Rituximab and High-Dose Methylprednisolone Debulking Prior to Venetoclax for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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Signature Page

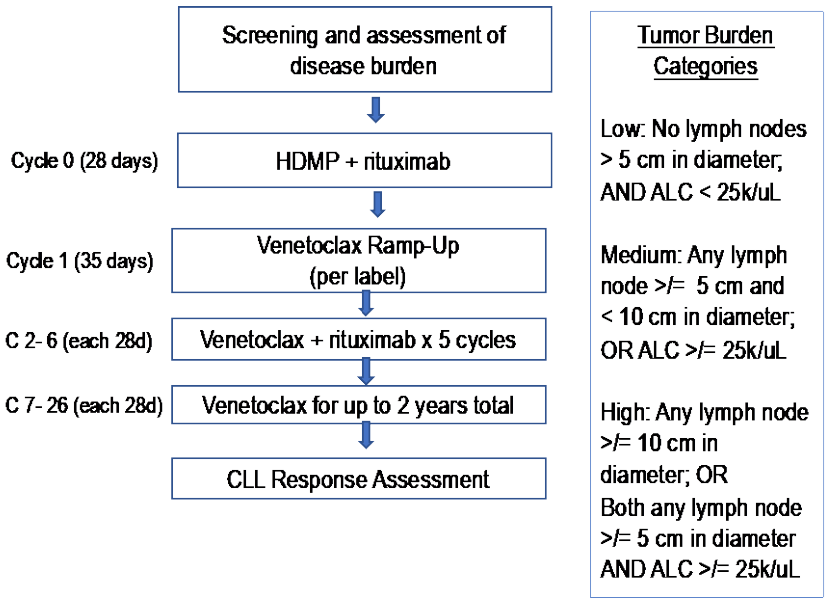
The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

Table 1. Synopsis (including required elements for IIS protocols with Venetoclax):

Section		
1.0	**General Information**	
	Study Flowchart	See Main Protocol Table of Events **Overall Study Schema:** 
1.1	**Study Title:**	Rituximab and High-Dose Methylprednisolone Debulking Prior to Venetoclax for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (Version Date 09/18/2019, Version 4)
1.2	**Institution Name:**	UC San Diego, Moores Cancer Center
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2.0	**Background Information**	
2.1	**Rationale & Background Information**	The combination of venetoclax and rituximab is an effective and FDA-approved regimen to treat patients with CLL or SLL who have previously received treatment. In a randomized phase 3 clinical trial, the 2-year PFS was 84.9% (bendamustine-rituximab comparator arm 2-year PFS was 36.3%); the ORR was 93.3% with a CR rate of 26.8% (Seymour et al, 2018). In part due to highly potent apoptosis induction, there is a known risk of tumor lysis syndrome (TLS) with venetoclax. This risk is mitigated by careful prophylactic and monitoring measures during the initiation of venetoclax, including inpatient hospitalization and serial lab monitoring for patients who have a high tumor burden. With such measures, the rate of grade 3 or 4 TLS was 3.1% in the venetoclax-rituxmab trial (Seymour et al, 2018). However, further TLS risk mitigation will improve outcomes with this treatment. This risk of TLS is associated with the amount of tumor burden. Patients with Low Tumor Burden (absolute lymphocyte count less than 25k/uL; all lymph nodes less than 5 cm in diameter) are considered to have low TLS risk, and can be monitored without hospitalization (Venetoclax prescribing information). Therefore, decreasing the CLL tumor burden prior to initiation of venetoclax can also be a risk mitigation strategy. The combination of High-Dose Methylprednisolone (HDMP) and rituximab has been evaluated as a treatment for patients with CLL (Castro et al, 2008 and Castro et al, 2009). For patients with fludarabine-refractory CLL, the ORR was 96%, the CR rate was 36%, and all patients would have met the above criteria for Low Tumor Burden at the completion of therapy. Imaging was not done after just 1 cycle, so the precise degree of debulking at that time point is not known; however, the ALC values reduced in majority of patients within the 1st cycle. Therefore, HDMP + Rituximab is a potential debulking strategy prior to initiation of venetoclax based on the following rationale: - high rate of improvement of lymphadenopathy and lymphocytosis in previous publications. - lack of added myelotoxicity; and manageable overall toxicity profile compared to rituximab + venetoclax alone. - administration in an outpatient setting.
3.0	**Core Protocol**	
3.1	**Study Objectives and Purpose**	**Purpose:** to determine the feasibility of treating patients with HDMP + rituximab as a means of debulking prior to initiating venetoclax. **Objectives:** <u>Primary:</u>

		1. To determine the percentage of patients who have a reduction of lymphadenopathy (from greater than to less than 5 cm in largest diameter) and/or absolute lymphocyte count (from greater than to less than 25k/uL) following 1 or 2 cycles of HDMP + rituximab. <u>Secondary:</u> 1. To determine the rate of laboratory or clinical TLS with this strategy. 2. To determine the safety (CTCAE4) of this approach. 3. To determine the overall efficacy (iwCLL) of this overall strategy. 4. To determine the percentage of patients who have undetectable minimal residual disease in the bone marrow. **Endpoints:** <u>Primary:</u> 1. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" criteria to meet "Low tumor burden" criteria for disease burden following 1 or 2 cycles of HDMP + Rituximab. <u>Secondary:</u> 1. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" c criteria to meet "Low tumor burden" criteria for disease burden following 1 cycle of HDMP + Rituximab. 2. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" criteria to meet "Low tumor burden" criteria for disease burden following 2 cycles of HDMP + Rituximab. 3. Rate of laboratory TLS (from start of treatment until completion of venetoclax ramp-up) 4. Rate of clinical TLS (from start of treatment until completion of venetoclax ramp-up) 5. Adverse events by CTCAE4 definitions 6. Overall Response rate, Partial Response rate, and Complete response rate per iwCLL criteria after 9 months of venetoclax and at completion of treatment. 7. Undetectable minimal residual disease (MRD) rate based on bone marrow biopsy after 9 months of venetoclax, and at completion of treatment.
4.0	**Study Design**	Single center, open-label, pilot/feasibility study to determine the feasibility of HDMP/R as a debulking approach prior to venetoclax. Patients with CLL/SLL who require therapy, and have disease burden meeting criteria for Medium or High Risk Tumor Burden (based on: lymph nodes >/= 5 cm in diameter and/or absolute lymphocyte count >/= 25k/uL) are enrolled.

		- Patients will receive HDMP + Rituximab for 1 cycle, followed by reassessment of Tumor Burden, - Patients will initiate venetoclax dose ramp-up, with ramp-up schedule according to venetoclax package insert. Upon completion of ramp-up (venetoclax to 400 mg), all patients will continue Venetoclax 400 mg (or highest tolerated dose) for up to 2 years. Patients will also continue rituximab 500 mg/m2 q 28 days through Cycle 6. Endpoint Assessment: 1. Assessment of the disease burden after a maximum of 2 cycles of HDMP + Rituximab is the primary endpoint. 2. Assessment of the disease burden after 1 cycle of HDMP + Rituximab. 3. Clinical and laboratory TLS events between start of treatment and the completion of venetoclax dose-ramp up (Cycle 2, Day 1) 4. Presence or absence of detectable MRD in the marrow will be assessed after approximately 9 months of venetoclax and completion of treatment. 5. Radiology assessment after approximately 9 months of venetoclax and completion of study (unless prior imaging studies are without measurable disease)
5.1	**Inclusion Criteria**	<u>Patients must meet the following criteria for study entry:</u> 1. Subjects must be age 18 or older. 2. Both men and women of all races and ethnic groups are eligible for this trial. 3. Ability to understand and willingness to sign a written informed consent. 4. Diagnosis: CLL or SLL, as documented in the medical record 5. Disease Status/ Prior Therapy: - Must have had treatment for CLL/SLL with at least 1 line of prior therapy. (There is not requirement nor restriction for specific type of previous therapy, with the following exceptions: prior treatment with venetoclax within 6 months, prior progressive disease on venetoclax, or prior grade 3 or 4 toxicity (not including TLS) that directly lead to discontinuation of venetoclax; Prior HDMP/Rituximab is allowed unless there was no response (Stable Disease or Progressive Disease) or was within 3 months.) - Indication for CLL or SLL therapy based on international working group (iwCLL) guidelines, which include: constitutional symptoms, bulky or symptomatic lymphadenopathy, bulky or symptomatic splenomegaly, rapid doubling of the ALC (approximately 6 months or less), or Rai stage 3 or 4 disease. - Disease burden meets criteria for Medium or High Tumor Burden, based on Absolute lymphocyte count >/= 25k/uL or any lymph node 5 cm or greater in diameter. The ALC criteria must be met during the screening period. The imaging criteria may be based on radiologic study within 30 days of Cycle 0, Day 1.

		6. Has recovered from the toxic effects of prior therapy to their clinical baseline. 7. Women of child-bearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree to not become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 5 half-lives after the final dose of venetoclax (approximately 1 week), and at least 5 half-lives of final dose of Rituximab. 8. ECOG performance status of 0-2 9. Adequate hematologic function: Platelet count >/= 30k/uL, hemoglobin > 7 g/dL, AND ANC > 500/uL. (Values may be lower if due to marrow infiltration by CLL). 10. Adequate renal function: creatinine clearance based on 24 hr collection >/= 40 ml/min; OR Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)]. 11. Adequate hepatic function: - Aspartate transaminase (AST) and alanine transaminase (ALT) < 3.0X ULN - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
5.2	**Exclusion Criteria**	<u>Patients who meet any of the following criteria will be excluded from study entry:</u> 1. Subject is known to be positive for HIV. (HIV testing is not required.) 2. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to: - Uncontrolled and/or active systemic infection (viral, bacterial or fungal) - Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. Note: subjects with serologic evidence of prior vaccination to HBV (i.e. hepatitis B surface (HBs) antigen negative-, anti-HBs antibody positive and anti-hepatitis B core (HBc) antibody negative) or positive anti-HBc antibody from intravenous immunoglobulins (IVIG) may participate. 3. Treatment with any of the following within 7 days prior to the first dose of venetoclax: - Steroid therapy for anti-neoplastic intent - moderate or strong cytochrome P450 3A (CYP3A) inhibitors (see Appendix C for examples) - moderate or strong CYP3A inducers (see Appendix C for examples) 4. Prior CLL therapy: - Biologic agent (monoclonal antibody) within 30 days for anti-neoplastic intent.

		- Chemotherapy (purine analog or alkylating agent) or target small molecule agent within 14 days or 5 half-lives (whichever is shorter), or has not recovered to less than CTC grade 2 clinically significant adverse effect(s)/toxicity(s) of previous therapy. 5. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy 6. Known hypersensitivity to any of the study drugs 7. History of other malignancy that could affect compliance with the protocol or interpretation of results (example: patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are generally eligible. Patients with a malignancy that has been treated, but not with curative intent, will also be excluded, unless the malignancy has been in remission without treatment for 2 years prior to enrollment.) 8. Known active bacterial, viral, fungal, mycobacterial, or other infection (excluding fungal infections of nail beds); or any major episode of infection requiring treatment with IV antibiotics or hospitalization (related to the completion of the course of antibiotics) within 4 weeks before the start of Cycle 0 9. Major surgery (within 4 weeks prior to the start of Cycle 0), other than for diagnosis 10. Women who are pregnant or lactating 11. Uncontrolled diabetes mellitus (related to high dose steroid risk) 12. Myocardial infarction within 6 months of starting study drug or other clinically significant heart disease (NYHA class 3 heart failure, uncontrolled hypertension) (*Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.* See Protocol Section 5.3 for other Excluded and Cautionary Prior and Concomitant Medications.)
6.0	**Study Procedures**	<u>See Main Protocol for details.</u> <u>Procedures, in brief:</u> Screening Procedures: - Physical examination, CBC diff, CMP, Hepatitis B serologies (Standard of Care (SOC) prior to anti-CD20 therapy) and CT scan or MRI thorax, abdomen, pelvis. - Initiate allopurinol 3 days prior treatment initiation Cycle 0 (28 days in duration): HDMP + Rituximab - Methylprednisolone 1000 mg/m2 days 1-3 - Rituximab 100 mg day 1; 375 mg/m2 days 2-4 - Repeat CBC diff, CT scan or MRI thorax, abdomen, pelvis between Day 15 to Day 28 of Cycle 0. (SOC prior to venetoclax) Cycle 1 (35 days in duration): Venetoclax Ramp-Up

		- Continue allopurinol, acyclovir, and septra (or equivalent drugs, unless contraindication). Must stop fluconazole 7 days prior to first venetoclax dose. - Week 1: Venetoclax 20 mg daily - Week 2: Venetoclax 50 mg daily - Week 3: Venetoclax 100 mg daily - Week 4: Venetoclax 200 mg daily - Week 5: Venetoclax 400 mg daily - TLS Monitoring per venetoclax package insert. Cycles 2-6 (28 days in duration each): Venetoclax + Rituximab - Continue Venetoclax 400 mg PO daily (or highest tolerated dose) - Rituximab 500 mg/m2 on day 1 of each cycle. Cycle 7-26: Single agent Venetoclax - Continue Venetoclax 400 mg PO daily (or highest tolerated dose) End of Study: - Marrow biopsy and aspirate to assess for detectable CLL (MRD) Long-term f/up: No specific visits required. With patient consent, date of progression or next CLL therapy will be recorded. <u>Concomitant Medications:</u> - It is prohibited to take other intended CLL therapies concurrently, including purine analog, alkylating drugs, other anti-CD20 monoclonal antibody, ibrutinib, Idelalisib, etc. Corticosteroids are permitted (in cycle 0 as CLL therapy; in cycles 2-6 as anti-CD20 infusion reaction prophylaxis; and at other times for treatment of conditions other than CLL). - Required wash out for the above is 5 half-lives or 1 month, whichever is shorter. - GCSF, EPO, and blood transfusion are not restricted, and can be used as clinically indicated or as per clinician judgement. - TLS prophylaxis is recommended from 3 days prior to Cycle 0 Day 1 until Cycle 2 Day 1: Allopurinol 300 mg daily (dose modified if needed; alternative uric acid lowering medication can be substituted). - Anti-Infection Prophylaxis is recommended from 3 days prior to Cycle 0 day 1: - Fluconazole 100 mg daily (or alternative per clinician discretion) until Cycle 1 Day 21; - Acyclovir 400 mg BID (or alternative per clinician discretion) until Cycle 3 Day 1 (or may continue longer) - Septra DS BID 2 days/week (or alternative per clinician discretion) until Cycle 3 Day 1 (or may continue longer) It is prohibited to receive live viral vaccines or other investigational agents. <u>Subject Withdrawal or Treatment Discontinuation:</u>

		Patients who meet or develop the following criteria should be discontinued from the study - Active HBV infection or hepatitis. Patients who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis. - Severe or life-threatening anaphylaxis or hypersensitivity reaction to rituximab. Patients that discontinue rituximab for that reason can continue to receive HDMP and venetoclax if clinically indicated. - Patients who meet the following criteria should discontinue HDMP: Grade 4 psychosis; Active HBV infection or hepatitis as above. HDMP doses can be delayed for acute infection or as clinically indicated. - Inability of patient to comply with study requirements - Determination by the investigator that it is no longer safe for the patient to continue therapy For patients who withdraw from all study therapy: No specific visits required. With patient consent, date of progression or next CLL therapy will be recorded.
	Specific Drug Supply Requirements	1. Methylprednisolone 1000 mg/m2 IV days 1-3 of Cycle 0 will be obtained as a standard of care treatment for patients with CLL. 2. Rituximab 100 mg IV day 1 of cycle 0; 375 mg/m2 days 2-4 of Cycle 0; and 500 mg/m2 day 1 of cycles 2-6 will be obtained as a standard of care treatment for patients with CLL. Substitution of rituximab with other equivalent preparations is allowed, including the following: biosimilars of rituximab (including Ruxience or other FDA-approved rituximab product). 3. Venetoclax starter-kit (20 mg PO daily x 1 week, 50 mg PO daily x 1 week, 100 mg PO daily x 1 week, 200 mg PO daily x 1 week) and Venetoclax 400 mg PO daily for 24 months will be supplied by Abbvie and stored, dispensed, and/or destroyed by the UCSD Investigational Drug Services (IDS) Pharmacy, pursuant to ICH/GCP Guidelines.
9.7	**Statistical Analysis and Sample Size Justification**	This is a pilot/feasibility clinical trial, with the primary feasibility endpoint being debulking of tumor burden to meet criteria for Low Tumor Burden upon the completion of cycle 0. Sample Size Justification: 17 patients are enrolled to evaluate the primary endpoint. A success rate of 60% of patients adequately debulking (defined as having Low Tumor Burden at the end of cycle 0) will be considered compelling, establishing the feasibility of this approach, and support further studies. A success rate of 30% would be not compelling for further studies. With 17 patients, the study is adequately powered to evaluate this. A Simon's two-stage minimax design is utilized, with stopping for futility if an insufficient number of patients are debulked by HDMP/Rituximab:

		The null hypothesis that the true debulking rate is 30% will be tested against a one-side alternative. In the first stage, 10 patients will be accrued. If there are 2 or fewer responses (patients achieving Low Tumor Burden) in these 10 patients, the study will be stopped. Otherwise, 7 additional patients will be accrual for a total of 17. The null hypothesis will be rejected if 9 or more responses are observed in 17 patients. This design yields a type I error rate of 0.04 and power of 80% when the true response rate is 60%. Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 38.3%. The sample size calculation was done using PASS version 14.0.3 (released September 22, 2015).
10.0	**Safety Reporting**	**SAE definition:** An AE should be classified as an SAE if the following criteria are met: • It results in death (i.e., the AE actually causes or leads to death) • It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death). • It requires or prolongs inpatient hospitalization • It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions) • It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP • It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above) **SAE Reporting:** Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines: **7 Calendar Day Telephone or Fax Report** The Investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of HDMP, Rituximab, and venetoclax. An unexpected AE is one that is not already described in the venetoclax investigator brochure or the methylprednisolone and rituximab prescribing information. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event. **15 Calendar Day Written Report** The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any

		serious, unexpected AE that is considered reasonably or possibly related to the use of HDMP, rituximab, or venetoclax. An unexpected AE is one that is not already described in the venetoclax investigator brochure or the methylprednisolone and rituximab prescribing information. Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on. Written IND safety reports with analysis of similar events are to be submitted to the FDA, Abbvie, and all participating investigators within 15 calendar days of first learning of the event. MedWatch 3500 form or alternative formats will be used (e.g., summary letter). Contact Information for IND Safety Reports FDA fax number for IND safety reports: Fax: 1 (800) FDA 0178 In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall: a) Report to Abbvie all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition, report all non-serious adverse events of tumor lysis syndrome for studies involving ABT-199. b) Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and, c) Notify AbbVie upon any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery. AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be PPDINDPharmacovigilance@abbvie.com Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product

<table>
<tr><td></td><td></td><td>Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints shall be RD_PQC_QS@abbvie.com</td></tr>
<tr><td>12.0</td><td>References</td><td>Main References:

1. Castro JE, James DF, Sandoval-Sus JD, Jain S, Bole J, Rassenti L, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia. 2009;23(10):1779-89.
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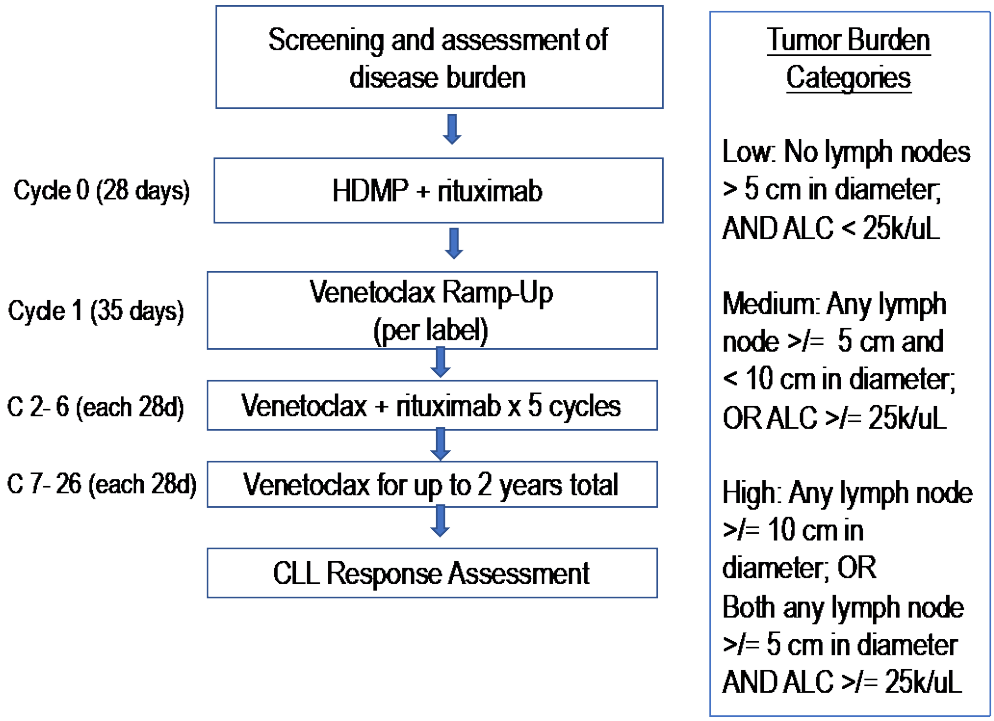
3. Seymour JF. Effective mitigation of tumor lysis syndrome with gradual venetoclax dose ramp, prophylaxis, and monitoring in patients with chronic lymphocytic leukemia. Ann Hematol. 2016;95(8):1361-2.
4. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med. 2018;378(12):1107-20.
5. Seymour JF, Ma S, Brander DM, Choi MY, Barrientos J, Davids MS, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. Lancet Oncol. 2017;18(2):230-40.
6. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.</td></tr>
<tr><td></td><td>Study Timelines</td><td>Provide the estimated study timelines below:

<table>
<tr><th>Milestone</th><th>Est. Date (Month/Year)</th></tr>
<tr><td>Duration*</td><td>Enrollment = 1 year; F/up and Treatment = 2 years.
Total study duration = 3 years</td></tr>
<tr><td>First Subject First Visit (FSFV)</td><td>Sept/2019</td></tr>
<tr><td>Last Subject Last Visit (LSLV)</td><td>Sept/2023</td></tr>
<tr><td>Final Report (e.g., manuscript/ publication)</td><td>Initial Reporting based on primary endpoint:</td></tr>
</table></td></tr>
</table>

				Dec 2023. Final Publication Dec 2023.

*Duration is defined as FSFV to LSLV in months.

1.0 Schema



2.0 Background

2.1 Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia (CLL) is a malignancy of B-cells and is the most common form of leukemia in the western world, with an incidence of 3-5 per 100,000 (1). Although treatment options for CLL have expanded considerably in the recent years, it remains incurable. In the front-line setting, chemoimmunotherapy, in particular, the combination of rituximab with purine analogs and/or alkylator therapy, is one standard treatment for young and/or fit individuals with CLL who require treatment (2-4). Ibrutinib, a small molecule therapy that inhibits the tyrosine kinase Btk, is also an approved standard initial treatment for patients with CLL, with a high overall response rate of 89% (29% complete response) and 5-year progression-free survival of greater than 90% of patients who continue on ibrutinib (5-7).

There is not a standard of care therapy in the relapsed or refractory setting. Many patients cannot tolerate chemoimmunotherapy in that setting due to age, comorbidities, or compromised bone marrow function [4, 5]. Ibrutinib is an approved standard of care, though some comorbid conditions such as bleeding, requirement for anticoagulation, or heart disease may increase the risk of adverse events.

The combination of venetoclax and rituximab approved by the US FDA in 2018 as a standard treatment for patients with CLL who have received 1 prior therapy, regardless of cytogenetics or the specific prior therapy. Background regarding venetoclax follows.

2.2 Venetoclax

2.2.1 Venetoclax Overview

Venetoclax (VENCLEXTA™) is a potent, orally administered inhibitor of B-cell lymphoma 2 (BCL-2) co-developed by AbbVie Inc and Genentech Inc for the treatment of B-cell malignancies. Venetoclax has been approved in the US for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL) where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains. Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2.

Venetoclax (also known as ABT-199) is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki <0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL and Bcl-w (>4,000-fold and >2,000- to >20,000-fold lower affinity than to Bcl-2, respectively). Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2- dependent human tumor cell lines (venetoclax IB).

2.2.2 Summary of Nonclinical Data

In vitro, venetoclax demonstrated broad cell killing activity against patient-derived CLL and acute myeloid leukemia (AML) cells, and a variety of lymphoma and leukemia cell lines including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), AMLs, and multiple myeloma cell lines. Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. A detailed discussion of the non-clinical toxicology, metabolism, and pharmacology can be found in the venetoclax IB.

2.2.3 Summary of Venetoclax Clinical Data

2.2.3.1 Clinical Pharmacokinetics

Following multiple oral administrations under fed conditions, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg.

Food can increase venetoclax exposure (3.4-fold with a low-fat meal and 5.1- to 5.3-fold with a high-fat meal). Venetoclax should be administered with a meal. The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4/5. Less than 0.1% of venetoclax is excreted renally.

Venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl <30 mL/min) or subjects on dialysis.

Venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function based on the NCI Organ Dysfunction Working Group criteria. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin >1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin >1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin >3.0 times ULN. The pharmacokinetics of venetoclax has not been studied in subjects with severe hepatic impairment.

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the venetoclax IB.

2.2.3.2 Summary of Clinical Safety

Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg. As of 28 November 2015 and version 7 of the Investigator's Brochure, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 1662 subjects have been exposed to at least 1 dose of venetoclax in the oncology and immunology development programs. A total of 1493 oncology subjects have data available in AbbVie and Genentech/Roche studies as of 28 November 2015. Of these 1493, there are 935 subjects with CLL/ SLL, 346 subjects with NHL, 110 subjects with MM, 102 with AML. An additional 66 subjects are healthy volunteers. A total of 560 oncology subjects received the drug as monotherapy, 933 have received the drug in combination with other therapies, and 1 subject received venetoclax as a single dose in a drug-drug interaction study and did not re-enroll into a subsequent monotherapy study. Additionally, 98 subjects have been exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093, as of 28 November 2015. Of the 935 subjects with CLL/SLL that have been treated in the venetoclax oncology clinical program: 336 patients have received venetoclax monotherapy and 599 have received venetoclax in combination with other agents including rituximab, obinutuzumab, and bendamustine.

The most common adverse events (incidence >20%) reported for all subjects in CLL/SLL monotherapy studies were diarrhea (40.2%), neutropenia (38.7%), nausea (37.8%), fatigue (27.4%), upper respiratory tract infection (26.5%), and anemia (25.3%). The most common Grade 3 and above adverse events were neutropenia (36.0%), anemia (14.6%), and thrombocytopenia (13.1%). The most common serious adverse events were pneumonia (5.7%), febrile neutropenia and malignant neoplasm progression (5.7% each). The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents.

In combination with rituximab, serious adverse reactions were reported in 46% of patients, with the most frequent (≥5%) being pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), cough (22%), and nausea (21%).

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with CLL. Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, have occurred in previously treated CLL patients with high tumor burden when treated with venetoclax. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with relapsed/refractory CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. The starting dose was reduced to 20 mg and prophylaxis and monitoring instituted, with 3 week ramp-up.

Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a ramp-up period of 5 weeks (starting from 20 mg) and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy, indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or non-serious event of clinical TLS (CTLS) or had study treatment discontinued because of TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing, especially with a higher initial dose of venetoclax, as well as being greater in subjects with a large tumor burden.

The earlier clinical trials identified risk factors for tumor lysis syndrome. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. In addition, measurements of tumor burden, including maximum lymph node diameter and absolute lymphocyte count define TLS risk.

Subjects have been classified in 3 risk categories based on risk for developing medically concerning TLS with venetoclax administration. The tumor burden assessed by the nodal disease and absolute lymphocyte count has been used to defined each category as below:

Tumor Burden Category	Criteria
Low	All measurable lymph nodes with the largest diameter < 5 cm by radiologic assessment AND ALC < 25k/uL
Medium	Any measurable lymph node with the largest diameter >/= 5 cm but < 10 cm by radiographic assessment OR ALC >/= 25k/uL
High	Any measurable lymph node with the largest diameter >/= 10 cm by radiologic assessment OR

	ALC >/= 25k/uL AND any measurable lymph node with the largest diameter >/= 5 cm

Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. Venetoclax prescribing information include standard of care recommendations for monitoring of blood chemistries, and use of more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk of TLS increases (see Appendix D and E: Prophylaxis and Management of TLS).

Grade 3 or 4 neutropenia occurred in 41% (98/240) of patients treated with venetoclax in the pivotal previously treated CLL 17p deletion study. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (eg, G-CSF). In addition, 49 patients with CLL were treated with venetoclax + rituximab in a phase 1 M13-365 clinical trial. The rate of neutropenia (grade 3 and above) was 53.1%.

Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Advise patients that vaccinations may be less effective.

2.2.3.3 Summary of Clinical Efficacy of Venetoclax with Rituximab

The combination of venetoclax and rituximab was evaluated in a randomized, open-label, phase 3 trial. 389 patients were randomized to receive venetoclax for up to 2 years (from day 1 of cycle 1) plus rituximab for the first 6 months (venetoclax-rituximab group) or bendamustine plus rituximab for 6 months (bendamustine-rituximab group). The trial design did not include crossover. The primary end point was investigator-assessed progression-free survival.

The treatment regimen utilized the same dose escalation/ ramp-up strategy as utilized in early monotherapy trials. Rituximab was added on week 6, after completion of the ramp-up. Patients received rituximab 375 mg/m2 for the 1st dose, then 500 mg/m2 for 5 additional monthly doses.

After a median follow-up period of 23.8 months, the rate of investigator-assessed progression-free survival was significantly higher in the venetoclax-rituximab group (32 events of progression or death in 194 patients) than in the bendamustine-rituximab group (114 events in 195 patients); the 2-year rates of progression-free survival were 84.9% and 36.3%, respectively (hazard ratio for progression or death, 0.17; 95% confidence interval [CI], 0.11 to 0.25; P<0.001 by the stratified log-rank test). The benefit was maintained across all clinical and biologic subgroups, including the subgroup of patients with chromosome 17p deletion; the 2-year rate of progression-free survival among patients with chromosome 17p deletion was 81.5% in the venetoclax-rituximab group versus 27.8% in the bendamustine-rituximab group (hazard ratio, 0.13; 95% CI, 0.05 to 0.29), and the 2-year rate among those without chromosome 17p deletion was 85.9% versus

41.0% (hazard ratio, 0.19; 95% CI, 0.12 to 0.32). The benefit of venetoclax plus rituximab over bendamustine plus rituximab was confirmed by an independent review committee assessment of progression-free survival and other secondary efficacy end points.

The rate of grade 3 or 4 neutropenia was higher in the venetoclax-rituximab group than in the bendamustine-rituximab group, but the rates of grade 3 or 4 febrile neutropenia and infections or infestations were lower with venetoclax than with bendamustine. The rate of grade 3 or 4 tumor lysis syndrome in the venetoclax-rituximab group was 3.1% (6 of 194 patients). (8)

2.3 High Dose Methylprednisolone

Corticosteroids have long been used in regimens to treat B-cell malignancies. High dose methylprednisolone (HDMP) has been studied as a single agent in treatment of advanced CLL. A small study was conducted using high dose methylprednisolone at a dose of 1 gm/m2 daily for five days repeated every four weeks in subjects with chemotherapy refractory CLL (Thornton et al., 1999). In this study no complete responses were noted, however, 6 of 11 (55%) subjects had partial responses following, on average four cycles of treatment. In addition to improving the subjects' sense of well-being and reducing lymphadenopathy, treatment with HDMP was associated with marked improvement in hematological parameters including rise in hemoglobin and platelet counts indicating improved bone marrow function.

In vitro and in vivo data suggest that there is a synergistic effect of methylprednisolone and Rituximab (9). This is demonstrated by the fact that CLL cells lose the survival protection conferred by stromal cells and undergo apoptosis when incubated in the presence of methylprednisolone and Rituximab. Our preliminary data from a study in subjects refractory to fludarabine has shown that the combination of HDMP-Rituximab can be safely administered with no major Grade III or IV side effects. All treated subjects showed response to this treatment regimen when evaluated at two months after completion of treatment (4 subjects with complete response and 3 subjects with partial response). A long-term follow up analysis of those subjects has shown that the median time to progression is 18 months, which is unexpectedly high in this group of fludarabine refractory CLL subjects.

In addition, the combination of HDMP-Rituximab in previously untreated subjects has been evaluated. (9) A total of 28 subjects with a median age of 65 years were enrolled in this study. Subjects received HDMP at 1 g/m2 each day for 3 days during each of the three 4-week cycles together with rituximab and prophylactic antimicrobial therapy. The treatment was well-tolerated and the main toxicities were Grade ≤ II and included, hyperglycemia, insomnia, fluid retention. We also observed 2 transient episodes of grade III-IV toxicity secondary to infection, resulting in pneumonia or sinusitis that resolved completely after antibiotic treatment. The overall response rate was 96% (N=27). Nine subjects (32%) achieved a complete remission (CR), two of which were without detectable minimal residual disease (MRD). Six subjects with MRD received consolidation with alemtuzumab; five of these subjects achieved an MRD-negative CR. With over 3 years of follow-up median progression-free survival was 30.3 months with only 39% of subjects requiring additional therapy, and an overall survival that was 96%. Most subjects showed normalization of the absolute lymphocyte count after the first cycle of treatment as well as rapid

recovery of cytopenias. Pharmacodynamic studies showed that leukemia cells from subjects responding to this combination regimen were induced to express pro-apoptotic molecules, such as Bid, Apaf-1, Smac-Diablo, and to down regulate expression of anti-apoptotic molecules, such as XIAP and Mcl-1.

2.4 Study Rationale

The combination of venetoclax and rituximab is an effective and FDA-approved regimen to treat patients with CLL or SLL who have previously received treatment, though brings risk of tumor lysis syndrome (TLS) upon initiation of venetoclax. This risk is currently mitigated by careful prophylactic and monitoring measures during the initiation of venetoclax, including inpatient hospitalization and serial lab monitoring for patients who have a high tumor burden. Further mitigating the TLS risk will improve this treatment.

This risk of TLS is associated with the amount of tumor burden, and patients with Low Tumor Burden (absolute lymphocyte count less than 25k/uL; all lymph nodes less than 5 cm in diameter) are considered to have low TLS risk, and can be monitored without hospitalization (Venetoclax prescribing information). Therefore, decreasing the CLL tumor burden prior to initiation of venetoclax can also be a risk mitigation strategy.

The combination of High-Dose Methylprednisolone (HDMP) and rituximab has been evaluated as a treatment for patients with CLL. For patients with fludarabine-refractory CLL, the ORR was 96%, the CR rate was 36%, and all patients would have met the above criteria for Low Tumor Burden at the completion of therapy. The ALC values reduced in majority of patients within the 1st cycle. Therefore, HDMP + Rituximab is an ideal potential debulking strategy prior to initiation of venetoclax based on the following rationale:

- high rate of improvement of lymphadenopathy and lymphocytosis in previous publications.
- lack of added myelotoxicity; manageable overall toxicity profile compared to rituximab + venetoclax alone.
- administered in an outpatient setting.

3.0 Objectives

Purpose: to determine the feasibility of treating patients with HDMP + rituximab as a means of debulking prior to initiating venetoclax.

Objectives:

Primary:

1. To determine the percentage of patients who have a reduction of lymphadenopathy (from greater than to less than 5 cm in largest diameter) and/or absolute lymphocyte count (from greater than to less than 25k/uL) following 1 or 2 cycles of HDMP + rituximab (only 1 cycle permitted if subject enrolled after protocol v5 approval).

Secondary:
1. To determine the rate of laboratory or clinic TLS with this strategy.
2. To determine the safety (CTCAE4) of this approach.
3. To determine the overall efficacy (iwCLL) of this overall strategy.
4. To determine the percentage of patients who have undetectable minimal residual disease in the bone marrow.

Endpoints:

Primary:

1. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" criteria to "Low tumor burden" criteria for disease burden following a maximum of 2 cycles of HDMP + Rituximab (following a maximum of 1 cycle if subject enrolled after protocol v5 approval).

Secondary:

1. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" to meet "Low tumor burden" criteria for disease burden following 1 cycle of HDMP + Rituximab.
2. Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" to meet "Low tumor burden" criteria for disease burden following 2 cycles of HDMP + Rituximab.
3. Rate of laboratory TLS (from start of treatment until completion of venetoclax ramp-up)
4. Rate of clinical TLS (from start of treatment until completion of venetoclax ramp-up)

5. Adverse events by CTCAE4 definitions

6. Overall Response rate, Partial Response rate, and Complete response rate per iwCLL criteria after 9 months of venetoclax and at completion of treatment.

7. Undetectable minimal residual disease (MRD) rate based on bone marrow biopsy after 9 months of venetoclax, and at completion of treatment.

4.0 Study Design

4.1 Description

This is a single center, open-label, pilot/feasibility study designed to evaluate the feasibility of HDMP/Rituximab as an approach to decrease TLS risk for patients who receive venetoclax for treatment of CLL/SLL.

Patients with CLL/SLL who require therapy, and have disease burden meeting criteria for Medium or High Tumor Burden (based on: lymph nodes >/= 5 cm in diameter and/or absolute lymphocyte count >/= 25k/uL) are enrolled.

- Patients will receive HDMP + Rituximab for 1 cycle, followed by reassessment of Tumor burden.
- Patients will then initiate venetoclax dose ramp-up, with ramp-up schedule according to venetoclax package insert.
- If Tumor Burden classification is still Medium/High after 1 cycle of HDMP + rituximab, patients are also given the option to repeat a 2nd cycle of HDMP + Rituximab prior to the venetoclax dose ramp-up.

Upon completion of ramp-up (venetoclax to 400 mg), all patients will continue Venetoclax 400 mg (or highest tolerated dose) for up to 2 years. Patients will also continue rituximab 500 mg/m2 q 28 days through Cycle 6.

4.2 Endpoint Assessment:

1. Assessment of the disease burden after a maximum of 2 cycles of HDMP + Rituximab is the primary endpoint for HDMP/R as an approach to decrease risk of TLS.

2. Assessment of the disease burden after 1 cycle of HDMP + Rituximab.

3. Assessment of the disease burden after 2 cycles of HDMP + Rituximab (for the subset of patients that do not meet criteria for low tumor burden after 1 cycle).

4. Clinical and laboratory TLS events between start of treatment and the completion of venetoclax dose-ramp up (Cycle 2, Day 1)

5. Presence or absence of detectable MRD in the marrow will be assessed after approximately 9 months of venetoclax and completion of treatment.

6. Radiology assessment after approximately 9 months of venetoclax and at the completion of therapy, and as clinically indicated (unless prior imaging studies are without measurable disease)

4.3 Rationale for study design

Rationale for Primary Feasibility Endpoint:

Classification of Tumor Burden into Low-, Medium-, and High- is a validated system that aids in TLS risk stratification based on prior venetoclax clinical trials, and is in accordance with standard clinical practice and the venetoclax prescribing information. This then serves as an appropriate endpoint to evaluate the feasibility of using HDMP/R as a means to lower the risk of TLS. Using actual TLS rate would require a much larger study as the absolute rate is relatively low. There is also clinical value in decreasing the Tumor Burden to “low” prior to venetoclax administration, as less intensive monitoring is required (ie, no inpatient hospitalization).

5.0 Study Population

Subjects will undergo screening procedures within 28 days prior to initial study drug administration. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Subjects must be age 18 or older.
2. Both men and women of all races and ethnic groups are eligible for this trial.
3. Ability to understand and willingness to sign a written informed consent.
4. Diagnosis: CLL or SLL, as documented in the medical record
5. Disease Status/ Prior Therapy:

- Must have had treatment for CLL/SLL with at least 1 line of prior therapy. (There is not requirement nor restriction for specific type of previous therapy, with the following exceptions: prior treatment with venetoclax within 6 months, prior progressive disease on venetoclax, or prior grade 3 or 4 toxicity (not including TLS) that directly lead to discontinuation of venetoclax; Prior HDMP/Rituximab is allowed unless there was no response (Stable Disease or Progressive Disease) or was within 3 months.
- Indication for CLL or SLL therapy based on international working group (iwCLL) guidelines, which include: constitutional symptoms, bulky or symptomatic lymphadenopathy, bulky or symptomatic splenomegaly, rapid doubling of the ALC (approximately 6 months or less), or Rai stage 3 or 4 disease.
- Disease burden meets criteria for Medium or High Risk for TLS, based on Absolute lymphocyte count >/= 25k/uL or any lymph node 5 cm or greater in diameter. The ALC criteria must be met during the screening period. The imaging criteria may be based on radiologic study within 30 days of Cycle 0, Day 1, if scans were done prior to consent or initiation of the screening period.

6. Has recovered from the toxic effects of prior therapy to their clinical baseline.
7. Women of child-bearing potential (not postmenopausal for at least one year or not surgically incapable of bearing children) must agree to not become pregnant for the duration of the study. Both men and women must agree to use a barrier method of contraception for the duration of the study and until 5 half-lives after the final dose of venetoclax (approximately 1 week), and at least 5 half-lives after the final dose of Rituximab.
8. ECOG performance status of 0-2
9. Adequate hematologic function: Platelet count >/= 30k/uL, hemoglobin > 7 g/dL, AND ANC > 500/uL. (Values may be lower if due to marrow infiltration by CLL).
10. Adequate renal function: Creatinine clearance based on 24 hr collection >/= 40 ml/min; OR Calculated Creatinine clearance (CrCl) ≥ 40 mL/min (based upon the Cockcroft-Gault Equation [CrCl = (140-age) * actual wt (in kg) * (0.85 if female) / (72 * Cr)].
11. Adequate hepatic function per local laboratory reference range as follows:
    a. Aspartate transaminase (AST) and alanine transaminase (ALT) < 3.0X ULN
    b. Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

5.2 Exclusion Criteria

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

1. Subject is known to be positive for HIV. (HIV testing is not required.)

2. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    a. Uncontrolled and/or active systemic infection (viral, bacterial or fungal)
    b. Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. Note: subjects with serologic evidence of prior vaccination to HBV (i.e. hepatitis B surface (HBs) antigen negative-, anti-HBs antibody positive and anti-hepatitis B core (HBc) antibody negative) or positive anti-HBc antibody from intravenous immunoglobulins (IVIG) may participate.

3. Treatment with any of the following within 7 days prior to the first dose of venetoclax:
    a. Steroid therapy for anti-neoplastic intent
    b. moderate or strong cytochrome P450 3A (CYP3A) inhibitors (see Appendix C for examples)
    c. moderate or strong CYP3A inducers (see Appendix C for examples)

4. Prior CLL therapy:
    a. Biologic agent (monoclonal antibody) within 30 days for anti-neoplastic intent.
    b. Chemotherapy (purine analog or alkylating agent) or target small molecule agent within 14 days or 5 half-lives (whichever is shorter), or has not recovered to less than CTC grade 2 clinically significant adverse effect(s)/toxicity(s) of previous therapy.

5. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy
6. Known hypersensitivity to any of the study drugs
7. History of other malignancy that could affect compliance with the protocol or interpretation of results (example: patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are generally eligible. Patients with a malignancy that has been treated, but not with curative intent, will also be excluded, unless the malignancy has been in remission without treatment for 2 years prior to enrollment.)
8. Known active bacterial, viral, fungal, mycobacterial, or other infection (excluding fungal infections of nail beds); or any major episode of infection requiring treatment with IV antibiotics or hospitalization (related to the completion of the course of antibiotics) within 4 weeks before the start of Cycle 0
9. Major surgery (within 4 weeks prior to the start of Cycle 0), other than for diagnosis
10. Women who are pregnant or lactating
11. Uncontrolled diabetes mellitus (related to high dose steroid risk)

12. Myocardial infarction within 6 months of starting study drug or other clinically significant heart disease (NYHA class 3 heart failure, uncontrolled hypertension)

5.3 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 beginning with the Screening visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate case report form.

Subjects should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone replacement therapy, or other maintenance therapy should continue their use.

Steroid therapy for anti-neoplastic intent is prescribed in Cycle 0. Aside from this, however, steroids for anti-neoplastic intent will not be allowed during or within 7 days of study treatment. Inhalational steroids for the treatment of asthma or COPD, topical steroids, replacement corticosteroid therapy for an inherited or acquired deficiency, or brief corticosteroids for rituximab infusion-reaction management or prevention are allowed.

In addition, limited corticosteroid treatment (i.e. for approximately 21 days with rapid taper) is allowed while on study for significant active autoimmune cytopenias, eg. Autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP). IVIG (intravenous immune globulin) is also allowable. Eltrombopag is another treatment option for ITP.

Guidelines regarding excluded and cautionary medications are summarized in the following table.

Table 2: Excluded and Cautionary Medications (See Appendix C for Examples of the Medications)

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration (except the HDMP/R prescribed on study) **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent:** Excluded 30 days prior to first dose and throughout venetoclax administration (except the HDMP/R prescribed on study)
Excluded during ramp-up phase and Cautionary during maintenance/target dose:
Strong and Moderate CYP3A inhibitors Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose. **Strong and Moderate CYP3A inducers** Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and contact PI for guidance.
Cautionary (See Appendix C for examples)
Warfarin **P-gp substrates** **BCRP substrates** **OATP1B1/1B3 substrates** **P-gp inhibitors** **BCRP inhibitors**

Furthermore, administration or consumption of any of the following starting 3 days prior to the first dose of venetoclax is restricted:

a. grapefruit or grapefruit products
b. Seville oranges (including marmalade containing Seville oranges)
c. star fruit

<u>Recommended concomitant therapies:</u>

In addition to the cautionary/excluded medications, there are also recommended concomitant prophylactic therapies:

- Allopurinol (or alternative uric acid reducing drug, dosing per clinician judgement) is recommended starting 3 days prior to first treatment, until the completion of the venetoclax ramp-up (Cycle 1, Day 30)

- Acyclovir (or alternative anti-VZV / HSV drug, dosing per clinician judgement) is recommended for prophylaxis for patients in Arm 1, starting C0D1 to C2D28.

- Septra (or alternative anti-pneumocystis agent, dosing per clinician judgement) is recommended for prophylaxis for patients in Arm 1, starting C0D1 to C2D28.

- Fluconazole (or alternative anti-fungal agent, dosing per clinician judgement) is recommended for prophylaxis for patients in Arm 1, starting C0D1 to C0D21 (stopping 7 days prior to venetoclax).

6.0 Treatment Plan / Study Procedures

Table 3. Schedule of Events

		Cycle 0								
Day (a)	Screen (within 30 day unless noted)	Day 1	day 2	day 3	day 4	day 22				
MD Visit	x	x								
Vitals signs	x	x	x	x	x	x				
CBC diff	x	x	x	x	x	x				
CMP (b)	x	x	x	x	x	x				
Phos		x	x	x	x	x				
Uric acid		x	x	x	x	x				
LDH		x	x	x	x	x				
Correlative Lab Draw		x								
Hep B serologies	x									
Methylprednisolone		1000 mg/m2	1000 mg/m2	1000 mg/m2						
Rituximab		100 mg	375 mg/m2	375 mg/m2	375 mg/m2					
Ct or MRI thorax (c)	x					x (d)				
CT or MRI abdomen/pelvis (c)	x					x (d)				
NOTES										
	(a) Protocol allowed date windows for Cycle 0 are - 3 days or + 3 days.(only 1 cycle permitted if subject enrolled after protocol v5 approval).									
	(b) CMP includes the following: Na, K, Chloride, Bicarbonate, BUN, creatinine, glucose; calcium; total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase									
	(c) MRI is allowed if CT if medically contraindicated.									
	(d) Areas that did not have enlarged lymph nodes greater than 1.5 cm in long-axis do not require re-imaging									

	Cycle 1 (35 days)										
Day (a)	1	2	8	9	15	16 (d)	22	23 (d)	29	30 (d)	
MD Visit	x										
Vital signs	x										
CBC diff	x	x	x	x	x	x	x	x	x	x	
CMP (b, c)	x (pre and 6-8 hr)	x (c)	x (pre and 6-8 hr)	x (c)	x	x	x	x	x	x	
Phos (b)	x (pre and 6-8 hr)	x (c)	x (pre and 6-8 hr)	x (c)	x	x	x	x	x	x	
Uric acid (b)	x (pre and 6-8 hr)	x (c)	x (pre and 6-8 hr)	x (c)	x	x (c)	x	x (c)	x	x (c)	
LDH (b)	x (pre and 6-8 hr)	x (c)	x (pre and 6-8 hr)	x (c)	x	x (c)	x	x (c)	x	x (c)	
Correlative Lab Draw	x										
Inpatient Admission for TLS monitoring in indicated (d)	x	x	x	x							
Venetoclax (IDS) (e)	20 mg x 1	20 mg x 6 day supply	50 mg	50 mg x 6 day supply	100 mg x 7 day supply		200 mg x 7 day supply		400 mg x 1 wk supply		

NOTES

(a) Protocol allowed date windows for Cycle 1 are - 0 days or + 14 days. In other words, patients should take 7 days of each venetoclax dose level prior to dose escalation.

(b) venetoclax dosing and lab monitoring is per label. Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

(c) CMP includes the following: Na, K, Chloride, Bicarbonate, BUN, creatinine, glucose; calcium; total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase

(d) For patients with high tumor burden OR median tumor burden AND creatinine clearance <80ml/min, TLS monitoring will be done according to US Prescribing Information, i.e. In hospital: For first dose of 20mg and 50 mg: Predose,4, 8, 12 and 24 hours; Outpatient: For subsequent ramp-up doses: Predose,6 to 8 hours, 24 hours. For patients with low tumor burden or medium tumor burden wuth creatinine clearance 80ml/min or greater, assessments will be done outpatient, and the day 16, 23, and 30 visits are not required.

(e) Venetoclax is dispensed AFTER CBC diff, CMP, phos, uric acid, and LDH results are reviewed by PI, subI, or study team.

Cycle	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Day (a)	1	1	1	1	1
MD Visit	x	x	x	x	x
Vitals signs	x	x	x	x	x
CBC diff	x	x	x	x	x
CMP (b)	x	x	x	x	x
Phos	x	x	x	x	x
Uric acid	x	x	x	x	x
LDH					
Correlative Lab Draw					
Rituximab	500 mg/m2	500 mg/m2	500 mg/m2	500 mg/m2	500 mg/m2
Venetoclax (IDS)	400 mg x 1 month supply	400 mg x 1 month supply	400 mg x 1 month supply	400 mg x 1 month supply	400 mg x 1 month supply
	NOTES				
	(a) Protocol allowed date windows for Cycles 2-22 are - 14 days or + 14 days.				
	(b) CMP includes the following: Na, K, Chloride, Bicarbonate, BUN, creatinine, glucose; calcium; total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase				

Cycle	Cycle 7	Cycle 10	Cycle 13	Cyle 16	Cycle 19	Cycle 22	End of Study
Day (a)	1	1	1	1	1	1	C24D28 +/- 14 days
MD Visit	x	x	x	x	x	x	x
Vitals signs	x	x	x	x	x	x	x
CBC diff	x	x	x	x	x	x	x
CMP (b)	x	x	x	x	x	x	x
Phos	x	x	x	x	x	x	
Uric acid	x	x	x	x	x	x	
LDH							
Correlative Lab Draw							x
Venetoclax (IDS)	400 mg x 3 month supply	400 mg x 3 month supply	400 mg x 3 month supply	400 mg x 3 month supply	400 mg x 3 month supply	400 mg x 3 month supply	
Ct or MRI thorax (c)		x (d)					x (d)
CT or MRI abdomen/pelvis (c)		x (d)					x (d)
Marrow biopsy and aspirate procedure		x (e)					x (e)
Marrow flow cytometry		x (e)					x (e)
Hematopath review		x (e)					x (e)
	NOTES						
	(a) Protocol allowed date windows for Cycles 2-24 are - 14 days or + 14 days.						
	(b) CMP includes the following: Na, K, Chloride, Bicarbonate, BUN, creatinine, glucose; calcium; total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase						
	(c) MRI is allowed if CT if medically contraindicated.						
	(d) Areas that did not have enlarged lymph nodes greater than 1.5 cm in long-axis do not require re-imaging						
	(e) Marrow biopsy will be done only if exam and blood work is clinically consistent with a complete remission.						

6.1 Screening Procedures

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

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. Informed consent is also required for pharmacodynamic sample collections.

Medical and Oncologic History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical conditions.
- Detailed oncologic history, including:
    - Date of CLL diagnosis
    - Cytogenetics (if known from prior testing)
    - IgVH mutation status (if known from prior testing)
    - Somatic mutations in CLL cells (if known from prior testing)

    - Treatments administered (including approximate dates, response to treatment if known, and reason for treatment discontinuation).
- Detailed and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken.
- Prior to the first treatment visit (C0D1), any changes observed from the Screening assessments (prior to dosing) will be recorded in the subject's medical history.

Physical examination

Physical examination performed should include evaluate of presence and degree of enlarged lymph nodes in two dimensions in cervical, supraclavicular, axillary, and inguinal regions; hepatomegaly; and splenomegaly. Additional physical exam of other organ systems are per clinical standard of care.

If during physical examination, signs or symptoms suggestive of Richter's Syndrome are observed further assessment (i.e, node biopsy or PET scan) should be considered if clinically indicated to assess for or confirm Richters.

Vitals signs

Body temperature, weight, blood pressure, and pulse will be measured.

ECOG performance status

Subject's performance status will be assessed based on the ECOG system. See Appendix A for description/definition.

Clinical Laboratory Tests:

Local laboratories will be utilized to process and provide results for the clinical laboratory tests. Investigator should review, initial, and date the laboratory results. The following labs are collected during the screening period:

- CBC with differential (automated or manual)

- Comprehensive Metabolic Panel

- Hepatitis B and C serologies. This a standard of care assessment prior to administration of any anti-CD20 therapy and not done for the sole purpose of research). HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc, HCV ab or RNA. If during screening a subject present with a positive Hepatitis B core antibody, Hepatitis B Viral DNA PCR test should be performed to rule out an active infection. If there are known results of hepatitis serologies within 6 months without at risk exposure, they do not need to be repeated.

- If female of child-bearing potential: serum pregnancy test within 14 days of initiation of therapy on trial.

Computed Tomography (CT) Scans (or Magnetic Resonance Imaging [MRI])

A CT scan must be performed within 30 days prior to study drug administration for all subjects. A CT scans should include chest, abdomen, and pelvis sequences. Contrast is preferred though can be omitted if contraindication. A contrast-enhanced MRI of chest, abdomen, and pelvis may be used for subjects in whom a CT is medically contraindicated (example: contrast allergy). Whichever method is used at Screening is preferred to be used consistently through the duration of the study for that subject.

Justification: The CT or MRI scans at baseline is a standard of care assessment prior to initiation of venetoclax in order assess tumor burden and risk for TLS, as this will guide optimal management to mitigate the risk of TLS. This test is necessary to determine if some patients may safely start venetoclax with outpatient monitoring, infusion center monitoring, or inpatient monitoring. Although this is also part of the primary endpoint assessment, it is also a needed and standard test for patient safety and in accordance with the prescribing information when venetoclax is prescribed even outside of clinical trials.

Initiation and prescription of prophylactic medication

After confirmation of eligibility, patients are prescribed allopurinol 300 mg PO daily (or dose adjusted per clinical indication such as renal failure, or alternate medication per clinician judgement), and instructed to start 3 days prior to treatment initiation.

6.2 Cycle 0: HDMP + Rituximab

Cycle 0 is 28 days in duration.

On Day 1, the following are done:

- Medical history, physical exam, and vital signs
- Laboratory examinations: CBC w/ differential, comprehensive metabolic panel, phosphorous, uric acid, and LDH. (Potassium, Phosphorous, Calcium, uric acid, and creatinine are necessary and clinically indicated to assess for possible tumor lysis syndrome, and not simply as markers of disease burden).
- Collection of correlative pharmacodynamic sample, prior to treatment (4, approximately 8-10 mL anticoagulated tubes – ACD or heparin)
- Methylprednisolone 1000 mg/m2 IV
- Rituximab 100 mg IV

On Day 2 and 3, the following are done:

- Vital signs
- Laboratory examinations: CBC w/ differential, comprehensive metabolic panel, phosphorous, uric acid, and LDH. (Potassium, Phosphorous, Calcium, uric acid, and

creatinine are necessary and clinically indicated to assess for possible tumor lysis syndrome, and not simply as markers of disease burden).

- Methylprednisolone 1000 mg/m2 IV
- Rituximab 375 mg/m2 IV

On Day 4, the following are done:

- Vital signs
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Rituximab 375 mg/m2 IV

Between Day 15 and Day 28 of Cycle 0, disease burden is reassessed to determine risk of TLS prior to Venetoclax initiation, including:

- Laboratory examinations: CBC w/ differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- CT or MRI of thorax, abdomen, and pelvis. IF medically necessary to reassess TLS risk. Areas that did not have enlarged lymph nodes 1.5 cm or greater in long-axis diameter may be skipped for this radiographic reassessment. (Justification: This is again a necessary procedure to determine Tumor Burden and to optimally manage and mitigate TLS risk for patients prior to starting Venetoclax).

6.3 Cycle 1: Venetoclax Ramp-up

Cycle 1 is 35 days in duration and consists of venetoclax dose-ramp up, following standard dosing and TLS risk mitigation strategies as per Venetoclax prescribing information.

<u>On Day 1 of Cycle 1, the following are completed:</u>

- History and physical examination including vital signs.
- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH Collection of correlative research sample
- Dispense and take initial dose of Venetoclax 20 mg PO.
- Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

On Day 2 of Cycle 1, the following are completed:

- Laboratory examinations: hematology (CBC w/differential), comprehensive metabolic panel, phosphorous, uric acid, LDH.
- Dispensing Venetoclax 20 mg 6 day supply
- 2nd dose of venetoclax 20 mg PO after labs are resulted and reviewed by treating physician or investigator.
- Patients continue venetoclax 20 mg PO daily C1D2 – C1D7.

On Day 8 of Cycle 1, the following are completed:

- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Dispense and take initial dose of Venetoclax 50 mg PO dose level.
- Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

On Day 9 of Cycle 1, the following are completed:

- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Dispensing Venetoclax 50 mg 6 day supply
- 2nd dose of venetoclax 50 mg PO after labs are resulted and reviewed by treating physician or investigator.
- Patients continue venetoclax 50 mg PO daily C1D9 – C1D14.

On Day 15 of Cycle 1, the following are completed:

- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Dispense and take initial dose of Venetoclax 100 mg PO dose level. (7 day supply).
- Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

(Only required if High Tumor Burden prior to venetoclax initiation): On Day 16 of Cycle 1, the following are completed:

- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- 2nd dose of venetoclax 100 mg PO after labs are resulted and reviewed by treating physician or investigator.
- Patients continue venetoclax 100 mg PO daily C1D16 – C1D21.

On Day 22 of Cycle 1, the following are completed:

- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Dispensing and initial dose of Venetoclax 200 mg PO dose level. (7 day supply).
- Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

(Only required is High Tumor Burden prior to venetoclax initiation): On Day 23 of Cycle 1, the following are completed:

- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- 2nd dose of venetoclax 200 mg PO after labs are resulted and reviewed by treating physician or investigator.
- Patients continue venetoclax 200 mg PO daily C1D23 – C1D28.

On Day 29 of Cycle 1, the following are completed:

- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid, LDH
- Dispensing and initial dose of Venetoclax 400 mg PO dose level (7 day supply).
- Tumor lysis syndrome monitoring as per Appendix D and E, which includes additional chemistry monitoring, potential IV fluid administration, and potential inpatient hospitalization if clinically indicated and in accordance with venetoclax standard of care.

(Only required is High Tumor Burden prior to venetoclax initiation): On Day 30 of Cycle 1, the following are completed:

- Laboratory examinations: CBC w/differential, comprehensive metabolic panel,

phosphorous, uric acid, LDH

- 2nd dose of venetoclax 400 mg PO after labs are resulted and reviewed by treating physician or investigator.
- Patients continue venetoclax 400 mg PO daily C1D31 onward.

6.4 Cycles 2 to 6: Venetoclax + Rituximab

All subsequent cycles are 28 days each in duration.

On Day 1 of Cycle 2-6, the following are completed:

- History and physical examination including vital signs.
- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid
- Dispensing of Venetoclax 400 mg PO dose (or highest tolerated dose), 30 day supply.
- Rituximab 500 mg/m2 IV

6.5 Cycles 7-24: Venetoclax

Cycles 7-24 are 28 days each in duration

Patients are scheduled to be seen in clinic every 3 months

On Day 1 of Cycles 7, 10, 13, 16, 19, and 22, the following are completed:

- History and physical examination including vital signs.
- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel, phosphorous, uric acid
- Dispensing of Venetoclax 400 mg PO dose (or highest tolerated dose), 90 day supply.

In addition, on Day 1 of Cycle 10

- CT or MRI of thorax, abdomen, and pelvis. Areas that did not have enlarged lymph nodes (greater than 1.5 cm in long-axis diameter on the prior scan) or spleen may be skipped for this radiographic reassessment.

- Marrow biopsy and aspirate if clinical examination is consistent with a complete remission (ie, absolute lymphocyte count less than 4k/uL) and if clinically indicated to determine subsequent therapy (eg: stopping therapy if undetectable minimal residual disease).

6.6 End of Study Assessment

Within 2 weeks before or after Cycle 24, Day 28, the following are completed:

- History and physical examination including vital signs.
- Current medications will be recorded in the subject's medical record.
- Laboratory examinations: CBC w/differential, comprehensive metabolic panel.
- Collection of correlative sample.
- CT or MRI of thorax, abdomen, and pelvis.
- Marrow biopsy and aspirate if clinical examination is consistent with a complete remission (ie, absolute lymphocyte count less than 4k/uL) and if clinically indicated to determine subsequent therapy (e.g.: stopping therapy if undetectable minimal residual disease).

6.7 Long-term follow-up

No long-term follow-up visits are scheduled or required per study.

With patient consent, date of progression or next CLL therapy will be recorded based on chart review if data are available, or phone call no more than every 6 months.

6.8 Subject Withdrawal or Treatment Discontinuation:

Patients who meet or develop the following criteria should be discontinued from the study

- Active HBV infection or hepatitis. Patients who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

- Severe or life-threatening anaphylaxis or hypersensitivity reaction to rituximab. Patients that discontinue rituximab for that reason can continue to receive HDMP and venetoclax if clinically indicated.

- Patients who meet the following criteria should discontinue HDMP: Grade 4 psychosis; Active HBV infection or hepatitis as above. HDMP doses can be delayed for acute infection or as clinically indicated.

- Inability of patient to comply with study requirements

- Determination by the investigator that it is no longer safe for the patient to continue therapy

With the exception of following HBV, patients who withdraw from all study therapy do not have required follow-up visits and can enter long-term follow-up (6.7). With patient consent, date of progression or next CLL therapy will be recorded.

7.0 Study Medications

7.1 Methylprednisolone Sodium Succinate

7.1.1 Formulation Storage and Preparation

Each vial of methylprednisolone contains 1g of a white powder material. Inactive ingredients include: Benzyl Alcohol, Sodium Hydroxide, Sodium Phosphate, Dibasic Sodium Phosphate and Monobasic Sodium Phosphate. The product is reconstituted in 0.9% saline solution that should be protected from light. Once the product is reconstituted it may be stored at controlled room temperature (68 to 77 degrees F) for use within 48hours.

Methylprednisolone will be prescribed as a standard treatment. Supply: Commercial Supply

7.1.2 Dosage and Administration

Only methylprednisolone sodium succinate should be used for intravenous administration.

HDMP will be administered at 1gr/m2 on Days 1-3 of cycles 0 (with optional repeat for subset of patients who do not greater than low-risk for TLS after 1 cycle). HDMP will be given over 90 minutes and subsequent to the completed infusion, the infusion of Rituximab will be initiated. It will be diluted on 0.9% normal saline and administered directly into a vein over 90 minutes.

7.1.3 Adverse Reactions

Adverse Reactions Significant (Frequency not defined).

Cardiovascular: Arrhythmias, bradycardia, cardiac arrest, cardiomegaly, circulatory collapse, congestive heart failure, edema, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture (post MI), syncope, tachycardia, thromboembolism, vasculitis

Central nervous system: Delirium, depression, emotional instability, euphoria, hallucinations, headache, intracranial pressure increased, insomnia, malaise, mood swings, nervousness, neuritis, personality changes, psychic disorders, pseudotumor cerebri (usually following discontinuation), seizure, vertigo

Dermatologic: Acne, allergic dermatitis, alopecia, dry scaly skin, ecchymoses, edema, erythema, hirsutism, hyper-/hypopigmentation, hypertrichosis, impaired wound healing, petechiae, rash, skin atrophy, sterile abscess, skin test reaction impaired, striae, urticarial

Endocrine & metabolic: Adrenal suppression, amenorrhea, carbohydrate intolerance increased, Cushing's syndrome, diabetes mellitus, fluid retention, glucose intolerance, growth suppression (children), hyperglycemia, hyperlipidemia, hypokalemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium and water retention.

Gastrointestinal: Abdominal distention, appetite increased, bowel/bladder dysfunction (after intrathecal administration), gastrointestinal hemorrhage, gastrointestinal perforation, nausea,

pancreatitis, peptic ulcer, perforation of the small and large intestine, ulcerative esophagitis, vomiting, weight gain.

Hematologic: Leukocytosis (transient).

Hepatic: Hepatomegaly, transaminases increased.

Local: Thrombophlebitis.

Neuromuscular & skeletal: Arthralgia, arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, muscle weakness, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness.

Ocular: Cataracts, exophthalmoses, glaucoma, intraocular pressure increased.

Renal: Glycosuria.

Respiratory: Pulmonary edema.

Miscellaneous: Abnormal fat disposition, anaphylactoid reaction, anaphylaxis, angioedema, avascular necrosis, diaphoresis, hiccups, hypersensitivity reactions, infections, secondary malignancy, venous thrombosis.

7.1.4 Management of HDMP Induced Hyperglycemia

Subjects that received HDMP frequently present with hyperglycemia. This will be managed following institutional policies including consultation with Endocrinology or Diabetes clinic. A summary of management recommendations is the following:

Subjects will have blood glucose (BG) measured on Days 1-3 of each Cycle during the days of HDMP administration. BG will be measured using a finger stick glucometer after the infusion of HDMP is completed. If a subject has a BG over 201mg/dl, glycemic control will be achieved by giving regular insulin subcutaneously according to the sliding scale below:

BG - 201-250, 4U regular insulin SQ

BG - 251-300, 6U regular insulin SQ

BG - 301-350, 8U regular insulin SQ

BG - 351-400, 10U regular insulin SQ

Those subjects with BG >400 will be managed accordingly to institutional policies and at discretion of the treating physician. Management options will include hypoglycemic agents and insulin. Subjects with BG > 400 will have a fasting BG drawn on Day 3 of Cycle 0 when HDMP is

administered. If this fasting BG is > 200, the subject may be evaluated by an endocrinologist for recommendations regarding their blood sugar management. The same criteria will be applied to any subject with a fasting BG > 200 prior to HDMP administration; this practice will cover those subjects at risk for developing steroid induced diabetes. Long lasting insulin will not be used, nor will the subject be monitored with finger sticks BG during the rest of the treatment cycle unless recommended by Endocrinology-Diabetes clinic.

7.1.5 Dose Adjustment

There are no recommended or planned methylprednisolone dose adjustments. Dosing can be held or stopped for toxicity, as above.

7.2 Rituximab (RITUXAN) – Background information for Rituxan follow in sections 7.2.1 to 7.2.4. However, substitution of rituximab with other equivalent preparations is allowed, including the following: biosimilars of rituximab (including Ruxience or other FDA-approved rituximab product).

7.2.1 Formulation, Storage, and Preparation

RITUXAN vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2-8C (36F-46F). RITUXAN vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan is prescribed as a standard treatment, Supply: Commercial Supply

7.2.2 Dosage and Administration

Rituximab dosage: Cycle 0 (with HDMP): 100 mg day 1, 375 mg/m2 days 2-4. Cycles 2-6 (with Venetoclax): 500 mg/m2 day 1.

Rituximab is administered as per local clinical standard practices. Specific recommendations are below:

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur. Pre-medication, consisting of acetaminophen and diphenhydramine, may be administered before each infusion of rituximab. Pre-medication may attenuate infusion-related events. Since transient hypotension may occur during rituximab

infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

Rituximab will be administered as a split dose for the initial rituximab infusion. Routine premedications include diphenhydramine 25-50 mg orally or IV (or other antihistamine), and acetaminophen orally all administered approximately 30 – 60 minutes before the initiation of rituximab infusion. Antiemetics are not routinely administered with rituximab.

Administration of rituximab will be performed in a setting with access to emergency equipment and personnel who are trained to monitor for and respond to medical emergencies. Patients will be monitored during each infusion of study treatment for any adverse effects. Rituximab infusion should be interrupted for severe reactions, and resumed when symptoms have completely resolved. Decrease infusion rate or interrupt infusion if infusion-related events occur. Employ a slower infusion rate (i.e., at least 50% reduction in rate) when therapy is resumed following complete resolution of symptoms.

7.2.3 Adverse Reactions and Precautions

Infusion Reactions

RITUXAN can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. RITUXAN-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA and PV patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue RITUXAN. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3)

Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with RITUXAN. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of RITUXAN exposure. Discontinue RITUXAN in patients who experience a severe mucocutaneous reaction. The safety of re- administration of RITUXAN to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including RITUXAN. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

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

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN therapy. HBV reactivation has been reported up to 24 months following completion of RITUXAN therapy.

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

Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in RITUXAN-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of RITUXAN.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Discontinue RITUXAN and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12-24 hours after the first infusion of RITUXAN in patients with NHL. A high number of circulating malignant cells (>25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of RITUXAN-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN for serious infections and institute appropriate anti-infective therapy. RITUXAN is not recommended for use in patients with severe, active infections.

Cardiovascular Adverse Reactions

Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving RITUXAN. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of RITUXAN for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity

Severe, including fatal, renal toxicity can occur after RITUXAN administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving RITUXAN in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

Immunization

The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of RITUXAN.

The effect of RITUXAN on immune responses was assessed in a randomized, controlled study in patients with RA treated with RITUXAN and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with RITUXAN plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the RITUXAN plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with RITUXAN plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on RITUXAN plus MTX vs. 70% of patients on MTX alone).

Most patients in the RITUXAN-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

Embryo-Fetal Toxicity

Based on human data, RITUXAN can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN and for 12 months following the last dose of RITUXAN.

7.2.4 Dose Adjustment

There are no recommendations for or planned Rituximab dose adjustments. Doses can be held or skipped for toxicity, as summarized above.

7.3 Venetoclax

7.3.1 Formulation, Storage

It is a light yellow to dark yellow solid with the empirical formula C45H50ClN7O7S and a molecular weight of 868.44. Venetoclax has very low aqueous solubility.

Venetoclax must be stored at 15 to 25 degrees C (59-77 degrees F). Venetoclax is supplied from Research Supply, provided by Abbvie.

7.3.2 Dosage and Administration

Administration Guidelines from package insert:

Advise patients to take VENCLEXTA exactly as prescribed and not to change their dose or to stop taking VENCLEXTA unless they are told to do so by their doctor. Advise patients to take VENCLEXTA orally once daily, at approximately the same time each day, according to their doctor's instructions and that the tablets should be swallowed whole with a meal and water without being chewed, crushed, or broken.

Advise patients to keep VENCLEXTA in the original packaging during the first 4 weeks of treatment, and not to transfer the tablets to a different container.

Advise patients that if a dose of VENCLEXTA is missed by less than 8 hours, to take the missed dose right away and take the next dose as usual. If a dose of VENCLEXTA is missed by more than 8 hours, advise patients to wait and take the next dose at the usual time.

Advise patients not to take any additional dose that day if they vomit after taking VENCLEXTA, and to take the next dose at the usual time the following day.

7.3.3 Adverse Reactions and Precautions

The safety of single agent VENCLEXTA at the 400 mg recommended daily dose following a dose ramp-up schedule is based on pooled data of 240 patients with previously treated CLL from two phase 2 trials and one phase 1 trial. In the pooled dataset, the median age was 66 years (range: 29 to 85 years), 95% were white, and 69% were male. The median number of prior therapies was 3 (range: 1 to 12). The median duration of treatment with VENCLEXTA at the time of data analysis was approximately 10.3 months (range: 0 to 34.1 months). Approximately 46% of patients received VENCLEXTA for more than 48 weeks.

The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue.

Serious adverse reactions were reported in 43.8% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and TLS.

In combination with rituximab, serious adverse reactions were reported in 46% of patients, with the most frequent (≥5%) being pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), cough (22%), and nausea (21%).

Discontinuations due to adverse reactions occurred in 8.3% of patients. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and AIHA.

Dosage adjustments due to adverse reactions occurred in 9.6% of patients. The most frequent adverse reactions leading to dose adjustments were neutropenia, febrile neutropenia, and thrombocytopenia.

Specific warnings and precautions:

Tumor Lysis Syndrome

Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL patients with high tumor burden when treated with VENCLEXTA.

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases.

Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors and P-gp inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and may require VENCLEXTA dose adjustment. Strong CYP3A inhibitors are contraindicated during dose ramp-up. (see appendix C)

For patients who take a strong or moderate CYP3A Inhibitor or P-gp inhibitor during steady daily dosage (after ramp-up phase), consider alternate medications or adjust VENCLEXTA dosage (as shown in the following table) and closely monitor for signs of VENCLEXTA toxicities.

MANAGEMENT OF POTENTIAL VENCLEXTA INTERACTIONS WITH CYP3A AND P-GP INHIBITORS

Coadministered drug	Initiation and ramp-up phase	Steady daily dose[§] (after ramp-up phase)
Posaconazole	Contraindicated	Reduce VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitor	Reduce the VENCLEXTA dose by at least 50%	
P-gp inhibitor		

- Concomitant use of VENCLEXTA with strong or moderate CYP3A inhibitors or P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and requires dose adjustment due to increases in VENCLEXTA exposure.
- Resume the VENCLEXTA dose that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

Neutropenia

Grade 3 or 4 neutropenia occurred in 41% (98/240) of patients treated with VENCLEXTA. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for

severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, VENCLEXTA may cause embryo- fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using VENCLEXTA. Advise females of reproductive potential to avoid pregnancy during treatment. If VENCLEXTA is used during pregnancy or if the patient becomes pregnant while taking VENCLEXTA, the patient should be apprised of the potential hazard to the fetus.

7.3.4 Dose Adjustment and Management of Toxicity

There is no specific antidote for venetoclax. For subjects who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt venetoclax and monitor carefully for signs and symptoms of TLS along with other toxicities. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

Dosing interruption and/or dose reduction may be required. See Table 3 for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (eg, all or some levels of the dose ramp-up schedule).

Table 4. Venetoclax Recommended Dose Modification for Toxicities:

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS (see Howard Criteria in Appendix E)	Any	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 5)
		For any events of clinical TLS[b], resume at a reduced dose following resolution (see Table 5).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
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 therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 5 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.

Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.

a. Adverse reactions were graded using NCI CTCAE version 4.03.

b. Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

Management of Neutropenia

Based on clinical observations with the 1st generation Bcl-2 inhibitor, navitoclax and in vitro colony-forming assays to assess Bcl-2-selective inhibitor effects on granulocyte precursors, it is possible that subjects treated with venetoclax might experience neutropenia. Subjects with a history of neutropenia, who have received multiple prior therapies and/or have significant bone marrow involvement, may be at particular high risk. If determined to be clinically indicated by the treating physician in compliance with ASCO guidelines, G-CSF may be administered during dosing of venetoclax. The use of G-CSF support is strongly recommended for subjects with Grade 4 neutropenia (ANC < 500/μL). If the subject presents with febrile neutropenia or Grade 4 neutropenia for more than one week despite the use of optimal G-CSF support, venetoclax dosing should be interrupted until ANC recovery to > 500/μL. Venetoclax may then be re-initiated at a

lower dose as defined in the following table. Subjects not responding to G-CSF despite venetoclax interruption should undergo further evaluation to determine the etiology of the neutropenia.

Table 5. Dose Modification for Toxicity during Venetoclax Treatment.

Venetoclax Dose	Reduced Dose
400 mg	300 mg
300 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	Re-challenge at 20 mg[a]

a. Subjects who do not tolerate 20 mg will discontinue venetoclax, but may remain on study to assess for progression.

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. Most anti-fungals are excluded and other commonly used agents may be cautionary or prohibited due to drug- drug interactions.

Management of Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Venetoclax treatment should be withheld for any Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant Grade ≥3 non-hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

Management of Decrease in Spermatogenesis

Based on findings in a preclinical study, there is a potential for decreased spermatogenesis. Male subjects should consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

8.0 Evaluation of Response

8.1 Assessment of Tumor Burden

Earlier clinical trials with venetoclax identified risk factors for tumor lysis syndrome, in particular measurements of tumor burden, including maximum lymph node diameter and absolute lymphocyte count. Subjects have been classified in 3 risk categories based on risk for developing medically concerning TLS with venetoclax administration. The tumor burden assessed by the nodal disease and absolute lymphocyte count has been used to define each category as below:

Tumor Burden Category	Criteria
Low	All measurable lymph nodes with the largest diameter < 5 cm by radiologic assessment AND ALC < 25k/uL
Medium	Any measurable lymph node with the largest diameter >/= 5 cm but < 10 cm by radiographic assessment OR ALC >/= 25k/uL
High	Any measurable lymph node with the largest diameter >/= 10 cm by radiologic assessment OR ALC >/= 25k/uL AND any measurable lymph node with the largest diameter >/= 5 cm

8.2 International Working Group CLL (iwCLL) Clinical Response Assessment

Criteria for response will utilize the 2008 IWCLL Guidelines for response, which includes clinical, hematological, and bone marrow feature:

Complete response: Requires all of the following for a period of at least two months from completion of therapy:

- Absence of significant lymphadenopathy (e.g. >1.5cm in diameter) on physical exam;
- No hepatomegaly or splenomegaly on physical exam;
- Absence of constitutional symptoms;
- Blood counts within the following values: lymphocytes < 4,000/uL, polymorphonuclear leukocytes >1500/μL, platelets >100,000/μL, hemoglobin >11.0 g/dL (untransfused); absences of clonal lymphocytes;
- Bone marrow aspirate and biopsy must be normocellular for age with <30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- The marrow should be analyzed by flow cytometry and/or immunohistochemistry to demonstrate that the marrow is free of clonal B- CLL cells.
- A CT scan or MRI documenting absence of significant lymphadenopathy should be performed if previously abnormal.

- Patients who fulfill the criteria for CR after induction with the exception of a persistent cytopenia that is believed to be treatment related will be considered CR with incomplete bone marrow recovery (CRi). Additionally, patients who fulfill the criteria of CR with exception of having bone marrow lymphoid nodules will be considered a nodular PR.

Partial response: Requires at least 2 of the following criteria from group A, and at least one of the criteria from group B, and for a period of at least 2 months:

Group A:

- ≥50% decrease in peripheral absolute lymphocyte count from pretreatment value, or less than 4,000/uL
- ≥50% reduction in lymphadenopathy by examination or scan, or less than 1.5cm in size.
- ≥50% reduction in splenomegaly (cm below costal margin) by examination or scan
- ≥50% reduction hepatomegaly (total liver span) by examination or scan
- 50% reduction in marrow infiltrate or B-lymphoid nodules

Group B:

- Polymorphonuclear leukocytes ≥1,500/μL or 50% improvement from pre-treatment value;
- Platelets >100,000/μL or 50% improvement from pre-treatment value;
- Hemoglobin >11.0 g/dl (un-transfused) or 50% improvement from pre-treatment value.

Progressive Disease: Characterized by any one of the following events:

- ≥50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥2 cm); appearance of new palpable lymph nodes.
- ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (i.e., Richter’s syndrome or prolymphocytic leukemia with ≥56% prolymphocytes).
- During therapy, patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin >2 gm/dL, decrease >50% in platelet or granulocyte

count will not be rated as progressive disease because these may occur as both a consequence of therapy. A bone marrow biopsy in such settings is strongly encouraged.

- After treatment, The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 × 109/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Stable Disease: Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

8.3 Minimal Residual Disease Assessment

Primary clinical efficacy analysis will be assessment of marrow for detectable CLL after 24 cycles (or sooner if treatment is discontinued early) by flow cytometry and immunohistochemistry per standard practice by local hematopathologist. A threshold of 0.01% will define undetectable versus detectable minimal residual disease (MRD).

8.4 Correlative Studies

Limited correlative studies will be performed in the Kipps laboratory to correlate with clinical responses. Samples will be taken at baseline/screening and during treatment and after treatment. However, not all assays will be performed for all time points for all patients, based on sample availability and leukemic cell number. Specimens will be banked in the CLL research consortium tissue repository (see below).

Isolation of leukemic cells by Ficoll-hypaque separation and assessment, which may include:
- ZAP-70 and Immunoglobulin heavy chain variable region (IgVH) mutation in CLL cells
- Genomic assessment including Next generation sequencing or gene expression analysis

Sampling Schedule:
Blood sample for correlative studies will be collected at the following time points:
- Day 1, cycle 0, pre-dose
- Day 1, cycles 1, pre-dose
- End of treatment visit

Sample Collection and Handling Instructions
Blood samples (approximately 40 ml on screening, 10 ml on other time points) will be collected in anti-coagulated (CPT) tubes for pharmacokinetic evaluation. The exact time that the sample is drawn along with the exact time that treatments are administered should be recorded.

Sample Processing
Samples will be processed in the translational lab of Dr. Thomas Kipps, with separation of plasma (for blood and apheresis products), followed by isolation of mononuclear cells by Ficoll differential centrifugation, respectively.

Sample Labeling

Each tube must be labeled with the patient's study number and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form, which must accompany the sample(s).

8.5 Specimen Banking

Patient samples collected for this study will be retained at the UCSD School of Medicine (Kipps Laboratory). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. Samples will be labeled with the subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

9.0 Statistical Considerations

9.1 General Considerations

This is a pilot/feasibility clinical trial, with the primary feasibility endpoint being debulking of tumor burden to meet criteria for low Tumor Burden upon the completion of cycle 0

.The primary efficacy endpoint is the percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" criteria to "Low tumor burden" criteria for disease burden following a maximum of 2 cycles of HDMP + Rituximab (called cycle 0 in the protocol schedule of events).

Tumor burden will be assessed prior to initiation of therapy, and after each cycle of HDMP + Rituximab (maximum 2 cycles). See section 8.1 for the definition of these categories of tumor burden.

The secondary endpoints are as follows:

- Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" to meet "Low tumor burden" criteria for disease burden following 1 cycle of HDMP + Rituximab.
- Percentage of patients that have a decrease in tumor burden from levels of disease that meet "Medium/High-tumor burden" to meet "Low tumor burden" criteria for disease burden following 2 cycles of HDMP + Rituximab.
- Rate of laboratory TLS (from start of treatment until completion of venetoclax ramp-up). See Appendix B for definition and grading of TLS.
- Rate of clinical TLS (from start of treatment until completion of venetoclax ramp-up)

- Adverse events by CTCAE4 definitions and iwCLL definition for hematologic AEs (see section 10.0 for iwCLL definition of hematologic AE).
- Overall Response rate (ORR), Partial Response (PR) rate, and Complete response (CR) rate per iwCLL criteria after 9 months of venetoclax and at completion of treatment. See section 8.2 for iwCLL criteria for definitions of each level of response. ORR includes all patients who have either a PR or CR.
- Undetectable minimal residual disease (MRD) rate based on bone marrow biopsy after 9 months of venetoclax, and at completion of treatment. Undetectable MRD is defined as less than 0.01% CLL cells.

9.2 Sample size justification

Seventeen patients are enrolled to evaluate the primary endpoint. A success rate of 60% of patients adequately debulking (defined as having low Tumor Burden at the end of cycle 0) will be considered compelling, establishing the feasibility of this approach, and support further studies. A success rate of 30% would be not compelling for further studies. With 17 patients, the study is adequately powered to evaluate this. A Simon's two-stage minimax design is utilized, with stopping for futility if an insufficient number of patients are debulked by HDMP/Rituximab. This design will have 80% power to reject the null hypothesis at 4% significance level and conclude that the true debulking rate at cycle 0 is above 30%, if the observed rate is ≥60%. Note that if patients are still meeting med/high tumor burden, they may repeat cycle 0 once more.

The null hypothesis that the true debulking rate is 30% at Cycle 0 will be tested against a one-side alternative. In the first stage, 10 patients will be accrued. The study enrollment will be put on hold for interim analysis until the response results for Stage 1 patients are known. If there are 2 or fewer responses (patients achieving low Tumor Burden) in these 10 patients, the study will be stopped. Otherwise, 7 additional patients will be accrual for a total of 20. The null hypothesis will be rejected if 9 or more responses are observed in 17 patients.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 38.3%. The sample size calculation was done using PASS version 14.0.3 (released September 22, 2015). Sample size calculation did not incorporate the safety endpoint. Statistics for safety outcomes will be presented descriptively.

Accrual and study duration

We expect to accrue 1-2 patients every month. All patients will be accrued within 12-24 months. Patients will be followed for 24 months. The total duration of this study will be about 36 months.

9.3 Analysis Populations

The Treated population will include all treated subjects who receive at least 1 dose of methylprednisone or rituximab.

9.4 Demographics and Baseline Characteristics

Subject baseline characteristics will be listed and summarized for the Treated population, including subject age, gender, prior therapy, IgVH mutational status, and molecular profiling including cytogenetics and mutation testing (if available).

9.5 Definition of Baseline Measurements

Baseline measurements will be the last measurement for the corresponding variable prior to the first study drug dose.

9.6 Study Drug Exposure, Concomitant Medications, and Nonprotocol Cancer therapy

Descriptive information will be provided regarding drug exposure: the number of cycles of HDMP + Rituximab, the number of months of venetoclax treatment, the number of prescribed dose modifications and interruptions; and the reasons for dose modifications and interruptions.

Concomitant medications will be listed and summarized as appropriate.

Subsequent non-protocol cancer therapy will be listed and summarized as appropriate, if available.

9.7 General considerations of statistical analyses

The statistical analysis of the data obtained for this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, and minimum and maximum values. Categorical variables will be summarized by frequencies and percentages. For proportions, a 95% confidence interval will be calculated using the exact method. For survival outcomes, median survival times together with their 95% confidence intervals will be estimated with the Kaplan-Meier method, and report number of events.

All statistical tests will be two-sided at the 5% significance levels, unless otherwise noted.

9.7.1 Primary Efficacy Analyses

If applicable, “Intention-to-treat” analyses will be performed for the primary efficacy endpoint. To be specific, if the endpoint for a subject cannot be

assessed (for example, a subject drops out early prior to the tumor burden assessments due to any reason), it will be considered to be an event that does not favor the study therapy (e.g., disease progression for the primary outcome).

Primary efficacy analysis includes interim efficacy analysis and final efficacy analysis for the primary endpoint.

The interim efficacy analysis will be conducted at the end of Stage 1. The study enrollment will be put on hold for interim analysis until debulking response results for Stage 1 patients are known.

The final efficacy analysis will calculate the UMVUE estimate, p-value and 95% CI for the primary endpoint. [10-11] The calculation will be performed using R *clinfun* package (www.r-project.org).

9.7.2 Secondary Analyses

Analysis for the secondary analyses will use the data combined from both the stages. Linear models, logistic models or Cox models will be used to adjust for covariates including the stage variable and whether a patient has a debulking response after the first cycle.

9.8 Analysis of Safety

The safety outcomes of this study include the frequency of adverse events (AE) and severe adverse events (as defined in section 10.0). Descriptive statistics will be presented, including the number and percentage of subjects with any AE.

Summaries will be prepared for all treatment emergent AEs, including:

- Study-drug-related AEs
- AEs that are Grade 3, 4, or 5 in severity
- AEs leading to dose modification
- AEs leading to study drug discontinuation
- SAEs

Safety analyses will be performed for all patients having received at least one dose of study treatment. The proportion of subjects experiencing adverse events, serious adverse events, and treatment delays will be summarized. Tolerability will be assessed based on dosage delays and discontinuation due to adverse events.

All AEs will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown.

9.9 Handling of Dropouts and Missing Data

No data imputation will be performed.

10.0 Adverse Event Reporting

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 know) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken.

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

The severity of non-hematologic adverse events will be rated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0).

The severity of hematologic adverse events will be rated according to 2008 iwCLL grade scale. As is the case with virtually all of the hematological malignancies, an evaluation of the hematological toxicity in patients with CLL must consider the high frequency of marrow involvement and consequent medullar compromise at the initiation of therapy. A substantial proportion of patients will have hematological parameters within the range of Grade 2 – 4 hematological toxicity before therapy is given; therefore, a modified schema will be used to monitor hematological toxicity in patients with CLL. The modified hematological toxicity schema (taken directly from Hallek et al, 2008 IWCLL criteria) is displayed:

Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/ μL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

† Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20×10^9/L (20000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡ Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§ If the absolute neutrophil count (ANC) reaches < 1×10^9/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1×10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

If the reported AE increases in severity, the initial adverse events should be given final outcome date and a new adverse event must be reported to reflect the change in severity.

SAE definition:

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).

- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

SAE Reporting:

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

7 Calendar Day Telephone or Fax Report

The Investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of HDMP, Rituximab, and venetoclax. An unexpected AE is one that is not already described in the venetoclax investigator brochure or the methylprednisolone and rituximab prescribing information. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of HDMP, rituximab, or venetoclax. An unexpected AE is one that is not already described in the venetoclax investigator brochure or the methylprednisolone and rituximab prescribing information.

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

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Abbvie, and all participating investigators within 15 calendar days of first learning of the event. MedWatch 3500 form or alternative formats will be used (e.g., summary letter).

Contact Information for IND Safety Reports

FDA fax number for IND safety reports:

Fax: 1 (800) FDA 0178

In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall:

d) Report to Abbvie all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition, report all non-serious adverse events of tumor lysis syndrome for studies involving ABT-199.

e) Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and,

f) Notify AbbVie upon any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be PPDINDPharmacovigilance@abbvie.com

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints shall be RD_PQC_QS@abbvie.com

11.0 Study Management

11.1 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.2 Data and Safety Monitoring

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office internal monitor. Monitoring frequency will be after 7 patients (part 1 of the trial) and then annually.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to

provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported every year, and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.

2) the number of patients enrolled to date

3) the date of first and most recent patient enrollment

4) a summary of all adverse events regardless of grade and attribution

5) a response evaluation for evaluable patients when available

6) a summary of any recent literature that may affect the ethics of the study.

11.3 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.4 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

12.0 References

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13.0 Appendices

Appendix A: ECOG Performance Status
Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Appendix B: Tumor Lysis Syndrome Definitions

Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine*,†	≤ 1.5 × ULN	1.5 × ULN	1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	–	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

This definition comprises ≥ 2 of the following metabolic abnormalities occurring within 7 days from first dose at initial dosing or at dose escalation.

Element	**Value**	**Change from Baseline**
Uric Acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mEq/L	25% increase
Inorganic Phosphorus	≥ 1.45 mmol/L	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Howard Definition of Laboratory Tumor Lysis Syndrome

This definition comprises ≥ 2 of the following metabolic abnormalities.

Element	Value
Uric Acid	≥ 476 µmol/L or 8 mg/dL
Potassium	≥ 6.0 mmol/L or 6 mEq/L
Inorganic Phosphorus	≥ 1.45 mmol/L
Calcium	≤ 1.75 mmol/L

Appendix C. Sample List of Excluded and Cautionary Medications

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, 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 and not allowed on trial.

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

[1] Moderate CYP3A inhibitor per venetoclax FDA USPI.

Appendix D: Risk Assessment and Prophylaxis for Tumor Lysis Syndrome: Recommendations for Venclexta Prescribing Information

Venclexta can cause rapid reduction in tumor and thus poses a risk of TLS in the 5-week ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of Venclexta and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Perform tumor burden assessments, including radiographic evaluation (e.g. CT scan), assess blood chemistry (potassium, uric acid, phosphorous, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with venetoclax. Reduced renal function (creatinine clearance < 80 ml/min) further increases the risk. The risk may decrease as tumor burden decreases.

The following table describes the recommends TLS prophylaxis and monitoring during venetoclax treatment based on tumor burden determination from clinical trial data.

Tumor Burden Categories and TLS Monitoring and Risk Mitigation Recommendations

Tumor Burden Category	**Tumor Burden at start of venetoclax**	**Prophylaxis**		**Blood chemistry monitoring [c,d]**
		Hydration [a]	Anti-hyperuricemics	Setting and Freqeuncy of Assessments
Low	All measurable LN with the largest diameter < 5 cm by radiologic assessment AND ALC < 25 × 10^9/L	Oral (1.5 – 2L)	Allopurinol [b]	Outpatient - Pre-dose, 6 to 8 hours, 24 hr at first dose of 20 mg and 50 mg - Pre-dose at subsequent ramp-up doses
Medium	Any measurable LN with the largest diameter ≥ 5 cm but < 10 cm by radiologic assessment OR ALC ≥ 25 × 10^9/L	Oral (1.5 – 2L) and consider additional intravenous	Allopurinol	Outpatient - Pre-dose, 6 to 8 hours, 24 hr at first dose of 20 mg and 50 mg - Pre-dose at subsequent ramp-up doses - Consider hospitalization for patients with CrCl < 80 ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any measurable LN with the largest diameter ≥ 10 cm by radiologic assessment OR ALC ≥ 25 × 10^9/L AND any measurable LN with the largest diameter ≥ 5 cm	Oral (1.5 – 2L) and intravenous (150 – 200 ml/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg - Pre-dose, 4, 8, 12 and 24 hours Outpatient at subsequent ramp-up doses - pre-dose, 6 to 8 hours, 24 hours.

ALC = absolute lymphocyte count; LN = lymph node

[a] Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[b] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of VENCLEXTA. [c] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d] For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

Any subject, who at any dose level develops clinically significant electrolyte abnormalities, must have their subsequent venetoclax dose held until the electrolyte abnormalities resolve. Electrolyte changes should undergo aggressive management and further monitoring as per Appendix E (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). The subject may resume dosing based on a risk assessment (including tumor burden status), as determined by the investigator. All subjects must receive the intended dose for at least 7 days before increasing to the next higher dose.

Appendix E: Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

Section 1: First Dose of Venetoclax on study or Dose Escalation

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

In addition to the recommendations in the table below, for subjects receiving the first dose of venetoclax:

- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.

Abnormality	**Management Recommendations**
Hyperkalemia (Including Rapidly Rising Potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis.

Abnormality	Management Recommendations
	• At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. ○ If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hrs., if no other evidence of tumor lysis.
Hyperkalemia (Including Rapidly Rising Potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. <u>Do not administer in same IV line as sodium bicarbonate.</u> • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on local guidelines and/or institutional standards). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L)	• Administer rasburicase (dose based on local guidelines and/or institutional standards). ○ When rasburicase is used, sodium bicarbonate

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

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose escalation (e.g., 48 or 72 hours) are as below.

***Note*:** If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
  - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).

Appendix F: Venetoclax Patient Calendar for ramp-up