PHASE II TRIAL OF VENETOCLAX AND RITUXIMAB AS INITIAL THERAPY IN OLDER PATIENTS WITH MANTLE CELL LYMPHOMA

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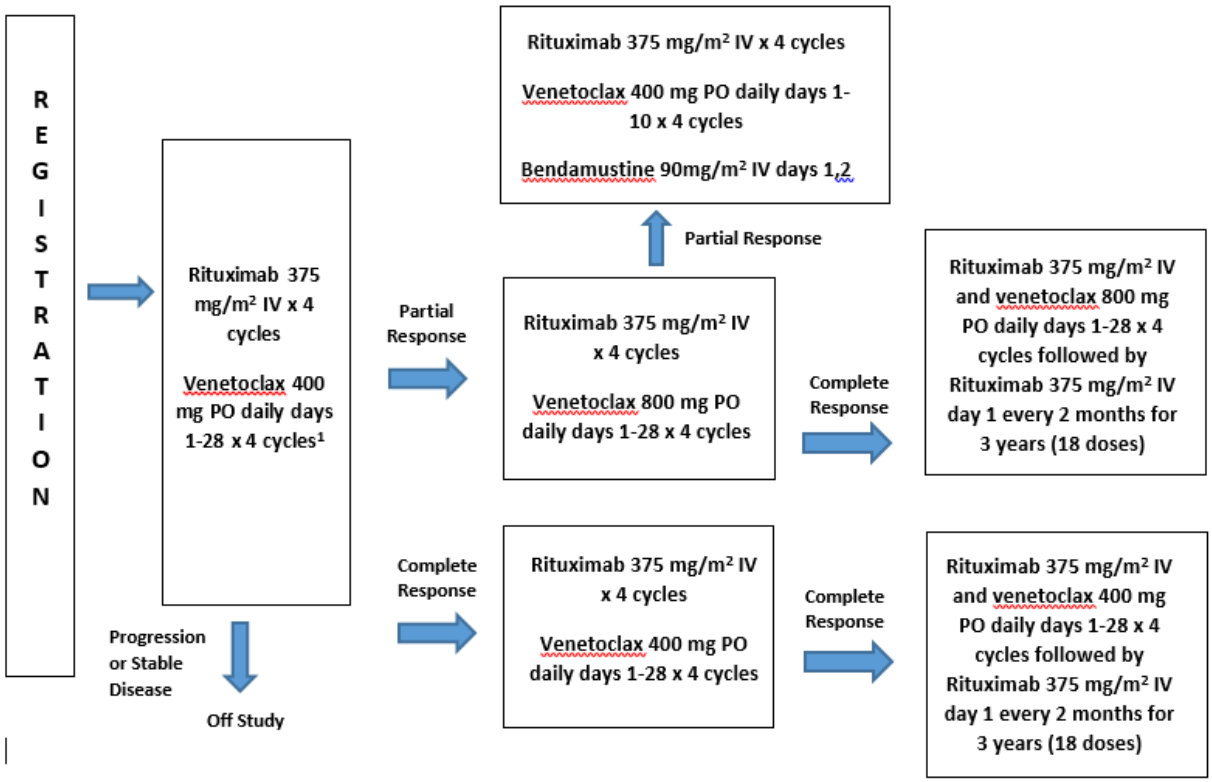
Brief Protocol Synopsis – see protocol document sections for complete details

Study Schema

Untreated Mantle Cell Lymphoma



[1] For the first cycle of venetoclax, there will be an intra-subject dose escalation to minimize risk of tumor lysis syndrome. Doses will start at 20mg daily for 7 days, then 50 mg daily for 7 days, 100 mg daily for 7 days, 200mg daily for 7 days, then 400mg daily.

Accrual goal: 40 patients

Cycle length: 28 days

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1. Introduction – Background and Rationale

1.1 Mantle Cell Lymphoma (MCL) – Disease Overview

Mantle cell lymphoma (MCL) is a distinct subset of B-cell non-Hodgkin lymphoma characterized by the (11;14) translocation resulting in an IGH/CCND1 fusion gene and aberrant expression of cyclin D1.[1] While generally incurable, clinical presentation is heterogeneous, ranging from indolent to aggressive biology. According to World Health Organization (WHO) classification, MCL can be divided into two categories. Classical MCL presents with nodal and extranodal sites and is characterized genetically by minimal mutations in IGHV and expression of SOX11. Leukemic nonnodal MCL is more indolent and develops from the germinal center with IGHV somatic hypermutation and lack of SOX11 expression. Patients commonly present with involvement of peripheral blood, bone marrow, and spleen[2].

1.2 Current Standard Approach to Frontline Therapy

Standard frontline treatment has evolved since MCL was first identified as a distinct clinical entity. Initial therapy utilized the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). Following the introduction of the antiCD20 monoclonal antibody rituximab into clinical practice, the German Low Grade Lymphoma Study Group conducted a randomized phase III trial comparing induction therapy with CHOP or CHOP plus rituximab (R-CHOP) for MCL.[3] This study revealed a superior time to treatment failure (TTF) following R-CHOP compared with CHOP; however, the median progression-free survival (PFS) with R-CHOP was only approximately 18 months. A randomized study of bendamustine plus rituximab (BR) compared to R-CHOP showed that BR improved PFS from 22 to 35 months compared to R-CHOP but did not improve OS[4]. As a result, several different approaches have subsequently been evaluated as intensification of therapy as a strategy to improve on these outcomes.

There have been several approaches to intensification of initial therapy for MCL, including HyperCVAD/MTX-Ara-c and the Nordic regimen of R-CHOP alternating with high-dose cytarabine, which have prolonged PFS compared to historical controls in non-randomized studies[5–8]. Consolidation with autologous stem cell transplantation (ASCT) is also often incorporated as consolidation in young, fit patients[9]. However, the toxicity of these regimens is high and intensive chemotherapy followed by ASCT is often not an option for elderly or unfit patients[5].

Recent studies in older patients have sought to achieve prolonged remissions without autologous stem cell transplantation. A study of fludarabine, cyclophosphamide, and rituximab (FCR) compared to R-CHOP with median age 70 showed worse overall survival at 4 years and increased hematologic toxicity for FCR[10]. In this study, maintenance rituximab did improve survival in patients with a response to R-CHOP. While not limited to elderly patients, the international randomized phase III BRIGHT study showed superior PFS with decreased rates of peripheral neuropathy for BR when compared to R-CHOP[4]. Another strategy is to eliminate chemotherapy entirely, such as a phase 2 study of lenalidomide and rituximab (R-R). Participants in this study, with a median age of 65, had a 2 year PFS of 85% and OS of 97%. One disadvantage of this approach is the need to continue therapy indefinitely[11].

In many patients who achieve a CR after initial chemotherapy for mantle cell lymphoma, it is possible to detect Minimal Residual Disease (MRD) from the blood or bone marrow by polymerase chain reaction, flow cytometry, or deep sequencing. The presence of MRD correlates with shorter disease free survival and overall survival in multiple studies of several different chemotherapy regimens[12–15].

1.3 Venetoclax

Bcl-2 Family Proteins

Programmed cell death (apoptosis) is responsible for removal of aged and damaged cells from a healthy multicellular organism, and the balance between cell survival and cell death, as maintained by apoptosis, is critical for normal development and homeostasis of multicellular organisms. The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway, and were first identified in FL where the t(14;18) chromosomal translocation results in significant overexpression of Bcl-2 in B cells. The Bcl-2 family of genes encodes a family of closely-related proteins that possess either pro-apoptotic or anti-apoptotic (pro-survival) activity and share up to 4 Bcl-2 homology (BH) domains[16–20].

In contrast to other known oncogenes, Bcl-2 does not stimulate cellular proliferation, but rather inhibits programmed cell death by protecting cells from a wide variety of proapoptotic stimuli, including cytokine withdrawal, irradiation, cytotoxic drugs, heat, and deregulated oncogenes[21].

Resistance to apoptosis is one hallmark of neoplasms[22]. Drug-induced restoration of the apoptotic pathway can therefore be a viable treatment strategy for cancer[23]. Selective killing of the tumor cells may be achieved because, unlike normal cells, tumor cells are under continuous stress and therefore reliant on aberrant apoptotic signaling to stay alive[23]. Overexpression of antiapoptotic Bcl-2 family members is associated with tumor initiation, disease progression, and drug resistance, and thus Bcl-2 family members are compelling targets for antitumor therapy.

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

Venetoclax Preclinical Toxicology

The primary toxicities associated with venetoclax were effects on the hematologic system (decreased lymphocytes and erythrocytes), the male dog reproductive system (testicular germ cell depletion), and embryofetal toxicity in mice. Other noteworthy but non-adverse findings were minimal to mild single cell necrosis in epithelial tissues (gallbladder, exocrine pancreas, epididymides, prostate, and stomach) of dogs and hair coat color change towards white in dogs that was a likely result of loss of melanin pigment in the hair. These effects of venetoclax were generally consistent with pharmacologic mechanism of action (selective Bcl-2 inhibition) of venetoclax. Reduction in red blood cell (RBC) mass and lymphocytes was reversible and is monitorable. There was no evidence of reversibility of testicular germ cell loss in dogs, and the risk of a similar effect in oncology subjects is balanced by the potential therapeutic benefit of venetoclax. Although there was no evidence of teratogenicity, fetal toxicity was observed in mice, suggesting a risk of fetal toxicity in humans. Therefore, women of childbearing potential should be advised to avoid becoming pregnant during venetoclax treatment and should be counseled on the use of effective birth control and to contact their healthcare provider if they become pregnant. There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity (tested in vivo in hairless mice). Nonclinical data on the M27 major human metabolite suggest that it has effects similar to venetoclax but of reduced

magnitude, consistent with its low in vitro potency, and that it is not genotoxic and has low off-target toxicity potential.

Venetoclax Clinical Data

As of 28 November 2018, on the basis of data available in the clinical databases for company-sponsored studies with unblinded data, a total of 2939 subjects have been exposed to at least 1 dose of venetoclax across company-sponsored studies. Of these subjects, 2906 are included in the overall pooled analyses for reporting Reference Safety Information, (RSI) available in the Investigator's Brochure: 2590 oncology subjects, 219 healthy volunteers, 24 subjects with hepatic impairment, and 73 SLE subjects. Of the 2590 oncology subjects, 2543 were adults in the venetoclax oncology program (1137 in monotherapy studies and 1406 in combination therapy studies): 1313 with CLL/SLL, 361 with AML, 218 with MM, 570 with NHL, 59 with myelodysplastic syndrome (MDS), and 20 with ALL, 1 with rhabdomyocarcoma, and 1 with Evans tumor. The remaining oncology subjects included 20 pediatric subjects in the venetoclax program and 27 subjects with various cancers from studies conducted with other investigational new drug (IND) compounds outside the venetoclax program. An additional 1317 subjects with blinded data have been treated with either venetoclax combination therapy or a comparator treatment in company-sponsored venetoclax oncology studies.

Clinical Pharmacokinetics: Pharmacokinetic data for venetoclax are available from studies in subjects with cancer (CLL/SLL, AML, NHL, and MM), healthy subjects, and subjects with hepatic impairment/

Following multiple-dose administration, the maximum plasma concentration of venetoclax was attained 5 to 8 hours after dosing. The harmonic mean terminal phase elimination half-life (t1/2) ranged from 17 to 41 hours following a single oral dose of venetoclax. In subjects with CLL, venetoclax showed minimal accumulation, and steady state AUC increased proportionally over the dose range of 150 to 800 mg. Venetoclax has been administered with food in all clinical studies, as food increased the bioavailability of venetoclax by approximately 3- to 5-fold. Venetoclax is highly bound to plasma proteins with unbound fraction (fu) < 0.01, and it is primarily eliminated as metabolites in feces with negligible renal elimination (< 0.1%). Drug-drug interaction (DDI) studies of venetoclax with ketoconazole, rifampin, warfarin, ritonavir, azithromycin, and digoxin were conducted to provide dosing recommendations for patients concomitantly taking CYP3A and/or P-gp inhibitors, inducers, and/or warfarin. Pharmacokinetic studies were conducted in healthy Chinese subjects and in Japanese subjects to provide dosing recommendations for those specific populations. Additionally, a dedicated study to evaluate the pharmacokinetics of venetoclax in subjects with hepatic impairment was conducted. Based on the population pharmacokinetic analysis, age, sex, race, weight, and mild and moderate renal or hepatic impairment do not have an effect on venetoclax clearance.

Clinical Safety and Efficacy in the Venetoclax Oncology Program: Multiple ongoing Phase 1/2/3 company-sponsored clinical studies are evaluating safety, tolerability, pharmacokinetics, and efficacy of venetoclax as monotherapy or in combination with other therapies (rituximab [R], obinutuzumab (GA101) [G], rituximab or obinutuzumab plus CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP or G-CHOP, respectively], BR, bendamustine plus obinutuzumab [BG], bortezomib plus dexamethasone, carfilzomib plus dexamethasone, azacitidine, decitabine, and cytarabine, navitoclax plus chemotherapy, daratumumab plus dexamethasone [with and without bortezomib], dinaciclib, alvocidib, and pomalidomide) in subjects with hematologic malignancies. Data are available from DDI studies of venetoclax interaction with ketoconazole, rifampin, warfarin, digoxin, ritonavir, azithromycin, and

posaconazole. Additionally, 9 Phase 3 studies are ongoing, including 2 monotherapy studies in R/R CLL (Studies M15-550 and M15-889) and 7 combination therapy studies (Study M13-494 exploring venetoclax + dexamethasone versus pomalidomide + dexamethasone, Study M14-031 exploring venetoclax + bortezomib + dexamethasone in R/R MM, Study M15-656 exploring venetoclax + azacitidine in AML, Study M16-043 exploring venetoclax + cytarabine in AML, Study M16-788 exploring venetoclax + obinutuzumab in first-line CLL, Study BO25323 exploring venetoclax + obinutuzumab versus obinutuzumab + chlorambucil in first-line CLL, and Study GO28667 exploring venetoclax + rituximab versus BR in R/R CLL).

Safety results in oncology subjects: Based on nonclinical and clinical data available with venetoclax administration, important identified risks are tumor lysis syndrome (TLS), neutropenia, and serious infection. Tumor lysis syndrome is a risk associated with venetoclax treatment and it is highest in CLL and MCL. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including, anemia, thrombocytopenia, and lymphopenia). Events of anemia, neutropenia, and thrombocytopenia are also commonly observed with the underlying hematologic malignancies. Infections, including serious infections, although also common with the underlying malignancies, have been reported with venetoclax treatment and their incidence is higher with combination treatments. Co-administration with CYP3A inducers and inhibitors can cause changes in venetoclax exposure. Decreased spermatogenesis has been observed in nonclinical studies with dogs. Embryofetal toxicity was observed in nonclinical studies; thus, venetoclax should not be used during pregnancy. In addition, as venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

Efficacy results in oncology subjects: Efficacy results are available for subjects with CLL/SLL, AML, MM, and NHL. These data indicate that venetoclax continues to show promising efficacy in oncology subject populations.

● In venetoclax monotherapy Study M12-175 (as of 30 March 2018), the overall response rate (ORR) (investigator-assessed) in Arm A (R/R CLL/SLL) was 78.4%. The ORR (investigator-assessed) in Arm B (R/R NHL) (as of 10 June 2016) was 38% for FL subjects and 18% for DLBCL subjects (Dose-Escalation and Safety Expansion Cohorts).

● In venetoclax monotherapy Study M13-982 (as of 15 June 2017), the ORR (investigator-assessed) for R/R CLL subjects in the main cohort was 77.2%.

● In venetoclax monotherapy Study M14-032 (as of 26 July 2017), the ORR (investigator-assessed) for R/R CLL subjects previously treated with either ibrutinib or idelalisb was 65.4%.

● In Study M13-365 (as of 04 June 2018) the ORR for R/R CLL/SLL subjects treated with venetoclax + rituximab was 85.7%.

● In Study GP28331 (as of 28 November 2018), the ORR in R/R and previously untreated CLL subjects was 96.1% with venetoclax + obinutuzumab.

● In Study GO28440 (as of 28 November 2018), the ORR in R/R and previously untreated CLL subjects was 98.7% with venetoclax in combination with BR or BG.

● In Study GO28667 (as of 08 May 2018), the investigator-assessed progression free survival (PFS) in R/R CLL showed a significant 84% reduction in the risk of disease progression or death for venetoclax + rituximab compared with BR treatment (stratified hazard ratio [HR] = 0.16; 95% CI: 0.12, 0.23).

● In Study BO25323 (as of 28 November 2018), during the safety run-in phase, the ORR for R/R and previously untreated CLL subjects was 100% with venetoclax + obinutuzumab (data are not yet available for the randomization phase).

● In Study M12-630 (as of 15 February 2017), the ORR for R/R NHL subjects treated with venetoclax + BR was 65.0%.

● In Study BO29337 (as of 28 November 2017), the Independent Review Committee (IRC)-assessed complete metabolic response (CMR) rate by positron emission tomography [PET]-scan at 6-month for R/R NHL subjects treated with venetoclax and BR was 74.5% and for R/R NHL subjects treated with venetoclax + rituximab was 11.3%.

● In Study GO27878 (as of 30 June 2017), the PET/CT-defined ORR at the time of primary assessment in previously untreated or R/R subjects receiving up to 1 prior treatment with mixed NHL histologies (including follicular, DLBCL, MZI, composite lymphoma) was 87.5% for subjects treated with venetoclax in combination with R-CHOP or G-CHOP in Phase 1 and 81.5% for venetoclax in combination with R-CHOP in Phase 2.

Updated data are described in detail in the Investigator's Brochure[24]

1.4 Rationale for the Dosing, Study Design, and Treatment Plan

1.4.1 Dosing Regimen Rationale

Rituximab is an antibody to CD20 approved to treat B cell malignancies, including mantle cell lymphoma. Dosing is based on the approved package insert.

Bendamustine is an alkylating agent used in combination with rituximab to treat mantle cell lymphoma. Dosing is based on the BRIGHT trial[4].

Venetoclax dosing is based on a phase 1 trial by Davids et al. of venetoclax monotherapy in non-Hodgkin lymphoma that included 28 patients with relapsed, refractory mantle cell lymphoma, as well as retrospective data published by Eyre et al. of off-label use of ventetoclax monotherapy in relapsed, refractory mantle cell lymphoma[25,26]. When combined with bendamustine and rituximab, venetoclax dosing will be based on the PrE0405 trial of venetoclax, bendamustine, and rituximab for untreated MCL. Venetoclax will be given at 400 mg daily on days 1-10 of a 28 day cycle.

1.4.1.1 Overview of evidence for venetoclax monotherapy in mantle cell lymphoma

Arm B of the M12-175 study enrolled subjects with relapsed or refractory non-Hodgkin lymphoma and assigned venetoclax monotherapy in a dose-escalation 3 + 3 design[25]. Patients received venetoclax until progression, unacceptable toxicity, or plan to proceed to allogeneic stem cell transplant. 56% of patients had grade 3-4 toxicity, primarily hematologic, and these were independent of dose. Of 106 patients enrolled, 28 had mantle cell lymphoma. The overall response rate (ORR) in MCL was 75% with 21% complete responses. The median progression free survival in MCL was 14 months. Doses up to 800mg daily were felt to be safe and were able to produce durable remissions. Retrospective data by Eyre et al. of venetoclax monotherapy in patients with MCL who had progressed after a BTK inhibitor[26]. The majority of patients achieved a final dose of 800mg or 1200mg daily. There were no cases of clinical tumor lysis syndrome and the majority of adverse events were grade 2 or less. The ORR was 53% (18% CR) and median PFS was 3.2 months. The median duration of response was 8.1 months.

1.4.1.2 Rationale for dose ramp-up schedule

The major toxicity concern with venetoclax is the ability to produce tumor lysis syndrome due to rapid tumor apoptosis. This risk is higher in MCL than in other NHL due to high activity in MCL. In the M12-175, subjects with MCL were started at a dose of 100mg and increased weekly to 200mg, 400mg, then 800mg with only one case of laboratory tumor lysis syndrome. However, subsequent evidence from investigator initiated trials and real world experience suggest that this dose escalation schedule may not be sufficiently cautious. Three patients receiving venetoclax on clinical trial and two in clinical practice developed clinical TLS, including one death. This occurred at doses of 50-100mg daily. Therefore, Davids et al. have proposed applying the dose ramp-up schedule from chronic lymphocytic leukemia to MCL. This consists of a 20mg per day starting dose, with increases weekly to 50, 100, 200, 400, and finally 800mg[27].

1.4.1.3 Safety of combining venetoclax with bendamustine and rituximab

A phase 1 dose escalation trial (M12-630) combined Venetoclax with Bendamustine (90 mg/m2) and Rituximab (375 mg/m2) in patients with FL, DLBCL and MCL. Venetoclax doses were escalated from 50 mg (intermittent) to 1200 mg (continuous daily). No dose limiting toxicities have been identified.

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

The combination of venetoclax, bendamustine and rituximab and in patients with R/R follicular lymphoma was explored in a Phase II study (Study BO29337, CONTRALTO). 49 patients were evaluable for safety in the treatment arm (V+BR) and 50 in the control arm (BR). Three deaths occurred, 1 due to pneumonia in the V+BR arm and 1 each due to PD and hypoxia in the BR arm. In the V+BR arm laboratory tumor lysis syndrome was seen in 3 patients and was manageable. In the V+BR arm 16 pts (33%) discontinued at least one drug to adverse events. In the control arm one patient stopped BR due to an AE.16

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

Grade 3/4 AEs occurring in more than 10% of patients were neutropenia (61% with V+BR, 30% with BR), thrombocytopenia (45%, 6%), anemia (14%, 2%) and febrile neutropenia (12%, 6%)[28].

In consideration of the added toxicity with venetoclax, bendamustine, and rituximab as compared to bendamustine and rituximab alone, the PrE0405 trial is investigating intermittent dosing of venetoclax when combined with bendamustine and rituximab in untreated MCL. This study is ongoing.

1.5 Study Design and Treatment Plan

For young, fit patients with mantle cell lymphoma, intensive chemotherapy and rituximab followed by ASCT is often used to achieve prolonged disease free survival. However, this therapy is not curative and has not been shown to improve overall survival. For older or frail patients, who are ineligible for stem cell transplantation, improved disease free survival can be achieved with chemotherapy and rituximab without ASCT, but at the cost of significant short and long-term toxicity. Venetoclax monotherapy has shown impressive single-agent activity in relapsed and refractory mantle cell lymphoma with low rates of adverse events.

Our hypothesis is that initial therapy with venetoclax and rituximab will result in rates of CR and PR that are comparable to historical rates with chemoimmunotherapy. Furthermore, this

regimen will have fewer side effects than traditional therapy. We also hypothesize that patients achieving a CR will have long durations of response that will continue after stopping venetoclax. We will test this hypothesis with an open label, single arm phase II trial at up to 3 sites with a target accrual of 40 participants. We will include patients over age 60 who are not candidates for aggressive upfront therapy . Subjects will receive venetoclax and rituximab for up to 12 cycles of 4 weeks each. All patients will stop venetoclax after 12 cycles. Participants who have stable disease or disease progression after 4 cycles will be removed from the trial in order to receive standard of care chemoimmunotherapy. Participants who do not achieve a CR after 8 cycles of venetoclax and rituximab will receive 4 cycles of standard of care bendamustine in addition to continuing rituximab and venetoclax. See section 3.1 for detailed investigational plan. This is the first phase II study of venetoclax and rituximab alone as initial therapy for mantle cell lymphoma. In the relapsed and refractory setting, venetoclax has shown high activity in MCL, and as such is a promising option for a non-chemotherapy approach to upfront treatment.

2. Study Objectives

2.1 Primary Objective

To estimate the ORR after four cycles of venetoclax and rituximab. The ORR will be the sum of complete (CR) and partial responses (PR).

2.2 Secondary Objectives

1. To estimate the proportions of CR, PR, stable disease, and disease progression after four cycles
2. To evaluate the rate of CR and PR after 8 cycles of venetoclax and rituximab
3. To evaluate the progression free survival (PFS) and overall survival (OS) in the intent to treat (ITT) population.
4. To evaluate the duration of response (DOR) for participants achieving a CR or PR
5. To evaluate the toxicities in patients receiving venetoclax and rituximab

2.3 Exploratory Objectives

1. To evaluate for mutations in TP53 and correlate with CR, PR, and duration of response

3. Investigational Plan

3.1 Overview

3.1.1 Venetoclax + Rituximab phase

Subjects who meet the inclusion criteria and do not meet the exclusion criteria will be enrolled with a target accrual of 40 subjects.

Initial treatment for all subjects will consist of rituximab infusion (375 mg/m^2) given on day 1 of each 28 day cycle. Venetoclax will be given in a single dose daily with an intra-subject dose ramp-up for the first 5 weeks. Starting dose of venetoclax will be 20 mg daily. If there is no evidence of clinical tumor lysis syndrome, subjects will increase the dose weekly as follows: 50, 100, 200, 400. Subjects will continue venetoclax at 400 mg daily on days 1-28 of subsequent cycles. After 4 cycles of 28 days, all subjects will undergo restaging evaluation. Subjects with a CR will continue venetoclax 400 mg daily and rituximab for 4 additional cycles. If restaging at that time shows a CR, subjects will continue on venetoclax 400 mg daily and rituximab for 4 additional cycles to complete 12 total cycles of therapy. At that time, venetoclax will be stopped

and subjects will receive standard of care maintenance rituximab every 2 months for 3 years for 18 total doses. For subjects who achieve a PR after 4 cycles of venetoclax 400 mg daily and rituximab, venetoclax will be increased to 800 mg daily with rituximab for 4 additional cycles. At this time, subjects who achieve a CR on restaging evaluation will continue with venetoclax 800 mg daily and rituximab for 4 additional cycles followed by maintenance rituximab every 2 months for 3 years for 18 total doses.

Table 3-1: Venetoclax dose escalation and dosing schedule for cycles 1-4

Agent	Dose	Route	Day(s)	Cycle Length
Venetoclax	20 mg 50 mg 100 mg 200 mg 400 mg	Oral	1-7 (Cycle 1) 8-14 (Cycle 1) 15-21 (Cycle 1) 22-28 (Cycle 1) 1-28 (starting Cycle 2)	28 days
Rituximab	375 mg/m^2	IV	1	28 days

Table 3-2: Dosing schedule for cycles 5-12 for subjects with CR after cycle 4

Agent	Dose	Route	Day(s)	Cycle Length
Venetoclax	400 mg	Oral	1-28	28 days
Rituximab	375 mg/m^2	IV	1	28 days

Table 3-3: Dosing schedule for cycles 5-8 for subjects with PR after cycle 4

Agent	Dose	Route	Day(s)	Cycle Length
Venetoclax	800 mg	Oral	1-28	28 days
Rituximab	375 mg/m^2	IV	1	28 days

Table 3-3: Dosing schedule for cycles 9-12 for subjects with PR after cycle 4 and CR after cycle 8				
Agent	**Dose**	**Route**	**Day(s)**	**Cycle Length**
Venetoclax	800 mg	Oral	1-28	28 days
Rituximab	375 mg/m^2	IV	1	28 days

Bendamustine + Rituximab + Venetoclax phase

Subjects with less than a PR after the first 4 cycles of venetoclax and rituximab will be removed from the study to receive standard of care therapy. Subjects who have a PR after 4 cycles and an ongoing PR after 4 additional cycles with venetoclax at 800 mg daily will receive bendamustine 90 mg/m^2 per package insert on day 1 and day 2 of subsequent cycles, in addition to continuing rituximab 375 mg/m^2 on day 1. Venetoclax will continue at 400 mg daily only on days 1-10 of each 28 day cycle. These subjects will receive bendamustine, rituximab, and venetoclax for 4 cycles. There will be no maintenance rituximab following this regimen, given no evidence for benefit of maintenance ritxumab after bendamustine based regimens for mantle cell lymphoma.

Table 3-4: Dosing schedule for cycles 9-12 for patients with a PR after cycle 8 of venetoclax and rituximab				
Agent	**Dose**	**Route**	**Day(s)**	**Cycle Length**
Venetoclax	400 mg	Oral	1-10	28 days
Rituximab	375 mg/m^2	IV	1	28 days
Bendamustine	90 mg/m^2	IV	1, 2	28 days

The study will employ a Simon two-stage model to assess for early signs of futility.

To mitigate the risk for tumor lysis syndrome, subjects will receive tumor lysis prophylaxis based on package insert guidelines for CLL[29] as detailed in section 6.7.4.

Given the risk for tumor lysis, if any of the enrolled patient experience clinical tumor lysis by Howard criteria, the study will stop accruing for redesign of tumor lysis syndrome prophylaxis[30]. If >20% of participants have significant adverse events, defined as unexpected hospitalization, or grade 3-4 non-hematologic toxicity the study will stop accruing for redesign of safety measures. The study will also be paused for review if there are any deaths attributed to tumor lysis syndrome, or any other adverse event that is not due to disease progression.

Subjects who discontinue treatment with venetoclax, rituximab, or bendamustine should remain on study with visits every 3 months until disease progression or an alternative therapy is required.

Venetoclax will be taken with approximately 240mL of water within 30 minutes of completion of a standard low-fat breakfast. Rituximab infusion (375 mg/m^2) will be administered per package insert. Bendamustine infusion (90 mg/m^2) will be given over 30 minutes. Rituximab and bendamustine infusions are given sequentially. Premedications will be given for rituximab infusion per package insert.

3.2 Selection of Patients

Subjects will undergo screening procedures within 14 days prior to initial study drug administration. Tumor assessment must be performed within 21 days prior to study drug administration. Adult male and female subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for enrollment into the study

3.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

- Subjects must have a histologically confirmed diagnosis of mantle cell lymphoma as defined by the World Health Organization (WHO) classification scheme.

- Age ≥ 60

- Subjects must be previously untreated for mantle cell lymphoma and deemed to require treatment by the treating physician

- ECOG performance status of 0-3

- Subject must have adequate bone marrow* without growth factor support as follows:

    - Absolute Neutrophil Count (ANC) ≥ 1000/μL

    - Platelets ≥ 75,000/mm3 (entry platelet count must be independent of transfusion within 14 days of Screening)

    - Hemoglobin ≥ 9.0 g/dL

* These criteria may be waived by study investigators if there is evidence of bone marrow involvement by MCL that is believed to be the cause of the cytopenias.

- Subject must have adequate renal, and hepatic function, per laboratory reference range at screening as follows:

    - Calculated creatinine clearance ≥ 40 mL/min; determined via the Cockcroft-Gault formula.

- AST and ALT ≤ 3.0 × ULN; Bilirubin ≤ 1.5 × ULN*. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN

* These criteria may be waived by study investigators if abnormal values believed to be due to lymphoma.

- Female subjects must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed as follows:

    - At Screening on a serum sample obtained within 14 days prior to the first study drug administration, and

    - Prior to dosing on a urine sample obtained on Cycle 1 Day 1 if it has been > 7 days since obtaining the serum pregnancy test results.

- All female subjects not surgically sterile or postmenopausal (for at least 1 year) and nonvasectomized male subjects must practice at least 1 of the following methods of birth control:

    - Total abstinence from sexual intercourse (minimum 1 complete menstrual cycle);

    - A vasectomized partner(s);

    - Hormonal contraceptives (oral, parenteral, vaginal ring or transdermal) for at least 3 months prior to study drug administration;

    - Double-barrier method (condoms and diaphragm with spermicidal [sponge, jellies or creams]).

- Ability to understand and willingness to sign IRB-approved informed consent

3.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

- Subject has blastoid-variant mantle cell lymphoma

- Subject requires immediate cytoreduction as determined by study investigators

- Subject has documented CNS involvement of mantle cell lymphoma

- Subject has Ann Arbor stage I or contiguous stage II mantle cell lymphoma

- Subject has an uncontrolled infection

- Subject has HIV infection

- All subjects will be screened for Hepatitis B (HBsAg, anti-HBs, anti-HBc IgM and total) and Hepatitis C (antibody or RNA). Subjects who are positive for Hepatitis B by HBsAg or DNA as well as subjects positive for Hepatitis C will be excluded. Subjects with anti-HBc positivity and DNA negative may be included but will be required to undergo monthly HBV DNA testing and liver function liver function testing (AST, ALT, alkaline phosphatase, total bilirubin). Patients with HCV antibody positivity and HCV pcr negativity are eligible to be included.

- Subject requires the use of warfarin

- Subject has received immunization with live virus vaccine within 28 days prior to the first dose of study drug

- A female subject is pregnant or breast-feeding

3.2.3 Prior and Concomitant Therapy

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary from 2 weeks prior to study drug administration through the end of the study, the name of the medication, dosage information including dose and frequency, date(s) of administration including start and end dates, and reason for use must be recorded.

General guidelines regarding excluded and cautionary medications with potential to cause pharmacokinetic drug-drug interactions are summarized below.

Excluded Until DLT assessment for a dose level is complete and Cautionary afterwards:

- **Strong and Moderate CYP3A inhibitors**
  - Consider alternative medications. If subject requires use of these medications, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.
- **Strong and Moderate CYP3A inducers**
  - Consider alternative medications. If subject requires use of these medications, use with caution

Excluded during ramp-up phase and Cautionary at the Cohort Designated Dose:

Strong CYP3A inducers - avasimibe,carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort

Moderate CYP3A inducers - bosentan, efavirenz, etravirine, modafinil, nafcillin

Strong CYP3A inhibitors - boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole

Moderate CYP3A inhibitors - amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil

Cautionary

Warfarin**

P-gp substrates

Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan*

BCRP substrates

Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan*

OATP1B1/1B3 substrates

Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan

P-gp inhibitors

Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor

BCRP inhibitors

Geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

* These are anticancer agents; consult contact AbbVie medical monitor before use.

** Closely monitor the international normalized ratio (INR).

[1] Moderate CYP3A inhibitor per venetoclax FDA USPI.

The following concomitant medications are not allowed 30 days prior to the first dose of study drug and during ABT-199 administration:

- Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent (except rituximab)

The following concomitant medications are not allowed 28 days prior to the first dose of study drug and during venetoclax administration:

- Live virus vaccines

The following concomitant medications are not allowed 14 days prior to the first dose of study drug and during venetoclax administration:

- Anticancer therapies including chemotherapy or radiotherapy;
- Other investigational agents, including targeted small molecule agents.

The following concomitant medications are allowed during venetoclax administration:

- Colony stimulating factors (G-CSF, GM-CSF) will be allowed per ASCO guidelines[31].
- Standard pre-medications administered with bendamustine and rituximab per package insert or institutional policy/standard of practice.
- Best supportive care and treatment (e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.).

If clinically indicated, antiherpes and anti-Pneumocystis prophylaxis should be considered. Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects, therefore Bactrim (trimethoprim sulfamethoxazole) can be considered for Pneumocystis prophylaxis, with close clinical monitoring.

An agent to reduce uric acid such as allopurinol or alternative agent if contraindicated should be taken daily for all participants through cycle 2 of venetoclax and rituximab.

3.3 Efficacy and Safety Assessments

Procedures	Screening[6]	Cycle 1 and 2 (1 cycle=28 Days) (+/- 3 days- Day 1 only)				Every cycle on VR or VBR(+/- 3 days)	Every 2 months on maintenance R (+/- 7 days)	Final Visit (+/- 14 days)	Follow-Up(+/- 14 days)
		Day 1	Day 8	Day 15	Day 22	Day 1			
Written Informed Consent	X								
Pathology Review	X								
Documentation of MIPI score	X								
Medical/Surgical History	X								
Assessment of Baseline Signs & Symptoms	X								
Height in cm	X								
Physical Exam	X	X	X	X	X	X	X	X	X
Weight in kg	X	X				X	X	X	X
Vital Signs (Temperature, Pulse, Blood Pressure)	X	X	X	X	X	X	X	X	X
Body Surface Area (BSA)	X	X				X		X	
Performance Status	X	X				X		X	
CBC/Differential/Platelets	X	X	X	X	X	X	X	X	X
Chemistry	X	X				X	X	X	X

HIV and Hepatitis B & C Testing	X								
Serum or Urine Pregnancy Test	X	X							
Tumor Lysis Labs[1]		X	X	X	X	X			
Research blood collection for plasma storage	X					X[2]			
PET CT	X					X[3]			
CT[4]						X	X	X	
Bone Marrow Biopsy	X					X[5]			
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X	X	X	X

[1] Tumor lysis labs will be drawn according to package insert for venetoclax use in CLL as detailed in section 4.7.4

[2]Blood will be drawn for plasma storage for future MRD assessment after cycles 4, 8 and 12 and for future mutational analysis at screening.

[3] PET/CT will be performed to assess for CR on cycle 5 day 1 and cycle 9 day 1

[4] CT will be done on cycle 3 day 3, cycle 7 day 1, cycle 11 day 1, cycle 13 day 1, and every 6 months while on maintenance rituximab

[5]Bone marrow biopsy will be performed on cycle 5 day 1 and cycle 9 day 1 for all participants with prior bone marrow involvement and who have a complete response by other measures of response.

[6] Baseline evaluations should occur within 30 days before initiation of therapy. Results of evaluations performed before study entry as standard of care may be used for research purposes and to fulfill study requirements.

3.3.1 Study Procedures

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of study drug.

Screening procedures must be performed within 14 days prior to study drug administration, except tumor assessments, including a PET/CT scan (or MRI) and bone marrow biopsy, which must be performed within 21 days prior to study drug administration.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study.

Medical and Oncology History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Detailed oncology history, including:
    - Histology
    - Date of cancer diagnosis
    - Stage
    - Any surgical procedures
    - Treatments administered
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken
- Pathology will be reviewed at Johns Hopkins Hospital or Sibley Memorial Hospital to confirm the diagnosis of mantle cell lymphoma, exclude blastoid variant, and evaluate TP53 mutational status per standard of care for mantle cell lymphoma.

On Cycle 1 Day 1, any additional medical history that is observed after signing of the informed consent but prior to initial venetoclax and rituximab administration and considered not related to study-required procedures will be recorded in the subject's medical history.

Concomitant Medications and Adverse Experiences

Medication (prescription or over-the-counter, including vitamins and herbal supplements) will be recorded beginning with the Screening Visit and continuing until 30 days following the last dose of study drug.

On Cycle 1 Day 1, any serious and nonserious adverse events observed from the time of signing of the informed consent but prior to initial venetoclax and rituximab administration will be reported, if considered by the Investigator to be causally related to the study-required procedures. At each visit, including the Final Visit and the 30-day Safety Follow-Up Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded.

ECOG Performance Status

The ECOG performance status will be assessed at the following visits:

- Screening
- Cycle 1 Day 1 and Day 1 of every cycle thereafter
- Final Visit
- 30-day Safety Follow-up Visit

Grade	Description
0	Fully active, able to carry on all predisease 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 housework, 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.

Pregnancy Test

For female subjects of childbearing potential, the local reference laboratory will perform pregnancy testing as follows:

- Screening – Serum test
- Cycle 1 Day 1 – Urine test, if it has been > 7 days since obtaining the serum pregnancy test results. (The test results must be reviewed and determined to be negative prior to dosing.)

Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal for at least 1 year.

Viral Serologies

Viral serologies for Hepatitis B (HBsAg, anti-HBs, anti-HBc, IgM anti-HBc); Hepatitis C (HCV) antibody or RNA will be conducted at the following visit:

- Screening
- As needed throughout the study

Subjects who are positive for Hepatitis B by HBsAg or DNA as well as subjects positive for Hepatitis C will be excluded as detailed in exclusion criteria. Subjects with anti-HBc positivity and DNA negative may be included but will be required to undergo monthly HBV DNA testing and liver function liver function testing (AST, ALT, alkaline phosphatase, total bilirubin).

Chemistry and Hematology

Chemistry labs include sodium, potassium, chloride, CO2, BUN, creatinine, glucose, AST, ALT, total bilirubin, albumin, total protein, magnesium, and phosphate.

Hematology labs include WBC, RBC, hemoglobin, hematocrit, platelet count, and WBC differential.

Tumor lysis labs

Tumor lysis labs include a basic metabolic panel (sodium, potassium, chloride, CO2, BUN, creatinine, glucose, calcium), uric acid, phosphate, lactate dehydrogenase.

Tumor lysis syndrome monitoring and prophylaxis will be done in accordance with the FDA prescribing information for use of venetoclax in CLL. Full details including management of TLS are in section 6.7.3. Monitoring is based on risk of tumor lysis syndrome. Clinical and laboratory tumor lysis syndrome will be assessed by Howard criteria.

Note: For all study visits after cycle 2, chemistry and hematology labs may be performed within 72 hours before the scheduled visit.

Positron Emission Tomography (PET) Computed Tomography (CT) Scans

A PET CT scan of involved anatomic regions will be performed at the following visits.

- Screening (within 21 days prior to the first dose of study drug)
- Cycle 5 Day 1
- Cycle 9 Day 1

A CT scan of involved anatomic regions will be performed at the following visits

- Cycle 3 Day 1
- Cycle 7 Day 1
- Cycle 11 Day 1
- Cycle 13 Day 1
- Every 6 months while on maintenance rituximab and as long as on study until disease progression
- Final Visit

Note: For all study visits after the Screening Visit, PET CT or CT may be performed 7 days prior to the scheduled visit.

Bone Marrow Biopsy

A bone marrow aspirate and biopsy with cytology and flow cytometry will be performed at the following visits

- Screening (within 21 days prior to the first dose of study drug)
- Cycle 5 Day 1 (all participants with prior bone marrow involvement by MCL and who have a CR by other response assessment)

Cycle 9 Day 1 (participants with prior bone marrow involvement by MCL and who have a CR by other response assessment) Note: For all study visits after the Screening Visit, bone marrow biopsy may be performed 7 days prior to the scheduled visit.

Post-Treatment Assessment

If a subject discontinues venetoclax, rituximab, or bendamustine, Post-Treatment visits will be performed after the 30-day Safety Follow-up Visit every 3 months until disease progression or alternate therapy is required. Analysis of peripheral blood, physical examination, vital signs and

(per Investigator discretion) PET CT scan of involved anatomic regions will be performed at the Post-Treatment Visit.

Survival Assessment

Survival information (i.e., the date and cause of death, post-treatment cancer therapies, etc.) will be collected at 3-month intervals after the last study visit for a period of 2 years after the subject has discontinued from the study.

3.3.2 Efficacy Variables

Efficacy endpoints include rates of CR, PR, ORR, SD, and disease progression after four cycles, CR and PR after eight cycles, progression free survival (PFS), overall survival (OS), and duration of response.

3.3.2.1 Measurement of Effect

Response and progression will be evaluated in this study using the revised international working group guidelines (Lugano classification)[32].

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD).

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

- Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Complete Response

- (1) Deauville Score of 1, 2, or 3 with or without a residual mass or nodal lesion:
  - 1, no FDG uptake above background;
  - 2, FDG uptake ≤ mediastinum;
  - 3, FDG uptake > mediastinum but ≤ liver;
  - 4, FDG uptake moderately > liver;
  - 5, FDG uptake markedly higher than liver and/or new lesions;
  - X, new areas of uptake unlikely to be related to lymphoma

- (2) In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- (3) No new lesions
- (4) No evidence of FDG avid disease in marrow unless as noted in (2).

Partial Response

- (1) Deauville score of 4 or 5 with reduced uptake compared to baseline and residual mass(es) of any size.
- (2) No new lesions
- (3) Residual marrow uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes 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 a bone marrow biopsy.

Stable Disease

- (1) Deauville score of 4 or 5 with no significant change in FDG uptake from baseline or end of induction treatment.
- (2) No new lesions
- (3) No change in marrow uptake from baseline

Progressive Disease

- (1) Deauville score 4 or 5 with an increase in intensity of uptake from baseline
- (2) New FDG avid foci consistent with lymphoma
- (3) New or recurrent FDG avid foci in the bone marrow

Duration of Response

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

Methods of Measurement

PET/CT is the preferred method to measure lesions selected for response assessment. PET/CT will be performed after cycles 4 and 8 to assess response. Interim disease evaluation will be performed with CT after cycle 2, cycle 6, cycle 10, and cycle 12. CT will also be performed every 6 months while on maintenance rituximab or surveillance while remaining on the study. Magnetic resonance imaging (MRI) may be used if medically indicated (e.g., severe contrast allergy). For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. However, US is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Cytology and histology can be used to differentiate between partial remission (PR) and complete remission (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions.

3.3.3 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, and laboratory assessments.

3.4 Removal of Subjects from Therapy or Assessment

3.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator will discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including:

- The investigator believes it is in the best interest of the subject;
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug or less than a partial response after cycle 4;
- The subject experiences toxicities related to study drug that require more than a 3-week dose interruption of venetoclax;
- The subject requires radiotherapy, cancer-related surgery as a result of tumor progression, or alternate anti-neoplastic agents during the study period;
- The subject becomes pregnant or begins breast-feeding;
- The occurrence of an adverse event that precludes further investigational drug administration;
- Noncompliance with the protocol.

All subjects will be included for analysis of safety data.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded. A physical examination, vital signs, hematology, chemistry, ECOG performance status assessment, tumor assessment, clinical disease progression assessment, collection of unused study drug, an assessment of adverse events, and an assessment of concomitant medications will be performed as soon as possible after discontinuation from the study.

A Safety Follow-up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event is achieved.

A separate Safety Follow-up Visit does not need to be performed for subjects who had a Final Visit conducted ≥ 30 days after discontinuation of study drug and did not require additional adverse event follow-up. If the subject refuses or is unable to attend the Safety Follow-up Visit, this should be noted in the subject's source documentation.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject report becoming pregnant during the study, the administration of study drug must be discontinued immediately.

3.4.2 Discontinuation of Entire Study

If, in the judgment of the investigator and AbbVie, the continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. The following procedures for discontinuation will be followed:

- If the sponsor has decided to prematurely discontinue the study, the sponsor will promptly notify in writing the investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.

- The investigator must promptly notify the IEC/IRB and give detailed reasons for the discontinuation.
- The investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

3.5 Treatments

3.5.1 Treatments Administered

Each dose of venetoclax will be taken with approximately 240 mL of water. Subjects will self-administer venetoclax within 30 minutes after the completion of a standard low-fat breakfast. In cases of vomiting, if vomiting occurs within 15 minutes of taking the dose and all tablets come out intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose is missed or forgotten, the subject should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

Rituximab (375 mg/m2) and bendamustine (90 mg/m2) infusions should be prepared per package insert.

Subjects should be premedicated with antihistamines and acetaminophen (corticosteroids, if necessary) for rituximab infusion per package insert and antiemetics and intravenous hydration per institutional policy/standard of practice.

3.5.2 Blinding

This is an open-label study

3.5.4 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

To document compliance with the treatment regimen, subjects will be instructed to return all unused tablets and/or bottles, even if empty and any other study related items as necessary, to the study coordinator at scheduled study visits. Compliance will be monitored and documented by the study coordinator on the appropriate form. The study coordinator will question the subject regarding adherence to the dosing regimen, record the number of tablets and/or bottles returned, the date returned, and determine treatment compliance before dispensing new study drug to the subject. Compliance below 80% will require counseling of the subject by study site personnel.

3.6 Discussion and Justification of Study Design

3.6.1 Suitability of Subject Population

Subjects with untreated mantle cell lymphoma will be selected to participate in this study. Subjects will be over age 60, which is a population at increased risk of complications from intensive upfront chemotherapy including high dose cytarabine containing induction and ASCT. Subjects with less than a PR after 4 cycles or progressive disease at any time will be removed from the study. Subjects with a partial response after 4 cycles and after 8 cycles will receive standard chemotherapy with bendamustine, in addition to rituximab and venetoclax.

3.6.2 Selection of Doses in the Study

Venetoclax dosing is based on a phase 1 trial by Davids et al. of venetoclax monotherapy in Non-Hodgkin lymphoma that included 28 patients with relapsed, refractory mantle cell lymphoma, as well as retrospective data published by Eyre et al. of off-label use of ventetoclax monotherapy in relapsed, refractory mantle cell lymphoma[25,26] Intra-patient dose ramp-up is based on recommendations for mantle cell lymphoma from Davids et al suggesting a slow increase of 20 mg daily then 50, 100, 200, 400, 800[27]. This was based on higher incidence of tumor lysis syndrome in mantle cell lymphoma with venetoclax, compared to other non-Hodgkin lymphoma. Given the potential for additional toxicity when added to rituximab, the target dose for the first 4 cycles is 400mg, which is 50% of the recommended phase II dose for venetoclax. Based on the AIM study of venetoclax and ibrutinib in relapsed MCL, participants with a PR after the first 4 cycles of venetoclax and rituximab can increase the dose of venetoclax to 800mg daily, which is the recommended phase II dose[37].

For participants receiving venetoclax in combination with bendamustine and rituximab, venetoclax will be given at a dose of 400mg for days 1-10 of each cycle. This is based on the dosing of the PrE0405 trial of bendamustine, rituximab, and venetoclax in untreated MCL[38].

The rituximab dose and schedule (375 mg/m2 administered once per cycle) was selected per package insert. The bendamustine dose and schedule (90 mg/m2 given over 30 minutes on 2 days per cycle) was selected based on the International Consensus Panel in combination with rituximab for follicular/low-grade NHL and aggressive NHL (DLBCL) dose of 90 mg/m2 for 2 days[33].

4. Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains:

- Biologic compound(s)

Complaints associated with any component of this investigational product must be reported to the Sponsor. For adverse events, please refer to Sections 6.1 through 6.7.

4.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered having "no reasonable possibility" of being associated to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

4.2 Definitions

4.2.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 6.7 regarding toxicity management), and/or if the investigator considers them to be adverse events.

As there is special concern regarding TLS in patients treated with venetoclax, laboratory abnormalities that meet one criterion within the Howard criteria for TLS should be reported as an AE (or SAE). Furthermore, if venetoclax dosing is modified in response to any single lab abnormality, that abnormality must also be appropriately recorded. An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

A treatment-emergent adverse event is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of study drug is administered until 30 days have elapsed following discontinuation of study drug administration.

4.2.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. 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.

Certain adverse events are anticipated to occur in the study population at some frequency independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population).

These adverse events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, if an event commonly associated with NHL or progression of NHL meets seriousness criteria (as defined in Section 6.1.1.2) it must be reported to AbbVie within 24 hours of the site being made aware of the serious adverse event. For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, but the event will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

4.2.3 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0)[34]. If a reported adverse event increases in severity, the initial adverse event should be given a final outcome date and a new adverse event must be reported to reflect the change in severity. The dates on the AE's cannot overlap. For all reported serious adverse events that increase in severity, the record must be updated to reflect any changes due to the increase in severity.

For adverse events not captured by the Common Terminology Criteria, the following should be used:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3 or Grade 4	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

4.3 Adverse Events Expected Due to Study Drug Related Endpoints

4.3.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting (see Section 6.5) that are more likely related to disease progression will therefore be an expected adverse event and will not be subject to expedited reporting.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

4.3.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

4.4 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of venetoclax, bendamustine and/or rituximab:

Reasonable Possibility:

An adverse event where there is evidence to suggest a causal relationship between the drug and the adverse event.

No Reasonable Possibility:

An adverse event where there is no evidence to suggest a causal relationship between the drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

4.5 Adverse Event Collection Period

All serious and nonserious adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration will be collected, whether elicited or spontaneously reported by the subject.

Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the first dose of the investigational product will be collected only if they are considered by the investigator to be causally related to the study required procedures.

4.6 Adverse Event Reporting

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

4.7 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued.

All subjects should be informed that contraceptive measures should be taken throughout the study and for at least 30 days after the last dose of venetoclax or 12 months after the last dose of venetoclax in combination with bendamustine and rituximab. Male subjects should be informed that contraceptive measures should be taken by their female partner. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

4.8 Toxicity Management

Dose limiting toxicities (DLTs) will be considered as any Grade 3, 4, or 5 adverse events that is judged as a "reasonable possibility" to the administration of venetoclax, bendamustine, and/or rituximab, which cannot be attributed by the investigator to a clearly identifiable cause such as

tumor progression, concurrent illness, or concomitant medication, will be considered a DLT with the exception of the following:

- Grade 3 or 4 thrombocytopenia that does not result in bleeding and improves to Grade ≤ 2 (or to ≥ 80% of the baseline value, whichever is lower) by Day 1 of the next cycle without platelet transfusion
- Grade 3 or 4 anemia
- Grade 3 or 4 lymphopenia, which is an expected outcome of therapy
- Grade 3 or 4 leukopenia because of lymphocyte depletion
- Grade 3 or 4 neutropenia that is not accompanied by temperature elevation (oral or tympanic temperature of ≥ 100.4°F [38°C]) and improves to Grade ≤ 2 (or to ≥ 80% of the baseline value, whichever is lower) by Day 1 of the next cycle
- Grade 3 neutropenic fever
- Grade 3 nausea, vomiting, and/or diarrhea unless unresponsive to treatment
- Grade 3 laboratory TLS without manifestations of clinical TLS (i.e., creatinine ≥ 1.5 × ULN, cardiac arrhythmias, sudden death, or seizures)
- Reversible Grade 3 rituximab infusion related toxicities (including symptoms such as fever, chills/rigor, nausea, vomiting, pruritus, headache, rhinitis, rash, and hypotension) occurring during or within 24 hours after completing an infusion and resolving within 24 hours of the onset of the toxicity with a reduced infusion rate, supportive care, and/or administration of corticosteroids

The investigator should reference the product labels for bendamustine and rituximab when assigning causality for events.

4.8.1 Dose Modifications

Table 4-1: Venetoclax Dose Delay or Modifications for Hematologic Toxicity

- **If a cycle is delayed by >28 days then patients will discontinue further treatment on protocol.**

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	• 1st occurrence: Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed. In the case of grade 3, resume at the same dose. In the case of grade 4, reduce dose according to Table 4-3. If the reduced dose is tolerated, investigators may choose to increase the dose after the first such occurrence according to the dose ramp up schedule.2nd occurrence: Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 4-3 when resuming treatment. A larger dose reduction may be done at the discretion of the physician.

Table 4-2: Venetoclax and Rituximab: Dose Delays and Modifications for Non-Hematologic Toxicity

Event(s)	Dose Delay or Modification

Grade 3 or 4 TLS (first episode and subsequent episodes)	• Withhold the next day's dose. For grade 3, if resolved within 24 to 48 hours of last dose resume at the same dose. In the case of grade 4, reduce dose according to Table 4-3. If the reduced dose is tolerated, investigators may choose to increase the dose after the first such occurrence according to the dose ramp up schedule. • For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 4-3).
Grade 3 or 4 treatment-related non-hematologic toxicity not specifically described above (excludes alopecia)	• 1st occurrence: Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed. In the case of grade 3, resume at the same dose. In the case of grade 4, reduce dose according to Table 4-3. If the reduced dose is tolerated, investigators may choose to increase the dose after the first such occurrence according to the dose ramp up schedule. • 2nd and subsequent occurrences: Interrupt venetoclax. Follow dose reduction guidelines in Table 4-3 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.

Table 4-3: Dose modification for Toxicity During Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg
800	600
400	300
200	100
100	50
50	20
20	10

Table 4-4: Venetoclax, Rituximab, and Bendamustine Dose Delay or Modifications for Hematologic Toxicity (G-CSF will be administered in all patients)

- **G-CSF will be used in all patients starting with first cycle of bendamustine treatment and will be continued unless contraindicated.**
- **If a cycle is delayed by >28 days then patients will discontinue further treatment on protocol.**

Event(s)	Dose Delay or Modification
Grade 3 or 4 neutropenia on Day 1 with or without infection or fever	• Delay doses of all study treatment by 7 days (+/-4 days) • If ANC recovers to ≥ 1000/mm^3 , resume treatment but reduce the dose of bendamustine to 70 mg/m^2 • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax

Recurrent Grade 3 or 4 neutropenia on Cycle 7 onwards	• Delay doses of all study treatment by 7 days (+/-4 days) • If ANC recovers to ≥ 1000/ mm^3 by Day 7 of the scheduled date for the next cycle, and bendamustine has been reduced to 70 mg/m^2, reduce venetoclax to next lower dose on dose ramp-up schedule. Rituximab will be restarted at full dose. • If ANC is <1000/mm^3 on or after Day 7, postpone therapy by 7 days (+/-4 days) of the scheduled date for the next cycle and bendamustine has been reduced to 70 mg/m^2, reduce venetoclax to next lower dose on dose ramp-up schedule. Rituximab will be restarted at full dose. • If ANC is <1000/mm^3 after reducing bendamustine to 70 mg/m^2 and reducing venetoclax, reduce venetoclax to next lower dose of dose ramp-up. • If recurrent grade 3 or 4 neutropenia requiring dose delays of >7 days at least 2 reductions of venetoclax and decreased bendamustine dose, patient will discontinue study treatment.
Recurrent Grade 4 neutropenia on Cycle Day 1	• If patient develops persistent Grade 4 neutropenia requiring dose delay despite growth factor support and following venetoclax dosing schedule changes and bendamustine dose reduction, and treatment is delayed by 28 days discontinue all study treatment permanently.

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

Table 4-5: Venetoclax, Rituximab and Bendamustine: Dose Delays and Modifications for Non-Hematologic Toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 TLS (first episode and subsequent episodes)	• Hold all study treatments until TLS resolves. Resume treatment once TLS resolves. • Following complete resolution of TLS, if venetoclax was held for 14 days or less, venetoclax should be changed to next lower dose in conjunction with prophylactic hydration and uricosuric agent; hospitalization for restarting the venetoclax dose may be considered at the discretion of the investigator. Dose escalation to the standard venetoclax should be considered in the following cycle.
Grade 3 or 4 treatment-related non-hematologic toxicity not specifically described above (excludes alopecia)	• Delay all treatment by 7 days for a maximum of 28 days. • First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax, rituximab and bendamustine for grade 3. For grade 4 treatment related AEs, reduce dose of venetoclax according to Table 4-3. • For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at next lower dose of dose ramp-up schedule and bendamustine at 70 mg/m^2 . Rituximab will be restarted at full dose.
Grade 2 treatment-related non-hematologic toxicity (excludes alopecia, nausea/vomiting and fatigue)	• Delay treatment with venetoclax, rituximab and bendamustine until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. After resolution, resume the full dose of venetoclax or dose before the delay. Rituximab will be restarted at full dose and bendamustine will be resumed at the previous dose (dose before the delay) for the next infusion. • **NOTE:** Bendamustine should not be used in patients with AST or ALT ≥ 3.0x ULN and total bilirubin ≥ 1.5x ULN.

4.8.2 Management of Lymphopenia

There is a potential for clinically significant lymphopenia in this study. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or Pneumocystis infections. Potential for drug-drug interactions should be considered.

4.8.3 Management of Neutropenia

There is a potential for clinically significant neutropenia in this study. If clinically indicated, standard management practices for neutropenia, including G-CSF and anti-infectives (for bacterial prophylaxis), should be implemented at the investigator's discretion.

4.8.4 Management of Tumor Lysis Syndrome

Tumor Lysis Syndrome Prophylaxis for venetoclax

There is a potential for tumor lysis in subjects especially in those in the presence of the following risk factors: bulky disease, elevated pretreatment LDH levels, elevated leukocyte count, and dehydration. To mitigate the risk for TLS, subjects will receive tumor lysis prophylaxis prior to, and during treatment. Prophylaxis for tumor lysis syndrome will be based on FDA package insert guidelines for the use of venetoclax in CLL as shown in the table below.

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring
		Hydration	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm and ALC <25x10^9/L	Oral (1.5-2 L)	Allopurinol	Outpatient • First dose of weeks 1, 2 and 6, predose, 6-8 hours, 24 hours • For Subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC >25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • First dose of weeks 1, 2, and 6, predose, 6-8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of weeks 1-2 and 6, consider hospitalization for patients with CLcr <80ml/min
High	Any LN >10cm OR ALC >25 x10^9/L AND any LN >5cm	Oral (1.5-2L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of weeks 1, 2, and 6: Pre-dose, 4, 8, 12, 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6-8 hours, 24 hours

ALC = absolute lymphocyte count; CLcr = creatinine clearance; LN = lymph node.
Administer intravenous hydration for any patient who cannot tolerate oral hydration.
Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of ventoclax.
Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

TLS prophylaxis (e.g., hydration, allopurinol administration) will not be captured as an AE. Hospitalization of a subject to allow observation and management (e.g., for IV hydration) for the

purpose of TLS prophylaxis will not be captured as an SAE, unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal TLS labs that necessitate therapeutic medical intervention, etc.).

4.8.5 Toxicities Related to Other Drug Used in Study Dosing

The following serious adverse events have been reported in patients treated with rituximab as a single agent: serious or fatal infusion reactions, tumor lysis syndrome, hepatitis B reactivation with fulminant hepatitis, progressive multifocal leukoencephalopathy (PML), or other viral infections. A full description of the adverse events associated with rituximab can be found in the Rituxan® (rituximab) label[35].

The following serious adverse events have been associated with bendamustine in clinical trials: myelosuppression (neutropenia, febrile neutropenia, red blood cell and platelet transfusions); infections including pneumonia and sepsis; infusion reactions and anaphylaxis; tumor lysis syndrome; and skin reactions. A full description of all adverse events associated with bendamustine can be found in the Treanda® (bendamustine) package insert[36].

A dose reduction for bendamustine to 70 mg/m2 should be considered. If a subject requires a dose reduction, the investigator will notify the AbbVie medical monitor and a decision regarding treatment options or subject discontinuation will be made jointly.

5. Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the sponsor and in accordance with the Independent Ethics Committee (IEC)/Independent Review Board (IRB) and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

6. Statistical Methods and Determination of Sample Size

6.0 Overview

The proposed study is an open-label, single arm phase II study of venetoclax in combination with rituximab in patients over the age of 60 with previously untreated mantle cell lymphoma. The primary objective of the trial is to determine whether the combination of venetoclax with rituximab in this patient population yields a clinically acceptable proportion of overall responses (ORR, assessed by PET/CT with Lugano criteria) without chemotherapy.

6.1 Study Objectives

Primary Objective

To estimate the ORR after four cycles of venetoclax and rituximab. The ORR will be the sum of complete (CR) and partial responses (PR).

Secondary Objectives

- To estimate the proportions of CR, PR, stable disease, and disease progression after four cycles
- To evaluate the rate of CR and PR after 8 cycles of venetoclax and rituximab
- To evaluate the progression free survival (PFS) and overall survival (OS) in the intent to treat (ITT) population.
- To evaluate the duration of response (DOR) for participants achieving a CR or PR

- To evaluate the toxicities in patients receiving venetoclax and rituximab

Exploratory Objectives

- To evaluate for mutations in TP53 and correlate with CR, PR, and duration of response

6.2 Study Design

The primary objective of this study is ORR following 4 cycles of treatment. Any patient progressing will go on to receive standard chemotherapy. The early time point for evaluation in this study will minimize the risk of delaying chemotherapy. Enrollment will be carried out in two stages so that the study can terminate early if venetoclax in combination with rituximab is not sufficiently effective. Approximately 40 patients over the age of 60 with previously untreated mantle cell lymphoma will be enrolled. Simon's optimal two-stage design will be used to test the null hypothesis that the true ORR is 50% or less (not considered clinically acceptable). In the first stage, 16 subjects will be accrued. If 8 or fewer patients respond, the study would terminate after the first stage. Otherwise, 21 additional subjects will be accrued to a target total of 37 treated and response evaluable patients. If 23 or more responses are observed in these 37 patients, we will conclude the combination of venetoclax and rituximab is sufficiently active without chemotherapy. The study could also be terminated early as soon as 23 responses with the combination are confirmed. The probability of stopping the trial early for futility is 59.8% if the true ORR is 50% or less. This design has 85% power at a one-sided type I error rate of 10% when the true ORR is 70%. The study may enroll up to 40 subjects to ensure 37 would be evaluable for the primary efficacy endpoint.

6.3 Accrual

The single institution enrollment is estimated at 0.5 subjects/month. Conducting the trial at a total of three centers would result in an anticipated accrual period of less than three years.

6.4 Safety monitoring and early stopping rules for safety

Safety will be monitored continuously throughout the study. The following adverse events (AEs) will be applicable for stopping rule outlined below: clinical tumor lysis syndrome (TLS) by the Howard criteria, unexpected hospitalization for toxicity, and grade 3- 4 non-hematologic toxicities. If it becomes evident that the proportion of these failures convincingly exceeds 20%, the study will be suspended for a safety consultation. In addition, any deaths occurring during the study period, including those thought to be due to tumor lysis syndrome, would cause the trial to be immediately paused for review. The stopping rule will hold enrollment if the posterior probability of failure being larger than 0.2 is 75% or higher. The prior for this monitoring rule is beta (0.5, 4.5). This means that our prior guess at the proportion of failures is 10.0%, and there is 90% probability that this proportion is between 0.05% and 36.2%. The stopping rule is given in the table below:

Stop if AEs	2	3	4	5	6	7	8	9	10	11
and N participants	2	3-6	7-11	12-15	16-19	20-24	25-28	29-33	34-37	38-40

For example, the rule will call for stopping the study if 3 participants out of the first 6 experience AEs. The following table shows the percent of the time that the stopping rule will stop the study under different hypothetical risks of toxicity, along with the average sample size (based on 5000 simulations).

Risk of DLT	0.10	0.15	0.20	0.25	0.30	0.35
% of Time Study Stops	3.8%	13.6%	35.6%	59.4%	81.0%	93.3%
Expected Sample Size	38.8	36.3	31.0	25.1	18.8	13.9

6.5 Analysis Plans

The ORR, defined as the proportion of response evaluable subjects who have a CR or PR by PET/CT and Lugano criteria at the completion of four cycles of therapy, will be reported with an exact 95% confidence interval. An evaluable subject will have received at least 1 cycle of venetoclax. Patients withdrawing prior to completing all four cycles will be counted as not have had a response.

The proportions of CRs and PRs will also be reported separately with exact 95% confidence intervals. PFS and OS will be reported using non-parametric Kaplan-Meier estimates and 95% confidence intervals.

The safety analysis will be performed in all subjects who receive any amount of study drug. A complete list of all AE data will be provided along with an assessment of NCI CTCAE grade and relationship to study drug. The incidence of AEs will be tabulated by subgroups of interest (e.g. grade 3 or higher, organ class, relationship to study drug). For analyses at the individual level, the highest grade and relationship to study drug will be assumed if multiple events have occurred. Toxicity will be tabulated by type and grade and will be summarized with descriptive statistics.

7. Ethics

7.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent, all other forms of subject information related to the study (e.g., advertisements used to recruit subjects), and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent, and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain, and archive study essential documents according to International Conference on Harmonization (ICH) GCP.

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written

reports (e.g., ICH Expedited Reports or any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

7.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

7.3 Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Each informed consent will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

8. Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source document.

The investigator/institution will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

9. Data Quality Assurance

Prior to enrolling any subject in the study, an initiation meeting will be held with AbbVie personnel, the investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, case report form completion, and specimen collection methods.

Routine hematology, serum chemistry and serology, and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study.

10. Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative. The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving.

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