and 15). In the subsequent cycles (cycles 2 — 8), 1000 mg of obinutuzumab was administered on the first day of each cycle. For patients who received the 2000-mg doses, obinutuzumab was administered as follows: 100 mg on cycle 1, day 1; 900 mg on day 2; and 1000 mg on day 3. On days 8 and 15 of cycle 1, 2000 mg was administered on each day. For cycles 2 — 8, 2000 mg of obinutuzumab was administered on day 1 of each cycle. ORR was assessed at 2 months post-therapy according to the IWCLL criteria. The ORR for the 1000 mg and 2000 mg obinutuzumab treatment arms were 49% compared with 67%, respectively; 2-sided $p = 0.0779$. Complete response/complete remission with incomplete blood count recovery (CR/CRi) was achieved by 5% of patients (2/41) in the 1000-mg arm compared with 21% of patients (8/39) in the 2000-mg arm.

The most common Grade 3/4 AEs were IRRs (23% vs. 11%) and neutropenia (3% vs. 5%) for the 1000-mg and 2000-mg arms, respectively.[50]

Study GAO4779g (GALTON; NCT01300247) (Phase II)

GAO4779g is an open-label, non-randomized, multicenter, phase II study.[51] In the GALTON study, 41 patients with untreated CLL were treated with obinutuzumab 1000 mg (100 mg IV on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15 of cycle 1; 1000 mg on day 1 in cycles 2 — 8) and either fludarabine + cyclophosphamide (G-FC: 25/250 mg/m^2 IV on days 2 — 4 of cycle 1, then on days 1 — 3 of cycles 2 — 6) or bendamustine (G-B: 70 mg/m^2 IV on days 2 – 3 of cycle 1, then on days 1 – 2 of cycles 2 – 6. Each cycle was 28 days.

The most common AEs (any grade) occurring in the G-FC arm were obinutuzumab-related IRRs (91%), nausea (76%), fatigue (57%), constipation (48%), and neutropenia (43%); in the G-B arm, they were obinutuzumab-related IRRs (90%), nausea (65%), neutropenia (55%), diarrhea (50%), and pyrexia (45%). The most common Grade 3/4 AEs were obinutuzumab-related IRRs (29%, 10%), neutropenia (43%, 55%), and infections (19%, 5%) for G-FC and G-B, respectively. Fourteen patients experienced SAEs (G-FC, $n = 6$; G-B, $n = 8$), with events including febrile neutropenia (5 events); infections (4 events); IRRs (3 events); nausea, vomiting, pyrexia (2 events each); and diarrhea, fatigue, tachycardia, tumor lysis syndrome, syncope, mental status changes, neutropenia, face swelling, and hypertension (1

event each). Nine patients (G-FC, n = 7; G-B, n = 2) had AEs leading to treatment discontinuation, including grade 3/4 neutropenia (3 patients in G-FC [1 of these 3 patients also had grade 4 cellulitis] and 2 patients in G-B), grade 3 thrombocytopenia (2 patients in G-FC), grade 4 pancytopenia (1 patient in G-FC), and grade 4 aspartate aminotransferase (AST)/grade 3 alanine aminotransferase (ALT) elevation (1 patient in G-FC).
The ORR was 62% (CR, 2; CRi, 3; PR, 8) in patients who received G-FC and 90% (CR, 4; CRi, 5; PR, 9) in patients who received G-B, including 6 patients (G-FC, n = 4; G-B, n = 2) not evaluable due to inadequate response evaluation. Four patients in the G-FC arm (0 in G-B) had SD during and after therapy. No patient progressed during the study.

Study BO21004 (CLL11; NCT01010061) (Phase III)

CLL11/BO21004 is an open-label, multicenter, three-arm randomized, Phase III study to compare the efficacy and safety of obinutuzumab + chlorambucil (GClb), rituximab + GClb (RClb), or Clb alone in previously untreated CLL patients with comorbidities.[16] The primary endpoint of the study is PFS.

BO21004 enrolled 781 patients and an additional 6 patients during a safety run-in period before randomization. The median age of enrolled patients was 73, and the median Cumulative Illness Rating Score was 8 (score of >6 required for enrollment; range of rating score 0-56 with higher score indicating worse health). Toxicities that were more frequent in obinutuzumab-treated patients included infusion-related reactions (grade ≥3 IRR in 20% of obinutuzumab-treated patients compared with 4% of rituximab-treated patients) and neutropenia (35% of obinutuzumab-treated patients experiencing grade ≥3 neutropenia compared with 27% of rituximab-treated patients). However, risk of infection was not increased with obinutuzumab versus rituximab (grade ≥3 infections 14% versus 12%). In addition, rate of infection was not different compared with chlorambucil alone (rate of grade ≥3 infection 14% with chlorambucil alone).[16]

Overall response rates and CR rates were increased in obinutuzumab-treated patients. Patients treated with GClb had an ORR of 77.3% (22.3% CR's) compared with RClb (ORR 65.7%; CR 7.3%) and Clb alone (ORR 31.4%, all PRs). The response rate of GClb and RClb were statistically significantly improved when each were compared with Clb alone, and ***CR rates were significantly improved with GClb compared with RClb***.

Median PFS was significantly improved for both GClb and RClb compared with Chl alone. Median PFS was 26.7 months with GClb compared with 11.1 months with Chl alone (hazard ratio for progression or death, 0.18; 95% confidence interval [CI] 0.13-0.24; p<0.001). Patients treated with RClb experienced a median PFS of 16.3 months (compared with PFS of Chl alone, hazard ratio, 0.44; 95% CI, 0.34 to 0.57; P<0.001). ***Treatment with GClb compared with RChl resulted in prolonged PFS (hazard ratio, 0.39; 95% CI, 0.31-0.49; P<0.001)***. In addition, there was an overall survival benefit with GClb compared with Chl alone (hazard ratio for death, 0.41; 95% CI, 0.23-0.74; p=0.002).[16]

GAO4753g, GO01297 GADOLIN trial (NCT01059630)

The GADOLIN trial evaluated the efficacy of obinutuzumab in the treatment of rituximab-refractory indolent non-Hodgkin lymphoma. GADOLIN was an open-label, randomized, multicenter/multinational phase III trial including adult patients with CD20+ rituximab-refractory NHL.[15] Patient were randomized to receive either 6 cycles of induction chemotherapy with

bendamustine + obinutuzumab (BO) or 6 cycles of bendamustine alone (B-alone). Dosing for the BO arm was bendamustine 90 mg/m2 IV on days 1 & 2 of each 28-day treatment cycle (cycles 1-6), and obinutuzumab 1000 mg IV on days 1, 8 & 15 of cycle 1 and 1000 mg IV on day 1 of cycles 2-6. Dosing in the B-alone arm was bendamustine 120 mg/m2 IV on days 1 & 2 of each 28-day cycles (cycles 1-6). Patients not progressing in the BO induction treatment were eligible to receive obinutuzumab maintenance therapy 1000 mg IV every 2 months for up to 2 years.

The median age was 63 years in each treatment arm, and approximately 80% of enrolled patients have follicular lymphoma histology. This study did not include MCL patients. Over 90% of patients were refractory to their last chemotherapy regimen (in addition to being rituximab-refractory as eligibility criteria) and >75% were refractory to both rituximab and an alkylating agent.[15]

The study was closed after a pre-planned interim analysis determined a statistically significant improvement in the primary endpoint of PFS after a median follow-up of 21.0 months (BO arm) and 20.3 months (B-alone arm). PFS was not reached in the BO arm versus 14.9 months in the B-alone arm (hazard ratio 0.55, p=.0001).[15]

Obinutuzumab did not appear to significantly increase the risk of SAEs with treatment. As expected, IRRs were more common with BO versus B-alone (11% versus 16%). SAEs were observed in 38% of BO patients versus 33% of B-alone patients, with deaths due to AEs occurring in 12 patients in both treatment arms. Three of these deaths in the BO arm were treatment-related, and 5 deaths in the B-alone arm were treatment-related. Fatal AEs in the BO group during induction were (n=3): agranulocytosis, colorectal cancer, and vascular pseudoaneurysm. Fatal AEs in the BO group following induction were: Fatal AEs after induction were (n=9): acute myeloid leukemia (n=1), chronic renal failure (n=1), bacterial sepsis (n=2), fungal sepsis (n=1), sepsis unspecified (n=1), gastroenteritis (n=1), graft-versus-host disease (n=1), and T-cell lymphoma (n=1). Fatal AEs in the B-alone group during induction were: adenocarcinoma, Pneumocystis jirovecii pneumonia, sepsis (n=2), and tumor lysis syndrome.

Fatal AEs in the B-alone group after induction were (n=7): acute myeloid leukemia, ischemic stroke, leukemia, neutropenic sepsis, pneumonia, Pneumocystis jirovecii pneumonia, and sepsis.[15]

Other common toxicities observed with BO versus B-alone treatment included: neutropenia (33% vs 26%), thrombocytopenia (11% vs 16%), and anemia (8% vs 10%).[15]

Additional Clinical Experience with Obinutuzumab

For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure.

5.6 MRD testing in lymphoma

5.6.1 Background on MRD testing with next-generation sequencing in MCL

Therapy for MCL may result in sustained remissions for many patients, but disease relapse is inevitable. Residual lymphoma cells that are below the level or routine laboratory or

radiographic evaluation are the presumed source of relapse. Current standard strategies to determine the extent and depth of remission include radiographic imaging and bone marrow aspirate (BMA)/biopsy. The definition of bone marrow (BM) response is a morphologically normal marrow with <2% clonal B-cells detected by flow cytometry. Imaging assessment requires all lymph nodes to have been reduced to a maximum of <1-1.5 cm in size and/or be negative by PET imaging.[52] However, the presence of a CR by imaging assessment does not preclude the possibility of a substantial burden of microscopic disease. For example, the diagnostic accuracy of PET imaging is quite limited with nodal disease <1 cm in size. Further quantification of the burden of residual lymphoma post-treatment beyond what is assessed with standard imaging and biopsy practices may better predict depths and durations or remission.

Clinically relevant MRD information can be evaluated through several different techniques, including flow cytometric immunophenotyping (using aberrant or lymphoma-associated immunophenotypes and immunoglobulin light chain restriction), polymerase chain reaction (PCR) targeting specific chromosomal aberrations or clonally rearranged immunoglobulin genes, and most recently, next-generation sequencing (NGS) to detect clonally rearranged immunoglobulin genes. In MCL, the immunoglobulin heavy chain gene rearrangement is the most broadly applicable marker for MRD studies, as a rearrangement is detectable in approximately 80-85% of cases.[9] NGS is a high-throughput gene sequencing methodology that permits a tremendous depth of DNA sequencing. The modern NGS platform by Adaptive Biotechnologies (ClonoSEQ) is able to detect 1 in 10^{-6} lymphoma cells, which is superior to the level of MRD detectable by other methods (for example, 10^{-3} sensitivity achievable with four- color flow cytometry, and 10^{-4} to 10^{-5} achievable with PCR-based assays).[9]

5.6.2 Clinical experience with MRD testing in MCL

Prior to the availability of NGS technology, MRD evaluation with PCR-based techniques was explored in MCL, and confirmed to have prognostic value.[7,8] A retrospective analysis of 27 patients evaluable for MRD after autologous stem cell transplant (ASCT) for consolidation of initial cytoreductive chemotherapy showed a significant association between MRD status in the first year post-ASCT and PFS and OS. Of the 14 patients with clinical remission and MRD- negative status (defined as $\geq 10^{-4}$), median PFS was 92 months and median OS was not reached, which was significantly improved compared with median PFS of 21 months ($p<.001$) and median OS of 44 months ($p<.003$) among the 13 patients with residual MRD demonstrated during the first year post-ASCT (MRD from blood or marrow collected every 3 months for 12 months post-ASCT).[7] Another retrospective review of outcomes based on MRD status prior to ASCT in MCL was reported from the Fred Hutchison Cancer Center. This report described outcomes for 75 patients with MCL in complete remission prior to ASCT for MCL, using PCR- based techniques (for IgH rearrangement and translocation 11;14) as well was flow cytometry as part of the MRD assessment.[53] Eleven percent of patients were MRD-positive post-induction and prior to ASCT. Compared with patients who were MRD-negative, these MRD-positive patients had significantly worse outcomes, with a median PFS of 2.38 years (median PFS not reached for MRD-negative patients; 5-year PFS 75% for MRD-negative patients) and median OS of 3.01 years (median OS not reached for MRD-negative patients; 5-year OS 82% for MRD-negative patients).[53]

In the Nordic Lymphoma Group MCL-2 trial, patients were treated with an induction chemotherapy regimen of R-maxi-CHOP/R-cytarabine followed by consolidative ASCT. PFS differed significantly between patients with residual MRD-positivity by PCR-based techniques

within the first year of follow-up (median PFS 1.5 years) compared with those developing MRD positive >1 year post-treatment (median PFS 5 years). .[21] A subset of MCL patients treated with an intensive approach on CALGB 59909 had paired marrow and peripheral blood (PB) samples available for MRD assessment post-induction (2 cycles of rituximab, augmented CHOP, methotrexate), post-high-dose consolidation (rituximab, etoposide, cytarabine), and 3 months post-ASCT (following ASCT and 2 doses maintenance rituximab).[54] Thirty-nine patients had paired samples available for prognostic correlations. Three-year PFS was 82% versus 48% among those who were MRD-negative versus MRD-positive after induction chemotherapy.

However, post-induction MRD evaluations at later time points were not significantly associated with either time-to-progression or survival.[54] A report of CALGB 50403 investigated prognostic implications of MRD status using PCR-based technique in 49 MCL patients treated with intensive consolidation and consolidative ASCT for whom sequential MRD samples were available.[55] Patients with early eradication of MRD following 2 cycles of intensive induction therapy had significantly improved PFS (p=.017), and none of the patients who achieved MRD- negative status post-induction (n=15) have relapsed after a median of 3.3 years of follow-up.[55]

Pott et al described clinical outcomes as it relates to MRD status in 2 large international phase III trials of the European MCL Network in which MRD was a secondary endpoint.[8] The 2 trials included both younger patients treated with a more intensive induction and ASCT (MCL Younger) and older patients (MCL Elderly) treated with a less intensive induction (R-FC versus R-CHOP) followed by rituximab or interferon maintenance. Notably, there was a 90% success rate in obtaining PCR-amplifiable tumor tissue for MRD testing, which affirms the feasibility of MRD testing in these diverse populations enrolled at multiple centers.[8,56] PCR-based MRD testing evaluated clonal IgH VH-JH rearrangements as well as the translocation 11;14, with sensitivity to detect MRD to a level of at least 10^{-4}. Time points for MRD assessment by PB and/or BM samples included mid-term staging (after 3 or 4 cycles of induction), 4 weeks after completion of induction therapy, and every 2-3 months during maintenance or post-ASCT. A total of 156 patients had available MRD data and a documented clinical remission after induction. Patients in clinical remission who achieved an MRD-negative status after induction had an 87% chance of ongoing remission at 2 years compared with 61% of patients with residual MRD-positivity despite clinical remission (p=.004).[9] Sustained MRD negativity during maintenance therapy was also predictive of outcome. In the MCL Elderly trial, the response duration at 2 years was 76% in those with sustained MRD-negative status, compared with 36% of those with persistent residual disease by MRD analysis (p=.015).[9]

5.6.3 Next-generation sequencing in MRD assessment in MCL

More recently, MRD data have emerged using NGS technology. PCR-based assessments of MRD have multiple limitations which NGS may potentially overcome, including failure of amplification and/or identification of the clonal rearrangment in somatically hypermutated tumors and in cases of low-level lymphoma, residual disease below a feasible level of quantification by PCR-based assays.[57] In addition, NGS avoids the need for preparation of clonotype-specific primers for each patient and has the potential to achieve a higher level of sensitivity to 10^{-6} (compared with 10^{-4} to 10^{-5} in most PCR-based assays). Additionally, as an unbiased technique, NGS permits analysis of the clonogenic heterogeneity which may contribute to a better understanding of disease biology.[57]

A recent publication evaluated the concordance between MRD testing with real-time quantitative PCR (RQ-PCR) and NGS in multiple subtypes of B-cell lymphoproliferative disorders, including MCL.[57] Thirty patients with MCL were included in the analysis comparing RQ-PCR and NGS MRD assessments, which included 8 cases where an IgH marker by RQ-PCR was not detectable. Twenty-six (86%) of the MCL cases could be monitored by NGS, including 4 cases in which RQ-PCR failed to evaluate MRD. Among the MCL patients, there were 156 follow-up samples available for analysis, and 128 of the 156 (82%) follow-up samples were concordant between RQ-PCR and MRD.[57] Another report investigated concordance between MRD quantification in 22 patients with MCL treated on CALGB 10403 and CALGB 59909.[58] A high-frequency clonal rearrangement was observed in at least 2 receptors in 95% of MCL patients.

Good concordance was observed in the MCL patients with MRD assessed by PCR versus NGS, with NGS offering the improved ability to monitor multiple clonal sequences, having an improved turnaround time (about 1 week), and greater sensitivity (MRD detectable to 10^{-6}).[58]

Clinical data are emerging with NGS used prospectively for MRD assessments. For example, the results of S1106 (BR versus hyper-CVAD induction followed by autologous transplant) included MRD evaluation using NGS (Adaptive Biotechnologies) in 10 patients treated with BR induction therapy.[5] Eight patients achieved MRD-negative status post-induction, and 2-year PFS was 100% among these MRD-negative patients post-induction.[5]

A compelling retrospective analysis in diffuse large B-cell lymphoma using NGS demonstrated a strong correlation between 5-year time to progression and MRD status after only 2 cycles of chemotherapy.[6] Interim monitoring of circulating tumor DNA was available in 108 patients after 2 cycles of chemotherapy (EPOCH or rituximab + EPOCH chemotherapy). The 5-year time to progression was 80.2% for patients who were MRD-negative after 2 cycles of treatment compared with 41.7% in those who remained MRD-positive after 2 treatment cycles.[6] **These data are striking, and the basis for MRD testing of peripheral blood after 2 cycles of induction therapy in this protocol design.**

5.6.4 Use of blood and marrow samples for MRD analysis

The optimal tissue source of MRD assessment remains an important issue, and available data with PCR-based techniques suggest there may be disparity between PB and BM MRD assessments. Existing data supports about an 80-90% concordance between MRD assessments in the PB and marrow utilizing PCR-based techniques, while data regarding this concordance is yet to be definitively understood with NGS technology. For example, a German study with 40 paired BM and PB samples showed comparable results regarding MRD prediction in paired samples, although patients had not received rituximab + CHOP based induction regimens[7,9.] In a transplant population, 18 of 325 (5%) of BM samples after ASCT were discordant with PB.[59] The European MCL study group reported that 21 of 108 (19%) paired samples demonstrated MRD negativity in the PB while low-level MRD was detectable in the BM8.[8,9]

In the MRD assessment by PCR techniques utilized in CALGB 59909, 39 MCL patients had paired marrow and PB samples available for assessment after induction chemotherapy.[54] Nineteen patients were MRD-positive in both the marrow and the blood, and 12 patients were MRD-negative in both. Therefore, there was a discordance between PB and marrow in 8 of 39 patients (21%). Of these 8 patients, 6 were MRD-negative in the blood but positive in the

marrow, indicating that PB analysis underestimated MRD in approximately 15% of patients.[54] Two patients were MRD-positive in the PB and negative in the marrow, which was postulated to be related to focal presentation of lymphoma in the BM, or poor quality of BMA, or lack of marrow involvement by lymphoma.[54] Potts et al reported that among 44 paired PB and BM samples evaluated for MRD by PCR-based testing, concordance was observed in 86% (18 paired samples were MRD+ in marrow/blood and 20 samples were MRD-negative in marrow/blood).[7] There were 3 patients who were MRD negative in PB, but low-level MRD detectable in BM; in 3 patients with MRD-negative BM, MRD was detectable in PB.[7] The current ECOG protocol E1411 investigating and induction BR-based therapy is incorporating NGS (Adaptive Biotechnologies) as part of a prospective MRD analysis, including paired marrow and PB samples. Data from studies such as E1411 may help clarify if MRD testing using more easily attainable PB samples can yield consistent concordance with marrow samples.

5.6.5 Summary of rationale for NGS as MRD assessment tool

The NGS technology utilizing the ClonoSEQ platform by Adaptive Biotechnologies offers the opportunity to reliably evaluate MRD status during therapy for MCL, with good feasibility and rapid turn-around of results. The ClonoSEQ NGS assay is commercially available for use with multiple lymphoproliferative diseases, including MCL, and is performed by a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory. Given the uncertainties that remain about concordance of MRD testing results from PB and marrow, MRD assessment used for decision-making after consolidation therapy will include both marrow and blood samples. MRD testing at other time points (after cycle 2 induction, post-maintenance or EOT) will be primarily correlative in nature and will include only MRD analysis on PB.

5.7 Study rationale

Therapy options for older adults with MCL can be diverse depending on a patient's age and comorbidities as a primarily determinant of initial therapy intensity. In older adults, BR is a reasonable front-line regimen based on its efficacy and safety profile. In addition, multiple studies have suggested benefit of maintenance therapy with rituximab as a means of improving PFS with acceptable toxicity. However, there remains the need for improving depths and duration of responses and minimizing toxicity in older and frailer MCL patients.

Obinutuzumab is a more potent mAb compared with rituximab, which may improve the response rate and PFS when combined with bendamustine in this population of MCL patients. Although direct comparisons of obinutuzumab versus rituximab activity in previously untreated MCL are not available, inference from available data show an advantage in terms of higher rates of response and PFS in other histologies (i.e., CLL and indolent NHL), and could offer the possibility of higher rates of MRD negativity after a course of induction chemotherapy with bendamustine-based treatment.[15,16]

Multiple studies support a correlation between MRD-negative status and improved PFS. Evaluation of MRD status during the course of therapy may allow for treatment duration to be tailored based on the quality of an individual patient's response, thereby minimizing toxicity and offering the potential to preserve efficacy. In an older and frailer adult population, this focus on risk-adapted therapy to minimize toxicity is particularly relevant. In addition, up to one-third of mantle cell lymphomas will have a more indolent natural history of progression, which can be difficult to identify prospectively. Risk-adapting therapy offers the possibility of reducing over-treatment and minimizing toxicity in this heterogeneous population.

6 Study Objectives and Endpoints

6.1 Primary objective

The primary objective is PFS.

6.2 Secondary objectives

- To estimate the MRD status (MRD defined as reduction to $\geq 10^{-6}$ fold reduction in the IgV_H unique clone of MCL by NGS).
- To estimate the concordance rate between PB and bone marrow aspirates in predicting MRD status. To determine objective response rates (CR + PR) with induction BO in previously untreated MCL using the Lugano classification for response in lymphoma.[17]
- To determine overall survival.
- To determine toxicities observed with induction BO chemoimmunotherapy and obinutuzumab consolidation and maintenance.

7 Investigational Plan

Subjects meeting eligibility criteria will begin treatment as described below. All subjects will undergo BM biopsy, CT imaging, and/or PET imaging within 6 weeks prior to enrollment.

7.1 P53 mutation testing

Data on p53 mutation testing will be obtained from subject's baseline diagnostic tissue sample by either immunohistochemistry, fluorescence in situ hybridization, or molecular sequencing. P53 mutation testing can be obtained retrospectively in subjects already enrolled at the time that p53 mutation testing was added as a baseline characteristic, and have had prior p53 testing completed as standard of care. Subjects whom have not had prior p53 testing completed as standard of care on their baseline diagnostic tissue sample will be requested to have prospective p53 testing added to their baseline diagnostic tissue sample as research and will have this completed commercially. Although every effort will be made to obtain p53 mutation testing on enrolled patients, there may be cases where obtaining testing is not possible either retrospectively or prospectively due to circumstances such as cost issues (for non-UW sites obtaining p53 testing commercially) or lack of additional tissue. In those cases, p53 mutation testing is not a requirement for study enrollment. Commercial p53 testing results will be disclosed to subjects by their treating physician and be placed in their medical record.

Subjects enrolled at UW will have archived diagnostic research samples sentfor additional p53 mutation testing. This will be performed through a separate research protocol UW16068, which is performing p53 testing in mantle cell lymphoma via IHC, FISH, and molecular sequencing to validate the best testing method for reliably

establishing p53 mutation status in MCL. Samples submitted for protocol UW16068 (2017-0879) will be de-identified, glass slides assigned a separate subject ID. The investigator for protocol UW16068 will be blinded to the subject's identification and clinical information. 4-6 unstained biopsy slides will be obtained for each UW16086 subject enrolled at UW, with a minimum of 4 unstained slides required for p53 mutation testing though protocol UW16068. De-identification of these samples will include removing all protected health information and labeling obtained samples with the UW16068 study number, a separate subject ID, date of collection and sample type. No subject samples outside of UW Hospital will be included in the biopsy specimens shared with research protocol UW16068. Data generated from protocol UW16068 will not be included in UW16086. The p53 status obtained from protocol UW16068 will not be viewable to subjects in their electronic medical record and will not be disclosed to subjects by the treating physician.

Subjects may have commercial p53 testing done as part of their standard of care procedures and independent of this research protocol as this testing is available to all subjects. If commercial p53 testing is completed, these results will be made available outside of the research study and included in the subject's medical record.

7.2 MRD assessments

7.1.1 Baseline MRD samples

A pre-treatment tissue sample must be identified and submitted to Adaptive Biotechnologies for identification of the unique clones of immunoglobulin heavy gene (IgV_H) mutations present at baseline to use as comparison for subsequent MRD assessments. Preferably this sample would be from the dominant site of disease involvement (i.e., lymph nodes, BM, PB).

Samples submitted for baseline MRD testing must be collected within 12 months from the date of enrollment, or between enrollment and C1D1 of treatment. For example, a BMA may be collected for MRD evaluation at the time a staging BM biopsy is performed to fulfill eligibility requirements per protocol. Subjects with baseline lymphocytosis at enrollment may have a PB sample drawn for baseline MRD analysis. MRD samples collected after enrollment should be submitted immediately to allow for identification of the unique immunoglobulin heavy gene clones, but must be submitted no later than concurrent with the first interim MRD assessment after C2 of induction chemotherapy (i.e., the baseline MRD sample and the first interim PB MRD assessment after C2 of induction chemotherapy may be submitted concurrently).

It is anticipated that up to 8-10% of subjects with mantle cell lymphoma may not have a unique enough immunoglobulin heavy chain sequence to allow for MRD assessment (i.e., considered to be MRD-negative even in the situation of clinically evident disease). In this case, subjects may continue on protocol therapy to receive the full protocol therapy as if they are presumed to be MRD-positive at each MRD evaluation. The sample size has been adjusted to account for this situation of a non-unique heavy chain sequence for reliable MRD assessment (refer to section 14, Statistical Considerations).

Tissue samples acceptable for assessment of immunoglobulin heavy chain sequencing for MRD analysis include:

- Formalin-fixed, paraffin-embedded (FFPE) tissue, 3-5 slides should be unstained and preferably 8-10 um thick
- Fresh BMA (3 cc in EDTA tube)
- Fresh PB (10 cc in EDTA tube)
- Other acceptable specimens include frozen cells/cell pellet and purified DNA; refer to Adaptive Biotechnologies ClonoSEQ specimen requisition form for details.

Adaptive Biotechnologies is providing the sample collection kits. Refer to the WON Operations Manual for details.

7.1.2 MRD follow-up assessments

MRD assessment will be obtained at the following time points:

- After C2 of induction therapy (up to 7 days before C3D1 of induction therapy) – PB only
- After consolidation therapy (30 days (+ 5 days) following the final dose of consolidation therapy) – PB and BMA
- After maintenance therapy (between 4-6 weeks after the final dose of maintenance obinutuzumab) – PB only
- At the EOT visit (30 days (+/-5) post last dose) in subjects discontinuing protocol therapy early, in the absence of progression – PB only

Investigators should be aware that the time period from sample submission to Adaptive Biotechnologies and reporting of results is 7 business days. The timing of samples being drawn and submitted should be performed to allow for adequate processing time to allow adherence with the treatment calendar.

Tissue sample types acceptable for submission for MRD assessments are identical to the sample types listed in section 7.1.1.

7.1.3 Discordant MRD assessments

Discordance between BMA and PB MRD assessments

Based on the experience of Potts et al, it is anticipated that there may be 20% of patients with discordance between MRD assessments in the PB and BMA. Most commonly, this would be expected to occur with negative PB MRD assessments and persistently positive MRD assessments in the BM. The presence of MRD negativity in the BM but positive MRD assessments in the PB appears to be a relatively infrequent phenomenon, occurring in <5% of cases. Because MRD status is being utilized as a parameter for potentially omitting maintenance therapy, it is required that both PB and BM show MRD negativity for a patient to be considered MRD negative per the protocol therapy and be allowed to receive abbreviated therapy.

Discordance between restaging imaging and MRD assessments

Subjects do not need to meet criteria for CR by imaging to be considered MRD-negative. However, subjects who are felt to have clinical evidence of residual lymphoma by CT or PET imaging at restaging following consolidation obinutuzumab are allowed to continue receiving protocol therapy as if they are MRD positive regardless of the MRD status in the PB and BM. This discordance between imaging and MRD status is anticipated to be a rare event.

7.1.4 Interpretation of MRD assessments

Two distinct thresholds of disease detection are reported with the ClonoSEQ Assay: the Limit of Detection (LOD) and the Limit of Quantitation (LOQ). The LOD is the lowest level of residual disease that can be reliably detected with a 95% probability that the sequence(s) detected are true markers of the malignancy being tracked. LOQ refers to the lowest level of residual disease that can be reliably quantified. **For the purposes of MRD interpretation, only results showing residual sequences below the level of detection are considered to be MRD-negative.**

Subjects must have MRD-negative status of both PB and BM to be considered MRD negative for purposes of protocol therapy. Subjects determined to be MRD negative in both BM and PB after consolidation therapy will omit maintenance therapy and proceed directly to the follow-up phase. A copy of the MRD testing results will be generated and scanned into the electronic medical record (EMR) of enrolled subjects. A printed copy of the MRD results will additionally by offered to subjects.

7.2 Induction chemoimmunotherapy (28 day cycles)

Cycle 1 induction:

- Bendamustine 90 mg/m^2/day IV days 1 and 2
- Obinutuzumab 100 mg IV day 1, 900 mg IV day 2, 1000 mg IV days 8 & 15

Cycles 2-6 induction:

- Bendamustine 90 mg/m^2/day IV days 1 and 2 every 28 days, C2-6
- Obinutuzumab 1000 mg IV day 1 every 28 days, C2-6

All subjects will undergo a PB MRD assessment after C2 of induction therapy. Subjects will undergo repeat disease assessments after C4 of induction. Subjects with baseline marrow involvement who have achieved a possible CR based on imaging should be considered to have an unconfirmed CR until after the post-consolidation restaging BM biopsy. Subjects achieving an objective response to induction therapy, but with toxicities that may limit ability to receive 6 cycles of BO, may proceed to consolidation therapy as early as after 4 cycles of induction BO (following lymphoma restaging and MRD assessment).

Subjects achieving an objective response (i.e., PR, CR, or stable disease with tumor shrinkage not meeting criteria for PR) to bendamustine and obinutuzumab induction chemotherapy are eligible to proceed to obinutuzumab consolidation therapy. Subjects who have findings on clinical or laboratory exam suggesting progressive disease (PD) must undergo CT imaging at the time of suspected progression to reassess their disease status.

Subjects with possible CR with residual masses of undetermined significance at the time of disease assessments will undergo PET imaging to evaluate their remission status. Responses will be assessed according to the Lugano classification criteria.[17]

7.3 Consolidation therapy

- Obinutuzumab 1000 mg IV weekly X 4 doses

Consolidation therapy will begin no later than 12 weeks after the last dose of induction chemotherapy once there has been recovery of the neutrophils to ≥1000/μL.

Subjects will undergo reassessment of disease 30 days (+/- 5 days) following the final dose of consolidation therapy. All subjects will undergo a PB draw and BMA for assessment of MRD status. Subjects will undergo a restaging BM assessment to confirm objective response, and additional marrow aspirates will be sent for standard of care morphology and flow cytometry (in addition to research sample for MRD assessment), and a core biopsy will be collected to evaluate for morphologic involvement by lymphoma (standard of care to restage lymphoma).

Subjects achieving an objective response (i.e., PR, CR, or SD with tumor shrinkage not meeting criteria for PR) to obinutuzumab consolidation therapy and are MRD positive are eligible to proceed to obinutuzumab maintenance therapy. If subjects are MRD-negative and have clinical evidence of residual lymphoma by CT or PET, they are allowed to proceed to maintenance therapy, see section 7.1.3. Subjects who have findings on clinical or laboratory exam suggesting progression of disease must undergo CT imaging at the time of suspected progression to reassess their disease status.

Subjects with possible CR with residual masses of undetermined significance at the time of disease assessments will undergo PET imaging to evaluate their remission status. Responses will be assessed according to the International Working Group Criteria.[52]

7.4 Maintenance therapy (8 week cycles)

Obinutuzumab 1000 mg IV day 1 of each cycle X 8 cycles. Maintenance therapy will begin no later than 8 weeks after the last dose of consolidation chemotherapy once there has been recovery of neutrophils to ≥1000/uL.

Subjects will undergo reassessment of disease after C4 and C8 of maintenance obinutuzumab. The post C8 disease evaluation should be done at the same time as the EOT visit, approximately 30 (+/-5) days post last dose. Subjects with CT and/or PET imaging consistent with possible CR will undergo BM evaluation to verify a CR. All subjects will undergo a PB draw for assessment of MRD status 4-6 weeks after the final dose of obinutuzumab maintenance therapy.

7.5 Follow-up phase

At the time of treatment discontinuation for any reason, all subjects will undergo EOT evaluations at 30 days (+/-5) post last dose of treatment. Whenever possible, restaging CT scans (with or without repeat PET imaging) and a clinical assessment of any other sites of evaluable disease should be performed at 30 days (+/- 5) of last dose. In addition, a safety assessment will be done approximately 30 days (+/-5) following the last dose of study drug.

Subjects who are MRD-negative following consolidation, or who complete the full course of maintenance therapy, will continue in the follow-up phase of the protocol. During the follow-up phase, subjects will be evaluated at 3 month intervals, from the time of MRD-negative status or treatment completion, for 2 years with a physical examination and repeat imaging every 6 months to evaluate for evidence of disease progression. After 2 years of follow-up

in the absence of progression, the frequency of ongoing care and assessment will be at the discretion of the subject's treating physician. However, it is recommended that reassessment of the subject's disease status be performed by repeat imaging at least every 6 months. Information on the subject's survival and progression status will be updated annually for up to 5 years following the date of MRD-negative status or completion of therapy.

For subjects who discontinue therapy due to progression, or those who progress or start non-protocol therapy while on follow up, information on the subject's survival will be updated annually for up to 5 years following MRD-negative status or completion of therapy.

Subjects who discontinue treatment early due to toxicity or the subject's decision to discontinue treatment (but not to withdraw consent from the protocol), follow-up with clinical and/or radiographic reassessment approximately every 3 months will be continued until evidence of progression or up to 2 years. After 2 years of follow-up, the frequency of ongoing care and assessment will be at the discretion of the subject's treating physician, although it is recommended that reassessment of the subject's disease status be performed by repeat imaging at least every 6 months. Information on the subject's survival and progression status will be updated annually for up to 5 years after discontinuation of therapy.

7.6 Discontinuation of Study Treatment

Treatment will continue until completion of the protocol therapy or the occurrence of any of the following events:

- Disease progression, defined as clinical, laboratory, or radiographic criteria for progression as defined in the response criteria.
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of protocol treatment for any reason.
- Initiation of alternative anti-cancer therapy, even in the absence of progression.
- Major violation of the study protocol that in the opinion of the Study PI, warrants treatment discontinuation.
- Withdrawal of consent.
- Lost to follow up.
- Death.

7.7 Screening and Eligibility

The investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 3, Schedule of Study Assessments, and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

7.7.1 Inclusion criteria

1. Age ≥18 years at the time of signing the informed consent document.
2. Histologically confirmed mantle cell lymphoma (confirmation of cyclin D1 positivity on diagnostic biopsy).
3. Subjects must have at least one bi-dimensionally measurable lesion; one of the measurements must be ≥1.5 cm in one dimension.
4. No prior cytotoxic chemotherapy; prior therapy with single-agent rituximab is permitted. Prior involved-field radiotherapy to symptomatic nodal sites of involvement is also permitted.
5. Prior therapy with rituximab is permitted, even in the setting of rituximab-refractory disease.
6. Must meet one of the following criteria:
    a. Not eligible for more intensive cytotoxic chemotherapy or consolidative autologous stem cell transplant based on one or more of the following:
        i. Clinically significant heart or lung comorbidities, as reflected by at least 1 of the following:
            1. LVEF ≤ 50%
            2. Chronic stable angina or congestive heart failure controlled with medication
            3. NYHA class III or IV heart failure
            4. Symptomatic chronic pulmonary disease or requirement for intermittent or continuous oxygen therapy
        ii. Presence of other medical comorbidity or limitation in functional status which the investigator judges to be incompatible with an acceptable risk to the subject with the use of intensive chemotherapy. The associated comorbidity or functional limitation must be clearly documented in the medical record at the time of enrollment.

    OR

    b. Subject has been informed of the risks and benefits of intensive chemotherapy and autologous stem cell transplant for treatment of mantle cell lymphoma and has refused this option. This discussion must be clearly documented in the medical record at the time of enrollment.
7. ECOG performance status of ≤2 at study entry.
8. Laboratory test results within these ranges:
    - Absolute neutrophil count ≥1500/μL.
    - Platelet count ≥100,000/μL.
    - Subjects with neutrophils <1500/μL or platelets <100,000/μL with splenomegaly or extensive bone marrow involvement as the etiology for their cytopenias are eligible.
    - Subjects must have adequate renal function with a creatinine clearance of ≥40 mL/min as determined by the Cockcroft-Gault calculation.
    - Total bilirubin ≤2X upper limit laboratory normal (ULN); subjects with

non- clinically significant elevations of bilirubin due to Gilbert's disease are not required to meet these criteria.

- Serum transaminases AST (SGOT) and ALT (SGPT) ≤5X ULN.
- Serum alkaline phosphatase ≤5X ULN.

9. Disease-free of prior malignancies for ≥2 years with the exception of basal or squamous cell skin carcinoma, carcinoma "in situ" of the breast or cervix, or localized prostate cancer (treated definitively with hormone therapy, radiotherapy, or surgery).
10. Life expectancy of at least 3 months.
11. Understand and voluntarily sign an informed consent document.

7.7.2 Exclusion criteria

1. Subjects are not eligible if there is a prior history or current evidence of central nervous system or leptomeningeal involvement.
2. Concurrent use of other anti-cancer agents or treatments.
3. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent document or complying with the protocol treatment.
4. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical or breast cancer, or other cancer from which the subject has been disease free for at least 2 years.
5. Severe or life-threatening anaphylaxis or hypersensitivity reaction when previously exposed to rituximab or other mAb therapy.
6. Known to be positive for HIV or infectious hepatitis (type B or C).
7. Pregnant or breast-feeding females.
8. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

7.8 Registration

Each subject enrolled in the study is to be registered with the UWCCC OnCore database at study entry. If a registering institution were to be unable to access the OnCore database for any reason, an alternative registration option would be to call the Study WON Affiliate Coordinator at 608-265-5676 or 608-265-2867 between 8:30 am and 4:30 pm CST, Monday through Friday.

At the time of registration, the following will be verified in OnCore:

- IRB approval at the registering institution
- Subject eligibility
- Existence of a signed informed consent form
- Existence of a signed authorization for use and disclosure of protected health information
- Accrual assessed for subject to enter study

Documentation of current approval by the investigator's Institutional Review Board must be on file with the Central Research Coordinating Office (CRCO) affiliate coordinators at the University of Wisconsin before an investigator may register subjects.

In addition to submitting initial IRB approval documents, ongoing continuing review approval documentation must be submitted (no less than annually) to the affiliate coordinators at the University of Wisconsin. If the necessary documentation is not submitted in advance of attempting subject registration, the registration will not be accepted and the subject may not be enrolled in the protocol until the documents are received.

Treatment on this protocol must commence at an approved, participating center. ***Treatment cannot begin prior to registration and must begin ≤7 days following registration***. Pre-registration tests must be completed within the guidelines as outlined in Section 3, Schedule of Study Assessments. All required baseline symptoms must be documented and graded.

Reference the WON Operations Manual for additional details.

7.8.1 WON Registration

To register a patient onto the trial at a WON site:

The following documents should be completed by the research nurse or data manager and faxed [608-265-5676] or e-mailed [affiliatecoordinators@uwcarbone.wisc.edu] to the Affiliate Coordinator for WON sites:

- Copy of required laboratory tests
- Signed patient consent form
- HIPAA authorization form
- Other appropriate forms (e.g., Eligibility Screening Worksheet, Registration Form)

The research nurse or data manager at the participating site will then call [608-265-2867 or 608-262-9654] or e-mail [affiliatecoordinators@uwcarbone.wisc.edu] the Affiliate Coordinator to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- register the patient on the study
- fax or e-mail the patient study number to the participating site

8 Drug Administration, Formulation, and Procurement

8.1 Drug administration

8.1.1 Obinutuzumab

Dosage and Administration

Induction therapy (in combination with bendamustine) (28 day cycles):

- Obinutuzumab 100 mg IV C1D1
- Obinutuzumab 900 mg IV C1D2
- Obinutuzumab 1000 mg IV C1D8 and C1D15

- Obinutuzumab 1000 mg IV C2-6 D1

Consolidation therapy:

- Obinutuzumab 1000 mg IV weekly X 4 doses

Maintenance therapy (8 week cycles):

- Obinutuzumab 1000 mg IV D1 of cycle X 8 cycles

Obinutuzumab will be provided by Genentech for participants in this study. Obinutuzumab should be administered by IV infusion, per the package insert instructions.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient) where full emergency resuscitation facilities are immediately available, and patients should be under close supervision at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab, and should not be administered as an IV push or bolus. ***After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion; if no AEs occur after 1 hour, the IV line may be removed. Monitoring during the interval from completion of drug infusion until the IV line is removed will consist of observation for clinical signs or symptoms of a delayed infusion-related reaction, and vital signs are not required. Monitoring during this period may be performed according to the local institutional standard of care.***

If obinutuzumab dosing cannot be completed in a single treatment day for any reason (with the exception of C1D1 dosing of 100 mg), the remainder of the dose may be completed the following calendar day.

Subjects experiencing AEs may need study treatment modifications (See Section 9).

Additional information on drug formulation and preparation is summarized in Appendix F. Complete information including adverse effects are available in the GA101 (Obinutuzumab) Investigator Brochure, version 11 (September 2016).

Infusion-related reaction (IRR) prophylaxis and treatment

IRR prophylaxis:

Cycle 1, Days 1 and 2, all subjects require pre-medication with:

- Steroid: Dexamethasone 20 mg IV or methylprednisolone 80 mg IV administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
- Acetaminophen 1000 mg orally.
- Antihistamine such as diphenhydramine (50 mg orally or IV) administered at least 30 minutes before starting each obinutuzumab infusion. Hydroxyzine is an acceptable alternative in subjects who have allergies or intolerances to diphenhydramine.

Cycle 1, Days 8 and 15 and Cycles 2-6, Day 1:

- All subjects require pre-medication with oral acetaminophen (1000 mg) administered

at least 30 minutes before starting each obinutuzumab infusion.

- Patients who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50 mg) or an acceptable alternative administered at least 30 minutes before starting each subsequent obinutuzumab infusion.
- Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: Dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
- Patients who experience recurrent Grade 3 IRRs despite maximum prophylaxis with anti-histamines and IV glucocorticoid must discontinue obinutuzumab and protocol therapy.

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

8.1.2 Bendamustine

Dosage and Administration

Induction therapy (in combination with obinutuzumab) (28 day cycles):

- Bendamustine 90 mg/m^2 IV C1 – 6, Days 1 and 2

Bendamustine will be obtained commercially, and will not be supplied by the study supporters. Available bendamustine products for use include generic bendamustine, and Bendeka™.

Bendamustine will be infused over approximately 30-60 minutes for generic bendamustine, and will be infused over approximately 10 minutes for the Bendeka™ product.

The amount of drug to be administered will be based on body surface area (BSA). The preferred method for calculating body surface area is the Mosteller formula[60] on C1D1. At some participating community sites, the Dubois formula[61] is the primary BSA calculation used as part of an electronic medical record and drug ordering template. In such cases, calculations using the Dubois formula are permitted as long as there is no more than a 10% difference in dosing between the Mosteller and Dubois calculations. If a >10% difference in drug dosing is observed, then the Mosteller calculation must be used. The drug doses calculated on C1D1 of chemotherapy administration will be used at subsequent visits. However, if the subject experiences a >10% change in body weight from the baseline weight used for initial BSA calculation, then drug doses must be recalculated with the more recent body weight (Appendix B for BSA guidelines). Per institutional standards, bendamustine doses may be rounded within 10% of the calculated dose based on the subject's BSA to accommodate at least half

vial size increments (50 mg for bendamustine).

On treatment days when both bendamustine and obinutuzumab are administered, bendamustine should be the agent administered first.

Subjects experiencing AEs may need study treatment modifications (See Section 9).

Complete information on drug formulation, preparation, and adverse effects of bendamustine is summarized in Appendix G and available in the Package Insert.

8.2 Record of administration and treatment compliance

Accurate records will be kept of all study drug administration (including prescribing and dosing) and maintained in the source documents. Clear documentation will be recorded of dose modifications made based on observed toxicities.

9 Dose Modifications and Interruptions

9.1 General principles for dose modification

Dose modifications are only required and applicable for study drugs to which a toxicity is at least possibly attributed.

9.2 Dose modification guidelines during induction chemotherapy

9.2.1 Dose modification guidelines for obinutuzumab during induction therapy

Obinutuzumab administration must follow labeling instructions and guidelines. Please refer to the approved product label for instructions. Subjects who develop severe IRR should have the obinutuzumab infusion discontinued and have supportive care measures instituted as medically indicated (e.g., IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduced rate, after symptoms have completely resolved. Subjects requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary events, and those with high numbers of circulating malignant cells (>25,000/mm^3) with or without evidence of high tumor burden.

On the first day of each new induction treatment cycle, on day 1 of consolidation therapy, and on day 1 of each maintenance cycle, the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI-CTCAE version 5.0, and attribution or non-attribution to obinutuzumab must be documented.

The dose of obinutuzumab will not change based upon hematologic toxicity. Subjects who develop neutropenia with at least a possible attribution to obinutuzumab may receive growth

factor support as clinically indicated and may continue obinutuzumab administration per protocol. ***If obinutuzumab therapy must be held for >8 weeks due to neutropenia (neutrophil <1000/uL), then subjects must be withdrawn from protocol therapy.***

In subjects who develop viral hepatitis, obinutuzumab should be discontinued and appropriate treatment, including antiviral therapy, initiated.

9.2.2 Dose modification guidelines for bendamustine during induction therapy

On the first day of each new induction treatment cycle (i.e., before each day 1 bendamustine dose), the subject will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI-CTCAE version 5.0, and attribution or non-attribution to bendamustine must be documented.

The following dose-reduction rules for bendamustine should be followed (Tables 1 and 2):

If toxicities occurred at 90 mg/m^2, reduce to 70 mg/m^2; if toxicity occurred at 70 mg/m^2, reduce to 50 mg/m^2; if toxicity occurred at 50 mg/m^2, reduce to 40 mg/m^2, if toxicity occurred at 40 mg/m^2, discontinue bendamustine and withdraw the subject from the study protocol. If the dose of bendamustine is reduced due to toxicity, it will not be re-escalated later in the study.

Table 1. Bendamustine dose reduction steps†

Bendamustine dose level	Bendamustine dose reduction
Starting dose	90 mg/m^2
-1	70 mg/m^2
-2	50 mg/m^2
-3	40 mg/m^2
-4	Discontinue bendamustine and withdraw from study protocol.

†If subjects have disease-related splenomegaly or significant BM involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

Table 2. Dose modification guidelines for bendamustine

NCI-CTCAE category	Severity	Dose modification
Hematologic†	Neutrophil <1000/μL on day 1 of cycles 2-6	Initiation (day 1) of cycles 2-6 should be delayed until the neutrophil count is ≥1000/μL and the platelet count is ≥75,000/μL.† If day 1 is delayed by more than 2 weeks, then bendamustine should be resumed at the next lower dose level.
	Platelets <50,000/μL on day 1 of cycles 2-6	
	Grade 4 neutropenia with fever/infection	Initiation (day 1) of cycles 2-6 should be delayed until the neutrophil count is ≥1000/μL without evidence of fever or infection and the platelet count is ≥50,000/μL.† Bendamustine should then be resumed at the next lower dose level.
	Grade 4 neutropenia lasting ≥7 days	

NCI-CTCAE category	Severity	Dose modification
	Grade 4 platelets for ≥7 days or a platelet count <10,000/μL at any time	
Nausea, emesis, or diarrhea in the absence of maximal prophylaxis	≥Grade 3	Continue treatment, but with institution of maximum prophylactic therapy, including a 5-HT_3 antagonist for nausea and emesis, and loperamide, or a comparable antidiarrheal agent, for diarrhea. Events of grade 4 toxicity require holding treatment until resolution of toxicity to ≤grade 2 with use of maximum prophylaxis.
Nausea, emesis, or diarrhea with maximal prophylaxis	≥Grade 3	Hold bendamustine for up to 2 weeks or until the toxicity returns to ≤grade 2, and restart at the next lower dose. If treatment is delayed by more than 2 weeks, treatment with bendamustine must be discontinued.
All other non-hematologic toxicities	≥Grade 3	

[†]If subjects have disease-related splenomegaly or significant BM involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

9.2 Dose modification guidelines for consolidation and maintenance therapy

Consolidation therapy with obinutuzumab will begin no later than 12 weeks after day 1 of the last induction chemotherapy cycle. Maintenance therapy will begin no later than 8 weeks after the final consolidation dose of obinutuzumab.

On the first day of consolidation therapy and each new maintenance cycle, the subject will be evaluated for possible toxicities that may have occurred after the previous doses. Toxicities are to be assessed according to the CTCAE, version 5.0.

The neutrophils count must be recovered to ≥ 1000/μLprior to the start of consolidation and maintenance obinutuzumab.

Table 3. Dose modification of obinutuzumab for toxicities

NCI-CTCAE Toxicity	**Dose modification**
Grade 1-2 infusion reaction and/or cytokine release syndrome	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

NCI-CTCAE Toxicity	Dose modification
≥Grade 3 infusion reaction and/or cytokine release syndrome possibly or likely attributable to obinutuzumab	Grade 3 infusion reaction: Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If grade 3 infusion reactions and/or cytokine release syndrome occurs, increase steroid and anti-histamine prophylaxis with subsequent infusions as directed in section 8.1.1. If grade 3 infusion reaction and/or cytokine release syndrome recurs despite this maximum prophylaxis, then discontinue obinutuzumab. If grade 4 infusion reaction and/or cytokine release syndrome occurs (e.g., anaphylactic shock, severe hypotension), obinutuzumab must be discontinued.
≥Grade 3 toxicity likely attributable to obinutuzumab	If recurrent ≥grade 3 toxicity is observed that, in the opinion of the investigator, is likely attributable to obinutuzumab, consideration should be made for discontinuation of obinutuzumab.
Neutropenia, particularly in setting of severe and unexplained nadir in neutrophil count with relative stability in hemoglobin and platelet counts	Consider possibility of delayed immune-mediated obinutuzumab -induced neutropenia, which may be observed at any time during an extended treatment course with obinutuzumab. Immune-mediated obinutuzumab -induced neutropenia is not a contra-indication to ongoing obinutuzumab therapy. However, administration of growth factor is recommended to increase ANC > 1000/μL prior to next obinutuzumab dose if this etiology for neutropenia is suspected.
Hypogammaglobulinemia	Levels of serum immune globulins below the lower limits of normal in the setting of clinically significant and recurrent infections (i.e., sinusitis, upper respiratory infections, pneumonia, cellulitis, colitis, etc.) may warrant discontinuation of obinutuzumab.

9.3 Concomitant therapy

Subjects should receive full supportive care, including transfusions of blood products, antibiotics, and anti-emetics when appropriate. Growth factor support is permissible during any phase of protocol therapy to prevent or treat neutropenia.

9.3.1 Tumor lysis syndrome (TLS) prophylaxis

Tumor lysis syndrome (TLS) may be a risk in subjects with high tumor burden MCL initiating induction chemotherapy with bendamustine and obinutuzumab.

Allopurinol prophylaxis is to be considered (but is not mandatory) for subjects during induction chemotherapy based on the risk for tumor lysis syndrome. The recommended allopurinol dosing is 300 mg orally once or twice daily for 7 days. Alternatively, subjects at high-risk for TLS with intolerance to allopurinol or judged to be at increased risk for TLS even

with allopurinol prophylaxis, should be considered for treatment with rasburicase for TLS prophylaxis.
Allopurinol prophylaxis is not mandatory in any patient, but is to be considered at the discretion of the investigator. The following are guidelines for patients at higher risk for tumor lysis syndrome for which allopurinol prophylaxis should be considered:

- Baseline uric acid ≥7.5 mg/dL
- Bulky disease (one or more masses >10 cm, measuring >10 cm in at least one direction of a bi-dimensionally measurable lesion)
- Elevated LDH (> 2X/ULN)
- Serum creatinine >1.5X/ULN

9.3.2 Infections Prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis (160 mg trimethoprim/800 mg sulfamethoxazole orally twice daily or suitable alternative according to each site's institutional standards) and anti- herpetic viral prophylaxis (acyclovir 400 mg orally twice daily or suitable alternative) are recommended during treatment and for up to 6 months following treatment as appropriate.

9.3.3 Hematopoietic Growth Factors

Growth factor support is permissible during any phase of protocol therapy to prevent or treat neutropenia. Prophylactic G-CSF is permitted during cycle 1 of induction in subject judged to be at increased risk of treatment-related neutropenia. Growth factor support may include filgrastim, pegfilgrastim, or TBO-filgrastim (or other filgrastim biosimilar).

9.3.4 Hepatitis B reactivation

Positive serology for Hepatitis B is defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc). Patients who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are Hepatitis B viral DNA negative and are willing to undergo ongoing HBV DNA testing by real-time PCR. Patients with positive serology may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.

For the subset of patients who are Hepatitis B viral DNA negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed approximately every 4 weeks. Guidelines for the management of hepatitis B reactivation are outlined in Table 4.

Table 4 Management of hepatitis B reactivation

Hepatitis B Viral DNA Level by Real-Time PCR	Guideline

> 100 IU/mL	• Hold obinutuzumab. • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management. • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels.
> 100 IU/mL while on anti-viral medication	Discontinue obinutuzumab.
29–100 IU/mL	Retest within 2 weeks. If still hepatitis B viral DNA positive: • Hold obinutuzumab. • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management. • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels.

9.3.5 Prohibited concomitant therapy

Concomitant use of other anti-cancer therapies, including radiation or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

10 Data Safety Monitoring Plan

10.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all SAE requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.

- Ensures that notification is of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

10.1.1 Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

a) Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC. **Subjects being treated in this study protocol will be monitored according to this intermediate monitoring category.**

10.1.2 Protocol Summary Reports

Protocol Summary Reports (PSR) are required to be submitted to the DSMC semi-annually. The PSR provides a cumulative report of SAEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.), WON sites, and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

10.2 Safety Reconciliation

The Sponsor agrees to conduct reconciliation for obinutuzumab. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. 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.

11 Adverse Event Reporting Requirements

11.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after the initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination (prior to completing all protocol-directed therapy), whichever is earlier. After this period, investigators should only report SAEs that are possibly, probably, or definitely attributed to prior study treatment.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

11.2 Assessment of Adverse Events

An **adverse event** (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MCL that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- 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 AE reporting period.
- Changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention or if the investigator considers them to be adverse events.
- Clinically Significant Laboratory Abnormalities: The investigator must appraise and document all abnormal laboratory results for their clinical significance. If an abnormal laboratory result is considered clinically significant, the value must be recorded in the research chart on the Adverse Events Log.

Attribution of Adverse Events

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

RELATIONSHIP	DESCRIPTION
Unrelated	The AE is clearly NOT related to treatment. A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the patient's disease state, intercurrent illness, or environmental factors.
Unlikely	The AE is doubtfully related to treatment. A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the AE to a concomitant drug, past medical history of a similar event, the patient's disease state, inter-current illness, or environmental factors.
Possible	The AE may be related to treatment. A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Probable	The AE is likely related to treatment. A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Definite	The AE is clearly related to treatment. A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).

Expectedness of Adverse Events

Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator Brochure (IB).

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

11.2.1 Procedures for Eliciting, Recording, and Reporting Adverse Events

Genentech and the UWCCC have specific language regarding adverse event assessment and reporting. Participating investigators should review the following information carefully, and if an event meets criteria for reporting to any one of these entities, the event should be reported following the guidelines in section 11.3.

11.2.1.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs 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?"

11.2.1.2 Protocol Specific Instructions for Recording Adverse Events

Toxicities and adverse events will be scored using CTCAE, version 5.0. A copy of the CTCAE, version 5.0 can be downloaded from the CTEP homepage (https://ctep.cancer.gov/). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject's outcome. The investigator must evaluate each adverse experience for its relationship to the study drug(s) and for its seriousness.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. 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 ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

   All deaths that occur during the protocol-specified AE reporting period (see Section 11.1), 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".

c. Pre-existing 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 AE or SAE 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").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

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.

e. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if possibly, probably, or definitely attributed to prior study drug exposure per section 11.3. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE per section 11.3.

11.2.1.3 Protocol Specific Instructions for Reporting Adverse Events

a) General Adverse Event Reporting

All AEs and SAEs will be recorded in the research chart on the Adverse Events Log, regardless of whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means. Each reported AE or SAE will be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship (attribution) to the study drugs (see following guidance), and actions taken. A trained investigator should review each event.

Only the worst grade toxicity for a specific AE should be reported on the electronic case report form (eCRF) within each reporting period. A reporting period is defined as each treatment cycle of maintenance and induction, and the interval between each follow-up visit after completion or discontinuation of therapy.

Anticipated grade 1-2 toxicities that are excluded from reporting on the electronic case report form (must be recorded on the AE log if deemed clinical significant):

- Leukopenia (WBC decreased)
- Lymphopenia (Absolute lymphocyte count decreased)

- Neutropenia (Absolute neutrophil count decreased)
- Anemia (Hemoglobin decreased)

b) Expedited Adverse Event Reporting

Serious Adverse Events: See section 11.3 for details.

Pregnancy: See section 11.3.3 for details.

Adverse Events of Special Interest (AESI): See section 11.3.3 for details.

11.3 Expedited Adverse Event Reporting

Reference the WON Operations Manual for additional information, cover sheets, and forms.

11.3.1 SAE Reporting

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 5 below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Refer to section 11.4.1 regarding additional reporting guidelines to sponsor (Genentech).

Determine the reporting time line for the SAE in question by using Table 5. Then refer to sections A and B below if the SAE occurred at the UWCCC or sections C and D if the SAE occurred at 1 South Park or a WON Site.

11.3.2 SAE Definition

A SAE is one that at any dose (including overdose):

- Results in death.
- Is life-threatening, meaning that the subject was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.
- Requires subject hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity, which is defined as a substantial disruption of a subject's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important (significant) medical event, with medical and scientific judgment exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above has occurred.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.
    - Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

- Suspected pregnancy.
- A secondary primary malignancy.

Table 5. Reporting Requirements for Serious Adverse Events (UW Carbone Cancer Center requirements)

NOTE: Investigators MUST immediately report to the *UWCCC* and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		10 Calendar Days	

NOTE: See section 11.3.3 for additional protocol-specific exceptions to and requirements of expedited reporting

Expedited AE reporting timelines are defined as:

- 24-Hour; 5 Calendar Days – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- 10 Calendar Days – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 events

11.3.3 Additional Protocol-Specific Instructions, Requirements, and Exceptions to Expedited Reporting

11.3.3.1 Protocol-Specific Expedited Reporting Requirements

A. Pregnancy

If a female patient becomes pregnant while receiving obinutuzumab or within one year after the last dose of obinutuzumab, or the partner of a male patient becomes pregnant while receiving therapy or within three months of completing therapy, a report should be completed and expeditiously submitted to the Roche/Genentech, Inc by UWCCC staff per section 11.4.1. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to obinutuzumab should be reported as an SAE.

All Sites: Report to the UWCCC (saenotify@uwcarbone.wisc.edu):

Complete the following for all reports as soon as possible after becoming aware of the event and within 27 calendar days of the awareness date:

- FDA MedWatch Form 3500A
- UW16086 Pregnancy Report Cover Sheet

UWCCC: Report to Industry Collaborators:

Complete the following and submit along with the FDA MedWatch Form 3500A to Genentech as soon as possible after becoming aware of the event and within 30 days of the initial awareness date:

- Genentech Safety Reporting Fax Cover Sheet

B. Adverse Events of Special Interest (AESIs)

AESIs are defined as a potential safety problem, identified as a result of safety monitoring of the Product. AESI in clinical trials are sent to Genentech by UWCCC staff per section 11.4.1. **The following AEs are considered of special interest and must be reported to the Sponsor expeditiously, irrespective of regulatory seriousness criteria:**

- Grade ≥2 clinical tumor lysis syndrome, (see appendix H for details on grading TLS).
- Second malignancies.
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin) - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected

All Sites: Report to the UWCCC (saenotify@uwcarbone.wisc.edu):

For events that meet the seriousness criteria in section 11.3.2:

Follow the SAE reporting directions and time periods in section 11.3.4. Submit the following in addition:

- UW16086 AESI Report Cover Sheet

For events that do NOT meet the seriousness criteria in section 11.3.2 and are considered possibly, probably, or definitely related to obinutuzumab therapy:

Complete the following as soon as possible after becoming aware of the event and within 12 calendar days of the awareness date:

- FDA MedWatch Form 3500A
- UW16086 AESI Report Cover Sheet

For events that do NOT meet the seriousness criteria in section 11.3.2 and are considered unrelated or unlikely related to obinutuzumab therapy:

Complete the following as soon as possible after becoming aware of the event and within 27 calendar days of the awareness date:

- FDA MedWatch Form 3500A
- UW16086 AESI Report Cover Sheet

UWCCC: Report to Industry Collaborators:

For events that meet the seriousness criteria in section 11.3.2 or are considered possibly, probably, or definitely related obinutuzumab therapy:

Complete the following and submit along with the FDA MedWatch Form 3500A to Genentech as soon as possible after becoming aware of the event and within 15 days of the initial awareness date:

- Genentech Safety Reporting Fax Cover Sheet

For events that do NOT meet the seriousness criteria in section 11.3.2:

Complete the following and submit along with the FDA MedWatch Form 3500A to Genentech as soon as possible after becoming aware of the event and within 30 days of the initial awareness date:

- Genentech Safety Reporting Fax Cover Sheet

11.3.3.2 Protocol-Specific Exceptions to Expedited Reporting

The following toxicities are anticipated and will **NOT** require expedited reporting:

Induction

- Grade 3 – 4 Lymphocyte count decreased
- Grade 3 – 4 White blood cell decreased
- Grade 3 – 4 Neutrophil count decreased
- Grade 3 – 4 Platelet count decreased

Consolidation and Maintenance

- Grade 3 – 4 Lymphocyte count decreased
- Grade 3 White blood cell decreased

11.3.4 General procedures for SAE reporting

Serious adverse event – reported within 24 hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (Medwatch Form #3500A and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 5 calendar days a final initial report is required to be submitted, all available subsequent SAE documentation must be submitted electronically along with a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. Follow up reports should be submitted, as needed, when additional information becomes available. All information is entered and tracked in the UWCCC OnCore database.

As applicable, the study PI notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

For a multiple-institutional clinical trial the study PI is responsible for ensuring SAEs are reported to all participating investigators.

See Section 11.3.5 for detailed instructions on SAE reporting.

Serious adverse event – reported within 10 days

SAEs requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (Medwatch Form #3500A and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. Follow up reports should be submitted, as needed, when additional information becomes available. All information is entered and tracked in the UWCCC OnCore database.

As applicable, the study PI notifies all investigators involved with the study at the UWCCC, the IRB, the industry collaborators, and the FDA (if applicable) and provides documentation of these notifications to the DSMC.

For a multiple-institutional clinical trial the study PI is responsible for ensuring SAEs are reported to all participating investigators.

See Section 11.3.5 for detailed instructions on SAE reporting.

11.3.5 Expedited Reporting of Serious Adverse Events

All sites: Complete the following for all reports, regardless of reporting period:

- FDA MedWatch Form 3500A
- OnCore SAE Details Report
- Serious Adverse Event Routing Form

UWCCC Only: Complete the following for all reports regardless of SAE location

- Genentech Safety Reporting Fax Cover Sheet

A. **SAE Requiring 24 Hour Reporting Occurs at UWCCC:**

1. Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website, Data and Safety Monitoring page, (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A final initial report is required to be submitted within 5 calendar days of the initial 24 hour report.**

Submit the following items:

- FDA MedWatch Form 3500A
- SAE Routing Form
- OnCore SAE details report
- Source documentation as applicable

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Julie Chang, MD (Study PI) jc2@medicine.wisc.edu
c) Any other appropriate parties listed on the SAE Routing Form

2. Report to Industry Collaborators:

Submit the following items to Genentech:

- Genentech Safety Reporting Fax Cover Sheet
- FDA MedWatch Form 3500A
- Source documentation as applicable

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

3. Report to the IRB:

Consult the UW-IRB website (kb.wisc.edu/hsirbs) for reporting guidelines.

B. **SAE Requiring [10] Day Reporting Occurs at UWCCC:**

1. Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website, Data and Safety Monitoring page, (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for 10 day reports.

Submit the following items:

- FDA MedWatch Form 3500A
- SAE Routing Form
- OnCore SAE details report
- Source documentation as applicable

For this protocol, the following UWCCC entities are required to be notified:

a. saenotify@uwcarbone.wisc.edu
b. Julie Chang, MD (Study Chair) jc2@medicine.wisc.edu
c. Any other appropriate parties listed on the SAE Routing Form

2. Report to Industry Collaborators:

Submit the following items to Genentech:

- Genentech Safety Reporting Fax Cover Sheet
- FDA MedWatch Form 3500A
- Source documentation as applicable

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

3. Report to the IRB:

Consult the UW-IRB website (kb.wisc.edu/hsirbs) for reporting guidelines.

C. **SAE Requiring 24 hour reporting Occurs at 1 South Park (1SP) or a WON Site:**

1. Affiliate Site: Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP and WON Affiliates** on the UWCCC website, Data and Safety Monitoring page (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for 24 hour initial and follow-up reports. **A final initial report is required to be submitted within 5 working days of the initial 24 hour report.**

Submit the following items to UWCCC at saenotify@uwcarbone.wisc.edu

- FDA MedWatch Form 3500A
- SAE Routing Form
- OnCore SAE details report
- Source documentation as applicable

NOTE: After 1SP or a WON site has submitted the 24 hour SAE report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator or Study Chair is then responsible for ensuring the SAE is reported to the global sponsor, the UW IRB, and any other entity requiring notification, in accordance each entities' reporting requirements.**

2. UWCCC: Report to Industry Collaborators:

Affiliate sites will not submit directly to the sponsor, but will submit SAEs to the UWCCC. The Study PI will report all SAEs to Genentech within the timelines described in section 11.4.1.

Submit the following items to Genentech:

- Genentech Safety Reporting Fax Cover Sheet
- FDA MedWatch Form 3500A
- Source documentation as applicable

3. All Sites: Report to the IRB:

WON sites should follow their local IRB reporting guidelines for SAE submission. The Study PI is responsible for the submission of the SAE to the UW IRB for any sites for which the UW IRB serves as the IRB of record.

D. **SAE Requiring 10 Day Reporting Occurs at 1 South Park (1SP) or a WON Site:**

1. Affiliate Sites: Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for 1SP and WON Affiliates** on the UWCCC website, Data and Safety Monitoring page, (https://kb.wisc.edu/uwccc/internal/41020) for specific instructions on how and what to report to the UWCCC for *10* day reports.

Submit the following items to UWCCC at saenotify@uwcarbone.wisc.edu

- FDA MedWatch Form 3500A
- SAE Routing Form
- OnCore SAE details report
- Source documentation as applicable

NOTE: After 1SP or a WON site has submitted the 10 day SAE report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator or Study Chair is then responsible for ensuring the SAE is reported to the global sponsor , the UW IRB, and any other**

entity requiring notification, in accordance each entities' reporting requirements.

2. **UWCCC: Report to Industry Collaborators:**

   Affiliate sites will not submit directly to the sponsors, but will submit SAEs to the UWCCC. The Study PI will report all SAEs to Genentech within the timelines described in section 11.4.1.

   Submit the following items to Genentech:
   - Genentech Safety Reporting Fax Cover Sheet
   - FDA MedWatch Form 3500A
   - Source documentation as applicable

3. **All Sites: Report to the IRB:**

   WON sites should follow their local IRB reporting guidelines for SAE submission. The Study PI is responsible for the submission of the SAE to the UW IRB for any sites for which the UW IRB serves as the IRB of record.

11.4 Study PI Adverse Event Reporting Requirements

11.4.1 Adverse event reporting to Genentech

The study PI will report all SAEs to Genentech within the timelines described below. ***WON sites will not submit directly to Genentech, but will submit SAEs to UWCCC, and the PI will review and submit to Genentech on behalf of the WON site.*** The completed FDA MedWatch Form 3500A should be faxed immediately upon completion to Genentech Drug Safety at:

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

SAEs, pregnancy reports and AESIs, where the patient has been exposed to obinutuzumab, will be sent on a MedWatch form to Roche/Genentech. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:]

- **Serious Adverse Drug Reactions (SADRs)**
  Serious AE reports that are related to obinutuzumab shall be transmitted to Roche/Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to obinutuzumab shall be transmitted to Roche/Genentech within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**
  While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to obinutuzumab, shall be transmitted to Roche/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.

- **AESIs**
  AESIs that meet criteria for seriousness OR are at least possibly related to obinutuzumab require expedited reporting and shall be forwarded to Roche/Genentech within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

FDA MedWatch Form 3500A (Mandatory Reporting) is available at:
http://www.fda.gov/medwatch/getforms.html

Special situation reports

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

- Data related to the Product usage during pregnancy or breastfeeding.
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol.
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP).
- 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.

Aggregate Reports

A copy of the Final Study Report will be submitted to Roche/Genentech by the study principal investigator upon completion of the Study. Any publications of interim results will also be submitted to Roche/Genentech for review. The study principal investigator will forward a copy of the final publication to Roche/Genentech upon completion of the study. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Email: ga101-gsur@gene.com

Fax: 866-706-3927

The study PI will compile into a report all non-serious adverse events once all study subjects are off treatment.

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 report 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. D.O.B. initials, 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 an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative or the MSL 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.

11.4.2 Product complaints to Genentech

Recently the FDA announced an update to the Post Marketing Safety Reporting regulation which requires the Marketing Authorization Holder (i.e., Genentech/Roche) to report product complaints to the FDA. A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Product complaints **with** an AE should be reported via e-mail to: usds_aereporting-d@gene.com OR 650-238-6067

Product complaints **without** an AE should be reported via e-mail to Kaiseraust.global_impcomplaint_management@roche.com

All complaints must be filed within 15 calendar days. Complaints can be reported using a Medwatch, CIOMS, or any Genentech-approved response reporting form.

12 Response Criteria

Baseline lesion assessments must occur within 6 weeks of enrollment, as indicated in Section 3, Schedule of Study Assessments. Efficacy assessments are scheduled to occur at the end of cycle 4 of induction therapy, following consolidation therapy, and after cycles 4 and 8 of maintenance therapy.

Response and progression will be evaluated using the Lugano classification criteria.[17] The criteria are outlined in detail in Appendix E. PET/CT-based response criteria should be used if PET/CT is performed; otherwise CT-based response criteria will apply. For this study, a score of 1, 2, or 3 on a PET 5-point scale will be considered a complete metabolic response.[62] Radiological methodologies, techniques and/or physical examination, established at baseline for the assessment and measurement of each identified lesion will be used for all subsequent assessments. Spleen craniocaudal dimension of 13 cm is the upper limits of normal for response assessment.

For patients who had a positive BM by BMA and/or biopsy at baseline but negative by FDG-PET at baseline, a follow-up BMA and/or biopsy will be obtained to confirm CR. If the BMA and/or biopsy was negative at baseline, but FDG-PET was positive for marrow involvement, FDG-PET negativity will be sufficient to confirm CR. If both modalities were positive at baseline, either may be repeated to confirm CR. The follow-up bone marrow

biopsy sample must be negative for confirmation of a CR. If the follow-up morphology is indeterminate, the biopsy sample must be negative by immunohistochemistry or the patient will be assessed a response of PR.

13 Protocol Amendments and Deviations

13.1 Protocol amendments

Any amendment to this protocol must be agreed to by the PI and reviewed by Genentech. Amendments should only be submitted to the local IRB after consideration of study supporters' reviews. Written verification of IRB approval will be obtained before any amendment is implemented.

13.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the investigator will notify the IRB in writing of such deviation from protocol according to local policy. In addition, the investigator will inform the DSMC of the event around the protocol deviation, to determine if the subject should be removed from protocol therapy.

Non-emergency minor deviations from the protocol will be permitted with approval of the PI.

14 Statistical Considerations

14.1 Overview

This single arm, open-label phase II study will be carried out at an academic medical center as well as community practice sites. Participating centers will include the UWCCC and participating community practice sites within the WON. The primary efficacy endpoint of this study is PFS.

14.2 Study Endpoints

The primary efficacy endpoint of the study will be 2-year PFS. Secondary endpoints include 1.) MRD status after 2 cycles of induction chemoimmunotherapy with bendamustine and obinutuzumab, after 4 cycles of consolidation with obinutuzumab, and after an additional 8 cycles of maintenance with obinutuzumab and 2.) Response status with induction chemoimmunotherapy, both as a dichotomous variable. Safety endpoints include toxicity graded using CTCAE.

14.3 Sample Size Calculation

According to the literature, 2-year PFS with standard of care is 50% (p_c=0.50). We would be interested in the protocol regimen if it improves the 2-year PFS to at least 65% ($p_t \geq 0.65$).Therefore, we will test the null hypothesis that $H_0: p_t \leq p_c$ against the alternative

hypothesis H_1:p_t>p_c. In order to test H_0 at a one-tailed significance level a=0.10 with power 1-1=0.85 to detect p_t=0.65, 0.70 or 0.75, the study will require observing 24, 13 or 7 progressions or deaths, respectively. The table below shows the required number of subjects to be enrolled for different durations of accrual, with a minimum follow-up of 2 years.

	Accrual duration (in years)		
p_t	2	2.5	3
0.65	51	48	46
0.70	30	28	27
0.75	20	19	18

In order to detect an increase in 2-year PFS to 70% with the protocol therapy, we would need to enroll a total of 28 patients over 2.5 years for a total of 4.5 years of study, and the study will terminate when 13 progressions or deaths are observed. In addition, up to 10% of subjects enrolled may not have a unique enough variation in heavy chain domain for MRD testing to be performed; therefore, the sample size is increased from 28 to 32 in order to account for this anticipated number of subjects who will not be evaluable for MRD testing.

14.4 Statistical Analysis Plan

14.4.1 Primary endpoint

The analysis will be undertaken when each patient has been potentially followed for a minimum of 24 months. For each patient, profession-free survival (PFS) will be defined as the number of days from C1D1 of induction chemoimmunotherapy to the day patient experiences an event of disease progression or death, whichever occurs first. If a patient has not experienced an event at the time of analysis, patient's data will be censored at the date of the last available evaluation. The 2-year PFS probability will be estimated using the Kaplan-Meier method. The null hypothesis that the 2-year PFS probability is at most 0.5 will be tested versus that alternative hypothesis that it is greater than 0.7. PFS will be summarized using point estimate of the median PFS, and associated 95% confidence intervals. The confidence interval will be computed using the Brookmeyer-Crowley method. The data will be presented graphically using Kaplan-Meier plot. According to the design, we will reject the null hypothesis in favor of the alternative hypothesis that the 2-year PFS is 70% or greater if the observed 2-year PFS based on 13 PFS events is 61.5% or greater.

14.4.2 Secondary endpoints

Secondary endpoints of MRD status after 2 cycles of induction therapy with bendamustine and obinutuzumab, after 4 cycles of consolidation therapy with obinutuzumab, and after an additional 8 cycles of maintenance therapy with obinutuzumab and response status will be summarized using frequency and proportion with 95% confidence intervals.

Adverse events will be summarized with frequency and worst grade. Toxicities will be summarized in a similar way. Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTCAE, version 5.0 whenever possible. Frequency tables (type of toxicity and grade) for all toxicities will be provided.

Concordance between PB and BMA in predicting MRD negative status will be summarized with frequency and proportion.

For a given subject, OS will be defined as the number of days from C1D1 of the induction chemoimmunotherapy to the day the subject dies. Survival times of subjects who are still alive at the end of the follow-up period will be censored. OS will be summarized using point estimate of the median OS, along with the 95% confidence interval. Survival data will be presented graphically using Kaplan-Meier plot.

14.5 Early stopping rule for toxicity

An early stopping rule is in place for excessive toxicity. An AE will be considered excessive if it meets the following criteria:

- Any grade 5 event attributed to treatment (i.e., treatment-related deaths)
- Any grade 4 event excluding neutropenia and lymphopenia. Grade 4 neutropenic fever is also excluded, as this is an expected event. Essentially all event of neutropenic fever require hospitalization and IV antibiotics, which requires classification as a grade 4 event even if patients are clinically stable without any additional complications.
- Any patient that discontinues therapy due to grade ≥3 toxicities attributed to study treatment.

Toxicities will be evaluated after each patient and the trial considered for early termination for excessive adverse events (AEs) listed above using a sequential probability ratio test (SPRT) of the null hypothesis H_0: $p \leq p_0$ against the alternative hypothesis H_1: $p \geq p_1$ with a one-tailed significance level a=0.05 and power 1-b=0.95 where p denotes the probability of the above AEs. The protocol stopping rule considers p_1=0.25 to be unacceptable, and p_0=0.05. Early stopping will be considered only for excess toxicities (H_1). According to the SPRT, early stopping will be considered if the number of patients (x) experiencing the above listed AEs out of the number of patients (n) treated with the protocol regimen exceeds $1.60 + 0.128n$. For example, early stopping will be considered if 2 AEs are observed out of 2 to 3 patients, 3 AEs out of 4 to 10 patients, 4 AEs out of 11 to 18 patients, 5 AEs out of 19 to 26 patients, and 6 AEs out of 27 to 32 patients. This early stopping rule has power 0.95 to detect excessive toxicities (H_1: $p \geq 0.25$).

14.6 Accrual Rate and Feasibility

Based on our experience with studies involving MCL subjects at UWCCC and affiliated WON sites, we anticipate an accrual rate of approximately 10-12 subjects per year. Therefore, it is expected that accrual will be completed within 2.5 years.

15 Regulatory Considerations

15.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC), is responsible for monitoring data quality and subject safety for all UWCCC clinical studies. A summary of DSMC activities follows:

- Review of all clinical trials conducted at the UWCCC for data integrity and safety
- Review of all serious adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by the UWCCC data quality control review process
- Submit recommendations for corrective action to the Clinical Research Committee (CRC)
- Notify the Study Chair of the DSMC recommendation to the CRC
- The committee ensures that notification is provided to external sites participating in multiple-institutional clinical trials coordinated by the UWCCC of adverse events requiring expedited reporting.

15.2 Oversight of WON Sites

The UWCCC Affiliate Office serves as the coordinating center for WON. For this protocol, coordinating center responsibilities are shared between the Affiliate Coordinator and UWCCC Lymphoma/Myeloma DOT. A detailed description of coordinating center responsibilities, as well as other WON processes and procedures, including periodic routine auditing procedures, is provided in the WON Manual available on the UWCCC website (https://kb.wisc.edu/uwccc/internal/page.php?id=42878).

Regular communication between the UWCCC Affiliate Office and WON sites ensures that all participating parties are notified of protocol changes, informed consent document revisions, action letters, study status changes, reportable events/SAEs (as necessary), and any other applicable information. This communication is accomplished through regular email updates and conference calls. Reference the study specific WON Operations Manual for additional study- specific requirements.

15.3 Monitoring and Reporting Guidelines

Data related to these trials are discussed at regularly scheduled DOT meetings where the result of each subject's treatment is discussed and the discussion is documented in the minutes. The discussion will include the number of subjects, significant toxicities as described in the protocol, dose adjustments, and responses observed.

Twice yearly, summaries will be submitted to the DSMC for review. Summaries will be provided to the supporters of the study (i.e., Genentech).

15.4 Investigator responsibilities with study monitoring and auditing

Investigator responsibilities are set out in the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The investigator will permit study-related audits by Genentech or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA and TPD), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The investigator, or a designated member of the investigator's staff, must be available at some time during audit visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed

prior to each visit and be made available to the Genentech representative so that the accuracy and completeness may be checked.

15.5 Study records requirements

The case report forms will be completed. All documentation of adverse events and all IRB correspondence will be retained for at least 2 years after the investigation is completed.

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). These records and documents include copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]). The investigator agrees to adhere to the document/records retention procedures by signing the protocol.

15.6 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the investigator to the IRB/EC for approval. The investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

15.7 Informed consent

The investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The

original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the investigator's study files.

15.8 Subject confidentiality

Identifiable patient information will be maintained at the enrolling site. All source documentation will be maintained within the subject's research chart which will be accessible only to authorized personnel. Study data will be collected in the UWCCC OnCore database. The enrolling site is responsible for completing eCRFs per WON standard operating procedures. Subject data will be coded, with the link to demographic information maintained within the OnCore database. The study PI, statistician, and research team at UWCCC will have access to this information and will manage the study data. Data will be maintained per federal guidelines.

Genentech will affirm the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, the study supporters (i.e., Genentech and Adaptive Biotechnologies) require the investigator to permit representatives of Genentech and Adaptive Biotechnologies, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

15.9 Premature discontinuation of study

The responsible local clinical investigator as well as Genentech have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center or all participating centers. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

16 References

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Appendix A: ECOG performance status

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

Appendix B: Body surface area calculation

The preferred method for calculating body surface area is with the **Mosteller formula**:[60]

BSA (m^2)= [Height(cm) X Body weight (kg)/3600]$^{1/2}$

At some participating community sites, the Dubois formula is the primary BSA calculation used as part of an electronic medical record and drug ordering template. In such cases, calculations using the Dubois formula are permitted as long as there is no more than a 10% difference in dosing between the Mosteller and Dubois calculations. If a >10% difference in drug dosing is observed, then the Mosteller calculation must be used.

Dubois formula**:**[61]

BSA (m^2) = 0.007184 X [Body weight (kg)]$^{0.425}$ X [Height (cm)]$^{0.725}$

The same BSA will be used for each dose calculation of bendamustine and rituximab unless the subjects experiences a >10% change in body weight from the weight used for the most recent BSA calculation.

Appendix C: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl): (Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min) (Males)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

$$\text{CrCl (mL/min) (Females)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

Appendix D: Mantle Cell Lymphoma International Prognostic Index (MIPI)[20,63] score calculation

$$\begin{aligned}\text{MIPI score} = &[0.03535 \times \text{age (years)}] \times \text{age (years)}] \\ &+ 0.6978\ (\text{if ECOG} > 1) \\ &+ [1.367 \times \log10(\text{LDH/ULN})] \\ &+ [0.9393 \times \log10(\text{WBC count})]\end{aligned}$$

As described in section 3.0, Schedule of Study Assessments, baseline/screening values for age, ECOG performance status, LDH, and WBC (white blood cell count) must be used for calculation of baseline MIPI score.

*LDH is reported in standard values of U/L.

*WBC is reported in 10^9/L. For example, a lab result reported in standard US labs as 10.5 K/uL is equivalent to 10.5 X 10^9/L.

Determination of risk group

MIPI score	Risk group
<5.7	Low
5.7-6.2	Intermediate
≥6.2	High

Appendix E: Assessment of response: Lugano Classification[17]

Table 1. Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT*, biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
*PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within 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 extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Spleen craniocaudal dimension of 13 cm is the upper limits of normal for response assessment.

Time to Progression

Time to progression will be measured as the time from when the subject started treatment to the time the subject is first recorded as having disease progression, or the date of death if the subject dies due to causes other than disease progression.

Time to Treatment Failure

Time to treatment failure will be measured as the time from when the subject started treatment to the time the subject is withdrawn due to: AEs, progressive disease/insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. The date of last dose of treatment will be used as the date of event in the case that PD was not recorded earlier.

Survival

Survival will be measured as the time from start of treatment to the date of death or the last date the subject was known to be alive.

Time to Response

For subjects who achieve a major objective response (CR or PR of measurable disease), the time to response will be assessed as the time from start of treatment to the date of response.

Appendix F: Obinutuzumab formulation and preparation

Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 50-mL pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

Storage

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

Preparation

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

One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2°C — 8°C and administer the next day.

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

To prepare a 900-mg dose: The final drug concentration of a 900-mg dose should be in the

range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw 36 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1000-mg dose: The final drug concentration of a 1000-mg dose should be 0.4 mg/mL to 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw 40 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

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

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

References: Investigator's Brochure, GA101 (Obinutuzumab for injection, version 11 (September 2016).

Appendix G: Bendamustine formulation, preparation, and adverse effects

I. Drug formulation and preparation

I.A. Other names

Treanda™, SDX-105, Bendeka™

Bendamustine is available in several formulations, including Treanda™ (available in liquid and powder formulations infused over 30-60 minutes), and Bendeka™ (a ready-to- dilute formulation available to infuse over 10 minutes). Bendeka™ was introduced in the market in December 2015 by Teva Pharmaceuticals, with the simultaneous decision by Teva to stop manufacturing Treanda™ during roll-out of Bendeka™. Generic marketing and availability of bendamustine is anticipated to be unpredictable in the months following introduction of the Bendeka™ product. Bendeka™ and Treanda™ are nearly identical in action and toxicities, and can be used interchangeably for administration of induction chemotherapy per the study protocol depending on availability of the bendamustine product and institutional preference.

1.B. Classification and mode of action:

Bendamustine is a DNA alkylating agent with amphoteric properties due to the nitrogen mustard group and butyric acid side chain. Bendamustine has multiple mechanisms of action related to the alkylating activity of the 1-methyl-benzimidazole moiety and the nitrogen mustard group.

Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases, thus directly inhibiting DNA replication, transcription, and repair. At equitoxic concentrations, bendamustine induces more DNA double-strand breaks than other alkylating agents (i.e., melphalan, cyclophosphamide, and carmustine). In addition, these breaks also appear to be more durable and less easily repaired than those induced by other agents. Bendamustine has also demonstrated pro- apoptotic activity in combination with other anti-cancer agents in several in vitro tumor models, including in primary tumor cells from CLL and non-Hodgkin lymphoma subjects. Treatment with bendamustine HCl has also demonstrated down-regulation of several cell cycle mitotic checkpoint regulators, including polo-like kinase 1 (PLK-1), aurora kinase A and cyclin B1. Bendamustine shows only partial cross-resistance with other alkylating agents when investigated in a variety of cell lines, which may be related to the relatively slow repair rate associated with this agent. No evidence of *in vitro* drug resistance to bendamustine was observed when the drug was tested in paried tumor cells expressing various drug resistance mechanisms including the overexpression of P-glycoprotein, of multi-drug resistant-associated

protein (MRP), or dihydrofolate reductase (DHFR).

I.C Storage and stability

Bendamustine vials should be stored at refrigerated temperatures of 2º to 8ºC (36º to 46ºF) and protected from light. Bendamustine is stable for 5 hours when stored at normal room temperature conditions, 15ºC to 30ºC (59ºF to 86ºF). Bendamustine is a cytotoxic anticancer agent and should be handled according to the recommended procedures described in the current edition of the American Society of Health-System Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling cytotoxic drugs.

The Bendeka product is supplied in multi-dose vials. Although it does not contain any anti-microbial preservative, Bendeka is bacteriostatic. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration 2-8ºC or 36-46ºF). Each vial is not recommended for more than a total of 6 dose withdrawals.

1.D. Preparation

Bendamustine is available in several formulations, including Treanda™ (available in liquid and powder formulations) infused over 30-60 minutes, and Bendeka™ (newer formulation available to infuse over 10 minutes). Preparation should be followed according to the package inserts for Treanda™and Bendeka™.

1.E. Administration

The bendamustine solution should be used promptly after reconstitution and dilution. The route of administration is by IV infusion over 30-60 minutes for Treanda™ and over
10 minutes for Bendeka™The infusion line would be primed with drug solution. If medical conditions necessitate, e.g., fluid management issues of infusion reactions, the infusion may be given over a longer period of time, though the infusion should be ≤120 minutes. In-line filters are not required for administration. Refer to the Pharmacy Manual for more detailed instructions.

1.F. Availability

Commercial: Bendamustine is a white to off-white, crystalline powder. Mannitol is contained in the finished product as an excipient to enhance solubility during reconstitution of the powder. Bendamustine is lyophilized due to long-term instability in aqueous medium. Bendamustine is available in 100 mg single use vials. Bendeka is a clear colorless-yellow 25 mg/mL solution supplied in multi-dose vials (100 mg/4 mL vials).

1.G. Drug interactions

No formal pharmacokinetic drug-drug interactions have been determined for

bendamustine. However, bendamustine's active metabolites are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have the potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of P450 CYP1A2 (e.g., omeprazole, smoking) have the potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

1.H. Side effects – Please refer to package insert

Hematologic: neutropenia (grade 3 or 4 neutropenia in up to 25% of treated subjects), thrombocytopenia infrequently requiring transfusions, and anemia.

Infections: increased risk of infections (e.g., pneumonia) and sepsis have been reported following treatment with bendamustine.

Infusion reactions and anaphylaxis: have been reported commonly in clinical trials with symptoms including fever, chills, pruritis, and rash. Rare reports of anaphylactic or anaphylactoid reactions have occurred.

Tumor lysis syndrome: reported in several subjects treated with bendamustine, primarily during the first cycle of therapy.

Skin reactions: reported reactions include rash, toxic skin reactions, and bullous exanthema

Elevated LFT's: reported increase in total bilirubin and transaminases in up to 30% of subjects in some clinical trials.

Gastrointestinal: frequent reporting of nausea, vomiting, and stomatitis.

1.I. Frequency of adverse effects:

Frequent adverse events: asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis; nausea, vomiting, and diarrhea. Hematologic toxicity is very frequent including grade 3 and 4 neutropenia and thrombocytopenia. Mild elevation of liver function tests (total bilirubin and transaminases).

Less common adverse events: hypersensitivity reactions, skin eruptions, fevers, chills, hypertension, pyrexia, and neutropenic infection.

1.J. Nursing/subject implications

Subjects require close monitoring during the first infusion for evidence of hypersensitivity reaction, which is an uncommon but serious side effect with bendamustine.

Hematologic toxicity is the primary dose-limiting toxicity, and hematologic nadirs should be expected in the third week of therapy.

Infection, including pneumonia and sepsis, have been reported following treatment

with bendamustine, usually in combination with myelosuppression. Subjects with myelosuppression need education regarding monitoring for signs of fever or infection.

Prophylaxis for tumor lysis syndrome should be considered in subjects with high tumor burden, or elevated uric acid and/or LDH.

Subjects should be educated on supportive measures for management of nausea, vomiting, diarrhea, constipation, and stomatitis.

1.K. References

Bendamustine package insert.

Appendix H: Grading events of tumor lysis syndrome

Adverse of events of tumor lysis syndrome must be reported according to the Cairo-Bishop definition of tumor lysis syndrome (TLS).[64] Only clinical TLS is to be reported as an adverse event. The table describing criteria for laboratory evidence of TLS is only to be used for calculation of the clinical grade score for TLS. Grade ≥2 TLS requires reporting as AESI.

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a subject has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).	

Cairo-Bishop Grading System for Clinical TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death*	Death*	Death*

LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal; ADL, activities of daily living

*Probably or definitely attributable to clinical TLS