NCI Protocol #: N/A

DF/HCC Protocol #: 20-415

TITLE:  SAVE (Safe Accelerated Venetoclax Escalation): A phase Ib study of venetoclax with an accelerated dose ramp-up in patients with CLL

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Responsible Data Manager: TBD

NCI-Supplied Agent: N/A
Other Agent: Venetoclax (Venclexta™) – Commercial

IND #: Exempt
IND Sponsor: DF/HCC Investigator – Inhye Ahn, MD

Protocol Type / Version # / Version Date: Version 3 / March 25, 2022
Informed consent & confirmation of trial eligibility

Begin with enrollment to **Cohort A**
(5 participants)

Accelerated venetoclax ramp-up: dose increase daily x 5 days to reach full dose

Not tolerable. Stop enrollment.

Schedule is tolerable. Enroll **Cohort A and B** simultaneously (up to 20 participants in each cohort)

Accelerated venetoclax ramp-up: dose increase daily x 5 days to reach full dose

**Cohorts:**
- **Cohort A:** Low Risk for Tumor Lysis Syndrome (TLS)
- **Cohort B:** Medium or High Risk for TLS

**Study Duration:** The active portion of the study is through completion of cycle 3. Following the completion of the active study period, participants will be followed only for survival and disease response. Refer to Section 5.
Informed consent & confirmation of trial eligibility

Begin with enrollment to **Cohort A** (5 participants)

Accelerated venetoclax ramp-up: dose increase daily $\times$ 5 days to reach full dose

Inpatient TLS Monitoring

Not tolerable. Stop enrollment.

Schedule is tolerable. Enroll **Cohort A and B** simultaneously (up to 20 participants in each cohort)

**Cohorts:**
- **Cohort A**: Low Risk for Tumor Lysis Syndrome (TLS)
- **Cohort B**: Medium or High Risk for TLS

**Informed consent &**

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1. OBJECTIVES

1.1 Study Design

This is an open label phase Ib study of an accelerated venetoclax ramp-up in patients with chronic lymphocytic leukemia (CLL) in either the front-line or relapsed/refractory setting.

1.2 Primary Objectives

- To determine the highest risk tumor lysis syndrome (TLS) group among patients with newly diagnosed or relapsed/refractory CLL who are able to safely tolerate an accelerated, daily venetoclax dose ramp-up

1.3 Secondary Objectives

- To assess the safety and tolerability of an accelerated, daily venetoclax dose ramp-up
- To evaluate preliminary efficacy, including best objective response rate (ORR), complete response (CR) rate after approximately 3 months of venetoclax-based therapy, progression free survival (PFS), and overall survival (OS)
- To determine the rate of undetectable minimal residual disease (uMRD) in the peripheral blood

1.4 Exploratory Objectives

- Determine the rate of uMRD in the bone marrow
- To determine if overall mitochondrial priming, dependency on specific anti-apoptotic BCL-2 family members, or protein expression is associated with efficacy or toxicity, including risk of TLS
2. BACKGROUND

2.1 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the western world, with approximately 20,000 new cases diagnosed in the United States each year. Although a subset of patients will have an indolent disease course, some patients experience more rapidly progressive disease despite multiple lines of therapy, and few patients are cured. Over the past few decades there has been a pharmacologic revolution within the field, with the development of a variety of highly effective and well-tolerated novel targeted agents. One such novel targeted agent that is highly active in CLL is venetoclax, a potent, oral inhibitor of BCL-2.

In order to achieve durable response with good tolerability, cancer therapies should selectively kill tumor cells while sparing normal tissues. To accomplish this goal, a drug must potently hit a target that is critical to the survival of the tumor cells while less important for the survival of normal cells, providing a therapeutic window. Venetoclax clearly illustrates this principle and is generally well tolerated, including for those patients who are considered to be frail. In CLL, venetoclax leads to rapid killing of tumor cells resulting in deep remission with undetectable minimal residual disease (uMRD) in a substantial number of patients, a remarkable achievement for a small molecule oral therapy in a relatively indolent disease.

Based on the results of early phase trials, venetoclax received its initial accelerated Food and Drug Administration (FDA)-approval in the US in 2016 for high risk relapsed/refractory CLL, and subsequently in the European Medicines Agency (EMA) and other countries around the world. In the first-in-human, phase I trial in CLL, venetoclax was well-tolerated and active at all doses studied. There were a total of 116 patients enrolled in the study, which was divided into a dose escalation cohort (n=56), treated with doses ranging from 150 to 1,200 mg, and a dose expansion cohort (n=60), treated with a dose of 400 mg. An uncommon, but serious toxicity observed early in the study was tumor lysis syndrome (TLS). The three initial patients treated with venetoclax (with initial dosing at 100 mg or 200 mg) experienced laboratory TLS after the first dose. Despite further reduction in the starting dose to 50 mg, two patients experienced clinical TLS, with one patient requiring hemodialysis and one fatality due to presumed cardiac dysrhythmia. The risk of TLS was subsequently mitigated with a reduction of the initial dose to 20 mg, extended ramp-up of dosing with weekly increases to 50 mg, 100 mg, and 200 mg per day to the target dose of 400 mg, as well as close monitoring of and prophylaxis against TLS. With these modifications, only one of sixty patients in the expansion cohort had laboratory findings of tumor lysis and none had clinical sequelae.

Based on the phase III registrational study MURANO, venetoclax received full approval in combination with rituximab in relapsed/refractory CLL in 2018. And in 2019, based on the CLL14 study, venetoclax received full approval in frontline CLL in combination with obinutuzumab.

Given the outstanding efficacy of this agent, uptake of the drug in general, and particularly in community oncology settings, has been slow. Venetoclax is not being used widely in practice, resulting in a major lost opportunity for patients who could otherwise benefit from the drug.
When oncologists have a choice of selecting venetoclax or another active agent, the oral BTK inhibitor ibrutinib, they often select the latter because of its perceived superior toxicity profile. Yet patients on ibrutinib have ongoing risks of bleeding including central nervous system bleeds, cardiac risks including life-threatening ventricular arrhythmias, myalgias/arthralgias, hypertension and other chronic toxicities throughout the course of treatment, which must be indefinite due to the lack of achieving deep response for most patients on ibrutinib or other BTK inhibitors.

In contrast, other than some mild gastrointestinal side effects which are typically manageable with supportive care, and neutropenia managed with intermittent growth factor support, venetoclax therapy is very well-tolerated. Moreover, given the deep responses achieved, venetoclax may allow treatment discontinuation in patients achieving undetectable MRD (uMRD). Given these potential benefits to treating CLL patients with venetoclax, a crucial question is why venetoclax is currently being underutilized.

One potential reason for the slow adoption of venetoclax therapy is the potential for TLS. The 5-week dose ramp up scheme that was developed requires stringent TLS risk stratification, prophylaxis, monitoring, and management. Although this system has been effective at reducing the risk of clinical TLS, it has been very challenging for the practicing oncologist to implement in the real world setting due to many logistical challenges including awareness of the algorithm, timeliness of obtaining lab chemistry results, confusion over the risk stratification scheme, and complexity of the regimen. According to the venetoclax label, patients are categorized into low, medium, or high risk, as defined by absolute lymphocyte count and lymph node size. In Europe, patients are categorized into two main groups, at risk or at greater risk for TLS. To date, the strategy to overcome the issue of TLS taken across both industry-sponsored and investigator-initiated trials has been to use other agents to cytoreduce CLL disease burden prior to introducing venetoclax as part of a combination regimen; however, a major limitation of these studies is that they still require the complex 5-week dose ramp up scheme, even in patients who are cytoreduced by initial debulking therapy.

Finding a more convenient, yet still safe way to initiate venetoclax could potentially lead to more widespread adoption of venetoclax in both the frontline and relapsed/refractory setting.

Accelerated venetoclax ramp-up schedules of venetoclax have been safely utilized in patients with rapidly progressive disease in need of rapid therapeutic dosing. Patients with CLL with rapid progression of their disease after failing BTK inhibitor therapy were able to safely tolerate an accelerated ramp up of venetoclax with close monitoring and management of TLS. In this retrospective study, 34 patients who received a rapid escalation were evaluated. These patients received accelerated escalation due to rapid disease progression, often after failing a BTK inhibitor, and required more rapid disease control. Although TLS was common in the high-risk population (52%), all patients were able to be managed and none had lasting side effects. We hypothesize that in patients without rapid disease progression, the rates of TLS will much lower. An accelerated venetoclax ramp-up has also been successfully utilized in a clinical trial of venetoclax in combination with chemoimmunotherapy in patients with Richter’s syndrome. In this trial, of 27 patients who received a daily venetoclax ramp-up, none had evidence of TLS. These studies demonstrate that daily venetoclax ramp-up is feasible and can be safely performed.
in the inpatient setting with appropriate monitoring, though this dosing schedule has not been studied in a prospective fashion for patients with CLL.

Confirming that an accelerated venetoclax ramp-up can be safely utilized in CLL patients receiving standard of care therapy is the main goal of this study, the **SAVE** trial: Safe Accelerated Venetoclax Escalation, a phase Ib study of venetoclax with an accelerated dose ramp-up in patients with CLL. In this study, we aim to more systematically evaluate the safety of an accelerated ramp-up in patients with either frontline or relapsed/refractory CLL initiating commercial venetoclax.

### 2.2 Venetoclax (Venclexta™)

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. It has been FDA approved with or without rituximab for the treatment of adult patients with CLL and SLL who have received at least one prior therapy, with obinutuzumab for frontline therapy of CLL and SLL, as well in combination with azacitabine, decitabine, or low-dose cytarabine for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) who are age 75 or older, or have comorbidities that preclude the use of intensive induction chemotherapy. Increased dependence on BCL-2 has been demonstrated in CLL and AML cells, where it mediates tumor cell survival. Venetoclax helps promote selective tumor cell apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, thereby triggering mitochondrial outer membrane permeabilization and the activation of caspases.

### 2.3 Correlative Studies Background

#### 2.3.1 BH3 Profiling

This trial will incorporate a laboratory technique known as BH3 profiling, which is a functional assay that uses synthetic peptides that mimic the BH3 domains of pro-apoptotic BCL-2 family members to measure mitochondrial “priming”, or how close a cell is to its apoptotic threshold. This tool is also extremely powerful in that it can identify which anti-apoptotic proteins (i.e., BCL-2, BCL-XL, MCL-1) the cell relies on for survival. To perform a BH3 profile, individual BH3-only peptides are mixed with gently permeabilized living primary CLL cells, formalin-fixed, and then fluorescence activated cell sorting (FACS) is used to determine the amount of mitochondrial depolarization induced by each peptide as measured by cytochrome c release.

We have previously found that in a small, heterogeneously treated cohort of CLL patients, increased priming was associated with improved clinical response. We have also demonstrated that increased priming was associated with depth of clinical response in relapsed/refractory CLL patients on the M12-175 phase I study of venetoclax.

In the current trial, we will use BH3 profiling to determine whether increased priming or dependency on the anti-apoptotic protein BCL-2 is associated with response or risk of TLS or other toxicities. Similarly, we will determine whether dependency on other anti-apoptotic proteins (i.e., MCL-1 and BCL-XL) predicts resistance to therapy or reduced risk of toxicity. In a similar fashion, we will utilize dynamic BH3 profiling to determine whether short incubations of
CLL cells with venetoclax or other potential therapeutic agents ex vivo, enhances mitochondrial priming or BCL-2 dependency, and if these results correlate with clinical response.\textsuperscript{14}

2.3.2 Protein Expression

In addition to evaluating the functional role of anti-apoptotic proteins by BH3 profiling, we will evaluate BCL-2 family protein expression levels. We will determine whether pretreatment expression levels of BCL-2 family proteins by Western blot and/or FACS are associated with response or toxicity, in particular the development of TLS, following venetoclax therapy.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma per IW-CLL 2018\textsuperscript{15} requiring therapy based on at least one of the following criteria as listed below:

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <11.0 g/L) and/or thrombocytopenia (platelets <100 x 109/L)
- Massive (≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (at least 10 cm longest diameter), progressive, or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or LDT of <6 months. Lymphocyte doubling time may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months.
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Documented constitutional symptoms, defined as 1 or more of the following disease related symptoms or signs: unintentional weight loss >10% within 6 months prior to screening, significant fatigue (inability to work or perform usual activities), fevers >100.5° F or 38.0° C for 2 or more weeks prior to screening without evidence of infection, night sweats for more than 1 month prior to screening without evidence of infection

3.1.2 Both previously untreated and relapsed or refractory patients will be eligible, including those who will be receiving venetoclax as monotherapy or in combination with anti-CD20 monoclonal antibody therapy

3.1.3 Age greater or equal to 18 years

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)
3.1.5 Patients must meet the following hematologic criteria at screening, unless they have significant bone marrow involvement of CLL confirmed on biopsy:
   o Absolute neutrophil count $\geq$1000 cells/mm$^3$. Growth factor is allowed in order to achieve this
   o Platelet count $\geq$25,000 cells/mm$^3$ (25 x $10^9$/L) independent of transfusion within 7 days of screening

3.1.6 Adequate hepatic function defined as:
   o Serum aspartate transaminase (AST) and alanine transaminase (ALT) $\leq$ 3.0 x upper limit of normal (ULN), bilirubin $\leq$1.5 x ULN (unless bilirubin rise is due to Gilbert’s syndrome or of non-hepatic origin)

3.1.7 Adequate renal function as defined as:
   o Serum creatinine $\leq$1.5 times the ULN or creatinine clearance $\geq$ 50 mL/min using a 24-hour urine collection

3.1.8 Women of child-bearing potential and men must agree to use adequate contraception (hormonal, barrier method or abstinence) prior to study entry and for the duration of study participation

3.1.9 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Treatment with venetoclax within the past 6 months

3.2.2 Transformation of CLL to aggressive NHL (Richter’s transformation or pro-lymphocytic leukemia)

3.2.3 Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, surgery within 2 weeks of Cycle 1/Day 1 with the following exceptions:
   o CD20 antibody therapy (i.e. rituximab or obinutuzumab) if it is being used as part of the venetoclax regimen (see inclusion criteria 3.1.2)
   o For patients on targeted therapies, a washout of at least five half lives is required
   o Patients who experience clinical deterioration may start therapy after a shorter washout period with prior approval by the PI
   o Corticosteroid therapy (prednisone or equivalent $\leq$20 mg daily) is allowed

3.2.4 Confirmed central nervous system involvement

3.2.5 Allogeneic hematologic stem cell transplant within 6 months of starting study treatment or active graft vs. host disease (GVHD) requiring treatment or prophylaxis

3.2.6 Active malignancy requiring therapy that would interact with venetoclax as per the discretion of the treating investigator
3.2.7 Any active systemic infection requiring IV antibiotics or other uncontrolled, active infections

3.2.8 Known history of human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)

3.2.9 Major surgery within 4 weeks of first dose of study drug

3.2.10 Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months of initial dosing on study

3.2.11 Use of Coumadin for anticoagulation (other anticoagulants permitted)

3.2.12 Lactating or pregnant

3.2.13 Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A. The concomitant use of drugs or foods that are strong or moderate inhibitors or inducers of CYP3A are not allowed beginning 1 week prior to the first dose of venetoclax.

3.2.14 Patients with ongoing use of prophylactic antibiotics are eligible as long as there is no evidence of active infection and the antibiotic is not included on the list of prohibited medications

3.2.15 Unable to swallow capsules or malabsorption syndrome, active disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction resulting in malabsorption or chronic diarrhea

3.2.16 Active abuse of alcohol

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.
4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Venetoclax treatment ramp-up will be administered inpatient beginning on cycle 1 day 1 or cycle 1 day 22, depending on whether the patient is receiving venetoclax monotherapy, venetoclax plus rituximab, or venetoclax plus obinutuzumab standard of care options. Participants will remain inpatient at minimum for 7 days, refer to Section 10. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

All participants will begin venetoclax as an inpatient and follow the dose increase schedule depicted in the table below. Refer to Section 5.4 for tumor lysis syndrome (TLS) risk assessment, monitoring, and prophylaxis guidelines.

<table>
<thead>
<tr>
<th>Table 1: Venetoclax Dose Escalation Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5 and beyond</td>
</tr>
</tbody>
</table>
Patients will be separated into two cohorts. **Cohort A** will include patients at low risk for TLS. **Cohort B** will consist of patients with both median and high risk for TLS. These groups align with the at risk and at greater risk of TLS that utilized in European countries. TLS risk is defined as per the venetoclax label as outlined in **Table 4**. The first 5 participants will be from cohort A. If these first 5 participants tolerate the accelerated ramp-up, cohorts A and B will enroll simultaneously. Patients will be observed for signs and symptoms consistent with laboratory and clinical TLS (refer to **Section 5.5**). A maximum sample size of 20 patients will enroll in each cohort.

A continuous monitoring design will be utilized as described in **section 13.5**. If the accelerated ramp-up is seemed tolerable in the first 5 low risk patients, enrollment may occur in parallel in cohorts A and B, with no observation period or delay between the start of therapy for each participant within a given cohort. Participants will be closely monitored for signs and symptoms consistent with laboratory and clinical TLS (refer to **Section 5.5**).

If daily ramp-up is found to be intolerable in the first 5 patients, the trial will temporarily close to further accrual and the protocol may be amended to explore an alternate dosing scheme.

### 5.1.1 CD20 Antibody Use

Both previously untreated and relapsed or refractory patients will be eligible, including those who will be receiving venetoclax as monotherapy or in combination with anti-CD20 monoclonal antibody therapy.

If patients are receiving venetoclax in combination with obinutuzumab, the obinutuzumab can be administered as in the CLL14 trial. In this study, obinutuzumab was administered on days 1 (100 mg), 2 (900 mg), 8 (1000 mg) and 15 (1000 mg) of cycle 1 and on day 1 (1000 mg) of each cycle thereafter for a total of 6 cycles. Venetoclax was initiated on day 22. Therefore, no obinutuzumab will be administered at the time of the venetoclax ramp up.

If patients are receiving rituximab in combination with venetoclax, treatment will follow the
schema from the MURANO trial. In this study, rituximab was started after completion of the venetoclax ramp up and administered once per cycle for a total of six cycles. Patients receive 375 mg/m² for their first dose and 500 mg/m² thereafter. Patients will not be receiving rituximab at the time of the venetoclax ramp up.

If a patient is receiving venetoclax monotherapy, they will follow the same schedule as those patients receiving venetoclax plus rituximab (Table 12), though rituximab will not be administered on C2D1.

5.1.2 Subject Replacement

Unless dosing was held due to toxicity, to be considered evaluable for the purposes of cohort escalation decisions, participants must reach the full 400 mg dose of venetoclax and must be on study for at least five weeks. Participants who do not meet this requirement for reasons other than toxicity (e.g. withdrawal of consent for participation) will be replaced.

5.2 Pre-Treatment Criteria

Pre-treatment criteria for CD20 antibody therapy is per the discretion of the treating provider.

5.2.1 Prior to venetoclax administration

If pre-treatment laboratory assessments were completed ≤ 24 hours prior to the first dose of venetoclax, laboratory tests do not need to be repeated pre-dose and the pre-treatment laboratory values can be used. If pre-dose laboratories are performed, the values do not need to re-meet eligibility criteria, as long as the treating investigator confirms that such laboratory changes do not pose any significant risk to the patient.

5.2.2 Subsequent Days

Prior to dosing venetoclax, patients cannot meet criteria for active TLS. Detailed management guidelines for this and other toxicities associated with study treatment are located in Section 6.

5.3 Agent Administration

The active intervention portion of this trial involves 3 cycles of treatment. Continued treatment beyond the study period will be at the discretion of the treating investigator following local institutional guidelines and the FDA prescribing information.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Precautions</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule¹</th>
<th>Study Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venetoclax</td>
<td>Take with food (within approximately 30 minutes of a meal or snack)</td>
<td>Refer to Section 5.4 for TLS guidelines, monitoring, and prophylaxis</td>
<td>Oral</td>
<td>Once daily, beginning on day 1</td>
<td>5 weeks, then as per standard of care</td>
</tr>
</tbody>
</table>

5.3.1 Dosing Instructions

Venetoclax administration instructions:
- Venetoclax should be administered orally once daily, approximately every 24 hours.
- During the dose ramp-up period, ± 3 hour dosing window is allowed, and after this time a± 8 hour dosing window is allowed. After the dose ramp-up period, doses that would occur outside of this time frame should be considered missed and should not be administered.
- The tablets should be swallowed intact with water. Participants should not attempt to crush, chew, break, or dissolve the tablets.
- Venetoclax should be taken with food (within approximately 30 minutes of a meal or snack).
- If the participant vomits following a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.
- Refer to Section 5.4 for TLS risk assessment, monitoring, and prophylaxis guidelines.

Obinutuzumab and Rituximab Instructions:
- Obinutuzumab and rituximab will be administered per institutional standards
- Refer to section 5.1.1, 8.2 and 8.3 for additional information regarding dosing

5.4 Tumor Lysis Syndrome (TLS) Risk Assessment and Management

TLS, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with venetoclax. Participants must be assessed for patient-specific factors for level of risk of TLS and must be provided prophylactic hydration and anti-hyperuricemics prior to the first dose of venetoclax to reduce the risk of TLS. Refer to the tables below.

Venetoclax can cause rapid reduction in tumor and thus pose a risk for TLS in the dose 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 venetoclax and at each dose increase.
The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (creatinine clearance \([\text{ClCr}] < 80 \text{ mL/min}\)) further increases the risk. Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry in all patients and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

### Table 3: Tumor Lysis Syndrome (TLS) Risk Categorization

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Disease Characteristics</th>
</tr>
</thead>
</table>
| Low Risk      | No bulky adenopathy (all lymph nodes [LN] < 5 cm)  
-AND-  
Absolute lymphocyte count (ALC) < 25 \(\times 10^9/\text{L}\) |
| Medium Risk   | Bulky adenopathy: any LN \(\geq\) 5 cm and < 10 cm  
-OR-  
ALC: \(\geq\) 25 \(\times 10^9/\text{L}\) |
| High Risk     | Bulky adenopathy: any LN \(\geq\) 10 cm  
-OR-  
Any LN \(\geq\) 5 cm and ALC \(\geq\) 25 \(\times 10^9/\text{L}\) |

### Table 4: TLS Prophylaxis and Monitoring Based on Tumor Burden

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Prophylaxis</th>
<th>Blood Chemistry Monitoring During Dose Ramp-Up(^{c,d})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydration(^a)</td>
<td>Anti-hyperuricemics</td>
</tr>
</tbody>
</table>
| Low           | Oral (1.5 – 2 L) and IV (approximately 150 – 200 mL/hr as tolerated) | Allopurinol\(^b\)  
-AND-  
Rasburicase if uric acid is elevated above institutional ULN | • Pre-dose (any time prior to venetoclax dosing)  
• 4 hours post-venetoclax dosing (± 60 minute window)  
• 8 hours post-venetoclax dosing (± 60 minute window)  
• 12 hours post-venetoclax dosing (± 60 minute window)\(^e\)  
• 24 hours post-venetoclax dosing (± 120 minute window)\(^e\) |
| Medium        | Oral (1.5 – 2 L) and IV (approximately 150 – 200 mL/hr as tolerated) | Allopurinol\(^b\)  
-AND-  
Rasburicase if uric acid is elevated above institutional ULN | • Pre-dose (any time prior to venetoclax dosing)  
• 4 hours post-venetoclax dosing (± 60 minute window)  
• 8 hours post-venetoclax dosing (± 60 minute window)  
• 12 hours post-venetoclax dosing (± 60 minute window)\(^e\)  
• 24 hours post-venetoclax dosing (± 120 minute window)\(^e\) |
Table 4: TLS Prophylaxis and Monitoring Based on Tumor Burden

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Prophylaxis</th>
<th>Blood Chemistry Monitoring During Dose Ramp-Up&lt;sup&gt;c,d&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| High          | Oral (1.5 – 2 L) and IV (approximately 150 – 200 mL/hr as tolerated) | • Pre-dose (any time prior to venetoclax dosing)  
• 4 hours post-venetoclax dosing (± 60 minute window)  
• 8 hours post-venetoclax dosing (± 60 minute window)  
• 12 hours post-venetoclax dosing (± 60 minute window)<sup>e</sup>  
• 24 hours post-venetoclax dosing (± 120 minute window)<sup>e</sup> |
|               | Allopurinol<sup>b</sup> -AND- Rasburicase if uric acid is elevated above institutional ULN | |

IV = intravenous; ULN = upper limit of normal

a. Administer IV hydration for all patients, with rate of infusion dependent on what is tolerable for the individual patient. Concomitant diuresis is permitted as needed to help maintain fluid balance.
b. Start allopurinol or equivalent at least 3 days prior to initiation of venetoclax. Patients unable to take allopurinol or equivalent and thought to be at medium or high risk for TLS, should receive a prophylactic dose of rasburicase prior to administration of venetoclax.
c. Evaluate blood chemistries; review as quickly as possible. A full comprehensive metabolic panel should be performed pre-dose on each dose ramp-up day (albumin, alkaline phosphatase, total bilirubin, bicarbonate, LDH, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid). Limited chemistries (potassium, uric acid, phosphorus, calcium, LDH, BUN and creatinine) to be collected at subsequent collection times.
d. Blood chemistry monitoring will continue through the entire dose escalation process. If a participant’s dose is held during ramp-up, the frequent blood chemistry monitoring will extend to when the ramp-up is completed. For example, if day 4 dose is held and resumed the following day, ramp-up would complete a day later, and blood chemistry monitoring will be extended an additional day.
e. Where applicable, the pre-dose blood chemistries may also be considered the 24-hour post-dose blood chemistry for the previous day.

5.5 Definitions of Laboratory and Clinical TLS

The definitions for laboratory and clinical TLS are based on the 2004 Cairo-Bishop criteria for TLS incorporating modifications proposed by Howard et al. in 2011.18,19

Management and dose modifications associated with the below adverse events are outlined in Section 6.

5.5.1 Laboratory TLS

To meet the definition of laboratory TLS participants must experience two or more of the
following criteria within a 24-hour span, and within seven days of initiating venetoclax therapy or escalating the dose of venetoclax:

- Potassium \( \geq 6.0 \text{ mmol/L} \)
- Phosphorus \( \geq 1.45 \text{ mmol/L} \) (\( \geq 4.5 \text{ mg/dL} \))
- Corrected calcium \( \leq 1.75 \text{ mmol/L} \) (\( \leq 7.0 \text{ mg/dL} \)), OR ionized calcium \( \leq 0.3 \text{ mmol/L} \) (\( \leq 1.12 \text{ mg/dL} \))
- Urate \( \geq 476 \text{ μmol/L} \) (\( \geq 8.0 \text{ mg/dL} \))

5.5.2 Clinical TLS

To meet the definition of clinical TLS participants must experience one or more of the following, in addition to meeting the criteria for laboratory TLS:

- Creatinine increase of \( \geq 26.5 \text{ μmol/L} \) (\( \geq 0.3 \text{ mg/dL} \))
- Oliguria (< 0.5 mL/kg/h for 6 hours)
- Symptomatic hypocalcemia (includes tetany, muscle spasms, parathesia, bronchospasm, laryngospasm, hypotension)
- Cardiac dysrhythmia
- Seizure
- Sudden death

5.6 General Concomitant Medication and Supportive Care Guidelines

No investigational or commercial agents or therapies other than venetoclax and an anti-CD20 monoclonal antibody such as rituximab or obinutuzumab may be administered with the intent to treat the participant's malignancy.

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to anti-emetics, anti-diarrheals, hematopoietic growth factors and blood product transfusion.

5.6.1 Moderate or Strong CYP3A Inhibitors or P-gp Inhibitors

Concomitant use of strong CYP3A inhibitors is prohibited during trial therapy. Strong CYP3A inhibitors have the potential to increase the risk of TLS during venetoclax initiation/ramp-up. Moderate CYP3A and P-gp inhibitors may also increase venetoclax \( C_{\text{max}} \) and \( AUC_{\text{inf}} \), increasing the risk for toxicity and TLS, but can be used if needed in patients who have completely the venetoclax ramp-up period.

5.6.2 Strong or Moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases venetoclax \( C_{\text{max}} \) and \( AUC_{\text{inf}} \). Use of strong or moderate CYP3A inducers is prohibited during trial therapy.

5.6.3 Warfarin
Concomitant use of venetoclax increases warfarin $C_{\text{max}}$ and $AUC_{\text{inf}}$, which may increase the risk of bleeding, and is not permitted in patients on study, although other anticoagulants are allowed.

5.6.4 P-gp Substrates

Concomitant use of venetoclax increases $C_{\text{max}}$ and $AUC_{\text{inf}}$ of P-gp substrates, which may increase toxicities of these substrates. Avoid concomitant use of venetoclax with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

5.6.5 Prohibited Foods

The consumption of grapefruit (including juice) or Seville oranges (including juice) is prohibited while receiving trial therapy.

5.7 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), participants will receive a total of 5 weeks of study treatment as part of the active study intervention period, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant’s status must be updated in OnCore in accordance with REGIST-OP-1.

5.8 Duration of Follow Up

All participants will be actively followed for approximately 3 months after venetoclax initiation or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Following completion of the active study period, participants will be encouraged to return
for a response evaluation. Following this, patients will enter a long-term follow up period where they will be observed for survival status and disease response for a maximum of 5 years.

5.9 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Completion of the 5-year long-term follow up period
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant’s status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications for non-hematologic toxicity. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Hematologic toxicity will be graded and assessed based on the iwCLL 2018 criteria (Appendix B).15

6.1 Dose Delays

Venetoclax may be held for a maximum of 14 days to allow for recovery of toxicity thought to be at least partly attributable to venetoclax. Participants requiring a longer dose delay should be removed from protocol therapy.

In the event of a dose hold due to toxicity, the counting of days and protocol assessment schedule will also hold until the participant resumes dosing. For example, if a participant requires a dose hold on day 4 and resumes dosing the following day (as permitted per guidelines in Section 6.3), the day the participant resumes dosing will be considered “day 4.” All planned day 4 tests/assessments will be performed the day the participant resumes dosing, the following day will be considered day 5 with all planned day 5 tests/assessments, and so on.

6.2 Dose Modifications

Dose modifications for obinutuzumab and rituximab may be done per institutional standards.

Recommended dose reductions of venetoclax are detailed below. Following a dose reduction that occurs outside of the dose ramp-up phase, re-escalation is permitted. The need for repeating the
dose ramp-up, as well as the schedule for such ramp-up, will be at the discretion of the treating investigator, with approval by the PI.

<table>
<thead>
<tr>
<th>Dose at Interruption</th>
<th>Reduced Dose (once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>200 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>100 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>50 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

### 6.3 Toxicity Management

<table>
<thead>
<tr>
<th>Event</th>
<th>Occurrence</th>
<th>Management Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory TLS²</td>
<td>First</td>
<td>Hold venetoclax dosing until resolution to baseline. Initiate appropriate supportive care as indicated. Upon resolution, resume dosing, continuing to follow the planned accelerated dose escalation schedule.</td>
</tr>
<tr>
<td></td>
<td>Second and Subsequent</td>
<td>Hold venetoclax dosing until resolution to baseline. Initiate appropriate supportive care as indicated. No further accelerated escalation. Upon resolution, at the treating investigator’s discretion, participants may revert to following the weekly venetoclax escalation schedule as outlined in the FDA package insert.</td>
</tr>
<tr>
<td>Clinical TLS²</td>
<td>Any</td>
<td>Hold venetoclax dosing until complete resolution. Initiate appropriate supportive care as indicated. No further accelerated escalation. Upon resolution, at the treating investigator’s discretion, participants may revert to following the weekly venetoclax escalation schedule as outlined in the FDA package insert.</td>
</tr>
<tr>
<td>Event</td>
<td>Occurrence</td>
<td>Management Guidelines</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>First Hold venetoclax until resolution to ≤ Grade 1 or baseline. Initiate appropriate supportive care as indicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If event occurs during dose ramp-up:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Upon resolution, resume dosing, continuing to follow the planned accelerated dose escalation schedule.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If event occurs when participant is at full dose venetoclax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Resume venetoclax at the same dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other ≥ Grade 3 non-hematologic toxicity</td>
<td>Second and Subsequent Hold venetoclax until resolution to ≤ Grade 1 or baseline. Initiate appropriate supportive care as indicated.</td>
<td></td>
</tr>
<tr>
<td>If event occurs during dose ramp-up:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No further accelerated escalation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Upon resolution, at the treating investigator’s discretion, participants may revert to following the weekly venetoclax escalation schedule as outlined in the FDA package insert.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If event occurs when participant is at full dose venetoclax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Resume venetoclax at a reduced dose as guided by Table 6.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Grade 3 febrile neutropenia³</td>
<td>First Hold venetoclax until resolution to ≤ Grade 1 or baseline.</td>
<td></td>
</tr>
<tr>
<td>Grade 4 neutropenia or thrombocytopenia³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer granulocyte-colony stimulating factor (G-CSF) as clinically indicated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If event occurs during dose ramp-up:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Upon resolution, resume dosing, continuing to follow the planned accelerated dose escalation schedule.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If event occurs when participant is at full dose venetoclax:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Resume venetoclax at the same dose.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 6: Toxicity Management Guidelines for Venetoclax

<table>
<thead>
<tr>
<th>Event</th>
<th>Occurrence</th>
<th>Management Guidelines¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second and Subsequent</td>
<td>Hold venetoclax until resolution to ≤ Grade 1 or baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administer G-CSF as clinically indicated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If event occurs during dose ramp-up:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No further accelerated escalation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Upon resolution, at the treating investigator’s discretion, participants may revert to following the weekly venetoclax escalation schedule as outlined in the FDA package insert.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If event occurs when participant is at full dose venetoclax:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resume venetoclax at a reduced dose, as guided by Table 6.</td>
</tr>
</tbody>
</table>

1. In addition to the terms listed here, treating investigators may hold and/or dose reduce venetoclax at their discretion for intolerable ≥ Grade 2 toxicities.
2. Refer to Section 5.5 for definitions of laboratory and clinical TLS. Refer to Section 5.4 for TLS risk assessment and prophylaxis guidelines.
3. Hematologic toxicities will be graded and assessed based on iwCLL 2018 criteria (Appendix B).¹⁵

### 6.4 Overdose

There are currently no specific treatments in the event of overdose with venetoclax and symptoms of overdose are not established. In the event of an overdose, the participant should be monitored as clinically appropriate (e.g. vital signs, hematologic parameters, symptoms of TLS, etc.), and adverse reactions associated with the overdose should be treated symptomatically. Refer to Section 7 for adverse event reporting requirements.
7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Expected Toxicities

For the purposes of suspected unexpected serious adverse reaction (SUSAR) reporting, the toxicities in the table below will be considered expected for venetoclax. Also refer to the venetoclax FDA package insert.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Mucositis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Tumor lysis syndrome</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
</tr>
</tbody>
</table>

7.2 Adverse Event Characteristics

- **Term (AE description) and grade:** Dose delays and modifications will be made as
indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications for non-hematologic toxicity. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Hematologic toxicity will be graded and assessed based on the iwCLL 2018 criteria (Appendix B).\textsuperscript{15}

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution** of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

### 7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.
### DF/HCC Reportable Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Gr. 2 &amp; 3 AE Expected</th>
<th>Gr. 2 &amp; 3 AE Unexpected</th>
<th>Gr. 4 AE Expected</th>
<th>Gr. 4 AE Unexpected</th>
<th>Gr. 5 AE Expected or Unexpected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>Not required</td>
<td>Not required</td>
<td>5 calendar days*</td>
<td>5 calendar days</td>
<td>24 hours*</td>
</tr>
<tr>
<td>Likely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Not required</td>
<td>5 calendar days</td>
<td>5 calendar days*</td>
<td>5 calendar days</td>
<td>24 hours*</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* # If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.

* For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, events must be reported within 1 business day of learning of the event.

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### 7.4 Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

### 7.5 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

### 7.6 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Sponsor-Investigator on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

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### 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agent administered in this study can be found in Section 7.1.

#### 8.1 Venetoclax (Venclexta™)

##### 8.1.1 Description

Venetoclax is a light yellow to dark yellow solid with very low aqueous solubility.

- Molecular Formula: C_{45}H_{50}ClN_{7}O_{7}S
- Molecular Weight: 868.44 Daltons
- Chemical Structure:

8.1.2 Form

Refer to the FDA package insert. Venetoclax tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient.

8.1.3 Storage

The drug product should be stored in accordance with the FDA package insert.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Venetoclax is a commercially available FDA approved agent that will be obtained via commercial supplies.

8.1.6 Administration

Refer to Section 5.3.

8.1.7 Ordering

Venetoclax is a commercially available agent.

8.2 Obinutuzumab
8.2.1 Description

Obinutuzumab (GA101, RO5072759), is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering.

8.2.2 Form

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

8.2.3 Storage and Stability

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

8.2.4 Compatibility

N/A

8.2.5 Availability

Obinutuzumab is provided through commercial supply.

8.2.6 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment

8.2.7 Preparation

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.
One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2 degrees C to 8 degrees C and administer the next day.

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

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

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

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

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

8.2.8 Administration

Obinutuzumab is to be administered by IV infusion for 6 total cycles (28-day cycles) per institutional standard. Typically, obinutuzumab is administered according to the following schedule:

- On cycle 1, Day 1, 100 mg obinutuzumab will be administered
- On cycle 1, Day 2, 900 mg of obinutuzumab will be administered
- On cycle 1, Days 8 and 15, 1000 mg of obinutuzumab will be administered.
- On cycles 2-6, Day 1, 1000 mg of obinutuzumab will be administered (see section 5.4.2)

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator at all times. Obinutuzumab should be given as a slow IV
infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion; if no AEs occur after 1 hour, the IV line may be removed.

8.2.9 Ordering

Obinutuzumab will be available from commercial supply.

8.2.10 Destruction and Return

Destruction of used and unused study drug may be performed at the site as per institutional policy.

8.3 Rituximab

8.3.1 Availability

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the FDA-approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.3.2 Storage and Stability

Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.3.3 Preparation

The desired dose of rituximab should be diluted in 0.9% NaCl or D$_5$W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.3.4 Administration

Rituximab may be administered as per institutional standard.

8.3.5 Ordering

Rituximab will be available from commercial supply.

8.3.6 Desensitization

In patients who have a history of a significant rituximab infusion reaction or experience such a
reaction during this study, it is permitted that rituximab is administered through a desensitization program as per institutional standards.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Minimal Residual Disease Testing

All participants will have blood specimens collected during screening and again on cycle 2 day 1 (± 3 day scheduling window) and cycle 4 day 1 (±14 day scheduling window, see also Section 10) that will undergo minimal residual disease (MRD) analysis. A maximum of approximately 5 – 6 mL of peripheral blood will be obtained at each time point for performance of MRD assessment. If participants undergo bone marrow aspirate at any point during the study intervention period, a sample will be sent for MRD analysis. A maximum of approximately 5 - 6 mL of aspirate will be obtained at each time point for performance of MRD assessment.

Bone marrow and blood samples will be collected for minimal residual disease analysis by Mayo Clinic Genetics by flow cytometry.

These samples will be shipped priority overnight to:

Mayo Medical Laboratories
3050 Superior Drive NW
Rochester, MN 55901

For Customer Service regarding lab results, or changes in an order, please call Mayo Clinic lab services at: 855-516-8404

Investigative sites both local and external must create an account for their institution with Mayo Clinics if they do not already have an existing account.

Tests can be ordered online via the MayoAccess Portal at https://mmlaccess.com/ or via the Mayo Clinic Laboratories Hematopathology Test Request form must accompany the sample shipment.

Results will be faxed to the number provided by the team in the portal, or on the order form.

<table>
<thead>
<tr>
<th>Source</th>
<th>Collection Container*</th>
<th>Catalog ID</th>
<th>Shipment Conditions**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>6 ml Sodium Heparin Tube</td>
<td>CLLMV</td>
<td>Ambient</td>
</tr>
<tr>
<td>Bone Marrow Aspirate</td>
<td>6 ml Sodium Heparin Tube</td>
<td>CLLMV</td>
<td>Ambient</td>
</tr>
</tbody>
</table>

** Sent same day, first overnight

Although MRD by flow cytometry at a sensitivity of $10^{-4}$ is an acceptable surrogate endpoint in clinical trials, its reproducibility is variable. There is a need to develop high sensitivity quantitative MRD techniques with more reproducibility. One such assay is ClonoSEQ, a next-generation DNA sequencing assay that is now commercially available and may detect MRD at a
sensitivity of $10^{-5}$ to $10^{-6}$, although this requires further validation in prospective trials. Although flow-based MRD assessment will be the primary technique utilized in this study, we will also collect and store additional peripheral blood and bone marrow samples for cross validation with MRD by ClonoSEQ when possible. Depending on sample and funding availability, this will be performed at Adaptive Biotechnologies in Seattle, WA. Peripheral blood and/or bone marrow samples will be collected, processed and stored at Dana-Farber Cancer Institute for possible future analysis at Adaptive. Using Adaptive’s ClonoSEQ platform, rearranged immunoreceptor loci from genomic DNA will be extracted, amplified, and sequenced using V and J segment primers for each immunoreceptor gene. Tumor-specific clonotypes will be identified for each patient based on their high prevalence in peripheral blood or bone marrow. Sequences will be analyzed using standardized algorithms for clonotype determination. Adaptive MRD levels will be quantified using spiked-in reference sequences.

Adaptive Biotechnologies
151 Eastlake Ave E, Ste 200
Seattle, WA 098102

9.2 BH3 Profiling

All participants will have specimens sent for BH3 profiling which will be performed in the Davids Laboratory at Dana-Farber Cancer Institute (DFCI). Profiling will be done on circulating CLL cells from the peripheral blood drawn from patients.

If bone marrow aspirate is available at any point, BH3 profiling will also be performed on the aspirate samples to see whether the level of priming in CLL cells from these tissues is a better predictor of response than peripheral blood CLL cells.

All peripheral blood and bone marrow aspirate samples will promptly be hand delivered to the laboratory of Dr. Matthew Davids, where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be batched for BH3 profiling. The contact information for the Davids Lab is:

Mary Collins, Research Technician
Davids Laboratory
Dana-Farber Cancer Institute
440 Brookline Avenue, Mayer 540
Boston, MA 02215, USA
(p) 617-632-2362
Table 8: BH3 Profiling Sample Collection

<table>
<thead>
<tr>
<th>Day of Venetoclax Ramp Up^3</th>
<th>Sample Number</th>
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</thead>
<tbody>
<tr>
<td>Screening</td>
<td>BH3-00</td>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
<td>BH3-03</td>
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<tr>
<td>4</td>
<td>BH3-04</td>
</tr>
<tr>
<td>5</td>
<td>BH3-05</td>
</tr>
<tr>
<td>Off Treatment</td>
<td>BH3-06</td>
</tr>
</tbody>
</table>

1. A maximum of approximately 12 mL of blood (6 mL x 2) will be collected at each time point in sodium heparin tubes.
2. If available, a maximum of approximately 6 mL of aspirate will also be collected at each time point.
3. All blood samples must be drawn prior to venetoclax dosing on the given visit day. Sample may be drawn at any time prior to dosing. Refer to calendar to determine day that this corresponds to in the cycle.

9.2.1 BCL-2 Family Protein Expression Assessment

The Davids Laboratory at DFCI will analyze BCL-2 family protein expression by intracellular fluorescence activated cell sorting (FACS) and/or by Western blot. Additional or alternate markers may be explored as considered appropriate at the time of analysis.

All participants will have peripheral blood sent for analysis at the time points indicated in the table below. If bone marrow aspirate is available at any point, aspirate will also be collected for analysis.
**Table 9: BCL-2 Family Protein Expression Sample Collection**

<table>
<thead>
<tr>
<th>Day of Venetoclax Ramp Up</th>
<th>Sample Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>PE-00</td>
</tr>
<tr>
<td>1</td>
<td>PE-01</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>PE-04</td>
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<td>5</td>
<td>PE-05</td>
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<tr>
<td>Off Treatment</td>
<td>PE-06</td>
</tr>
</tbody>
</table>

1. A maximum of approximately 12 mL of blood (6 mL x 2) will be collected at each time point in sodium heparin tubes.
2. If available, a maximum of approximately 6 mL of aspirate will also be collected at each time point.
3. All blood samples must be drawn **prior** to venetoclax dosing on the given visit day. Sample may be drawn at any time prior to dosing. Refer to calendar to determine day that this corresponds to in the cycle.
10. STUDY CALENDAR

Screening evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of screening radiologic scans which may be conducted within about 30 days prior to the start of protocol therapy and the bone marrow biopsy / aspirate which may be obtained up to about 120 days prior to the start of protocol therapy. Assessments must be performed prior to administration of the study agent.
<table>
<thead>
<tr>
<th>Demographics</th>
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<th>Screening</th>
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</tr>
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<tr>
<td>TLS Laboratory Monitoring</td>
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<td>Serum β-HCG</td>
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<tr>
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<td>X</td>
</tr>
<tr>
<td>Bone marrow biopsy / aspirate / MRD assessment</td>
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<td>X</td>
</tr>
<tr>
<td>Peripheral Blood MRD Analysis</td>
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<td>X</td>
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<tr>
<td>Adverse event evaluation</td>
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<td>X</td>
</tr>
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</table>

Table 10: Study Calendar for Participants Receiving Ven/Obin
**DF/HCC Protocol #: 20-415**  
Version Date: March 26, 2020

<table>
<thead>
<tr>
<th>Correlative Samples</th>
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<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
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<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

Column only relevant for CRF builders

a. All dosing ramp-up will occur inpatient. Participants may be discharged on day 27 after the completion of day 27 study assessments. Participants not medically stable for discharge on day 27 will remain inpatient until discharge is considered medically appropriate by the treating investigator.

b. A ± 3-day visit scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.

c. Off study treatment evaluation. Continued treatment beyond the study period will be at the discretion of the treating investigator following local institutional guidelines and the FDA prescribing information. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of the study intervention period.

d. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response following the end of the study intervention period. To be completed every 3 months following the completion of 5 weeks of venetoclax dosing (±1 month window) for a maximum of 5 years or until death, whichever occurs first.

e. Heart rate, respiratory rate, temperature, blood pressure, and oxygen saturation; to be performed prior to study agent dosing on applicable visit days.

f. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, LDH, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid.

g. Refer to Section 5.4 for complete schedule and details.

h. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µIU/mL).

i. Screening neck/chest/abdomen/pelvis CT or MRI required for all participants within 30 days prior to the start of protocol therapy. Repeat imaging to be performed on C4D1 (±14 day scheduling window) as per standard of care guidelines. Refer to Section 11.

j. Screening bone marrow biopsy / aspirate may be performed up to 120 days prior to the start of protocol therapy. Repeat bone marrow biopsy / aspirate to be performed C4D1 (±14 day window) as per standard of care guidelines. Correlative analyses on collected aspirate specimens will be performed as described in Section 9. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care at any time point. RHP should be sent on marrow at baseline if not performed in the prior 6 months on marrow or blood. Flow cytometry (lymphoma panel), stimulated karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies. FISH and RHP may be performed on either marrow or blood and is not required on both but marrow is preferred if done. MRD should be performed on all marrows to evaluate response (see Section 9.1).

k. Refer to Section 9.1.

l. Refer to Section 9 for correlative study collection details.

m. Refer to Section 5 for venetoclax dosing details and instructions.

n. Obinutuzumab will be continued for a total of 6 cycles per standard of care even when patients are off study. Labs to be collected per standard of care.
Table 11: Study Calendar for Participants Receiving Ven/Ritux or Venetoclax Monotherapy

<table>
<thead>
<tr>
<th></th>
<th>Inpatienta</th>
<th></th>
<th>Outpatienta</th>
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<th>C4D1/Off active treatmentb</th>
<th>Long-term Follow-upc</th>
<th>EDC Timepointsd</th>
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<tr>
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EDC Timepoints:
- Screening
- N/A
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Version Date: March 26, 2020

<table>
<thead>
<tr>
<th>Medical Record Review / Care Provider Contact / Telephone Contact</th>
<th>X</th>
<th>Every 3 months following treatment discontinuation for a maximum of 5 years</th>
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</thead>
<tbody>
<tr>
<td>☞: Column only relevant for CRF builders.</td>
<td>o. All dosing ramp-up will occur inpatient. Participants may be discharged on day 7 after the completion of day 7 study assessments. Participants not medically stable for discharge on day 7 will remain inpatient until discharge is considered medically appropriate by the treating investigator.</td>
<td>☞: Column only relevant for CRF builders.</td>
</tr>
<tr>
<td>p. A ± 3-day visit scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.</td>
<td>q. Off study treatment evaluation. Continued treatment beyond the study period will be at the discretion of the treating investigator following local institutional guidelines and the FDA prescribing information. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of the study intervention period.</td>
<td>r. Long-term follow-up will involve medical record review, telephone and/or care provider contact to confirm survival status and ongoing disease response following the end of the study intervention period. To be completed every 3 months following the completion of 5 weeks of venetoclax dosing (±1 month window) for a maximum of 5 years or until death, whichever occurs first.</td>
</tr>
<tr>
<td>s. Heart rate, respiratory rate, temperature, blood pressure, and oxygen saturation; to be performed prior to study agent dosing on applicable visit days.</td>
<td>t. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, LDH, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, uric acid.</td>
<td>u. Refer to Section 5.4 for complete schedule and details.</td>
</tr>
<tr>
<td>v. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea &gt;12 consecutive months; or women with a documented plasma follicle-stimulating hormone level &gt;35µIU/mL).</td>
<td>w. Screening neck/chest/abdomen/pelvis CT or MRI required for all participants within 30 days prior to the start of protocol therapy. Repeat imaging to be performed on C4D1 (±14 day scheduling window) as per standard of care guidelines. Refer to Section 11.</td>
<td>x. Screening bone marrow biopsy / aspirate may be performed up to 120 days prior to the start of protocol therapy. Repeat bone marrow biopsy / aspirate to be performed on C4D1 (±14 day window) as per standard of care guidelines. Correlative analyses on collected aspirate specimens will be performed as described in Section 9. Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care at any time point. RHP should be sent on marrow at baseline if not performed in the prior 6 months on marrow or blood. Flow cytometry (lymphoma panel), stimulated karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies. FISH and RHP may be performed on either marrow or blood and is not required on both but marrow is preferred if done. MRD should be performed on all marrows to evaluate response (see Section 9.1).</td>
</tr>
<tr>
<td>y. Refer to Section 9.1.</td>
<td>z. Refer to Section 9 for correlative study collection details.</td>
<td>aa. Refer to Section 5 for venetoclax dosing details and instructions.</td>
</tr>
<tr>
<td>bb. Rituximab will be continued for a total of 6 cycles per standard of care even when patients are off study. In patients receiving venetoclax monotherapy, rituximab will be omitted.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. MEASUREMENT OF EFFECT

Response and progression of CLL participants will be evaluated using the 2018 iwCLL criteria for CLL.\(^{15}\)

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. All lymph node measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool.

11.1 Imaging Evaluations

All participants will have screening CT or MRI scans of the chest, abdomen, and pelvis within about 30 days prior to the start of protocol therapy. Scans will be repeated on cycle 4 day 1 (± 14-day scheduling window) as per standard of care guidelines. Scans may also be repeated at any other time at the discretion of the treating investigator.

Conventional CT or MRI should be performed. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

11.2 Bone Marrow Biopsy / Aspirate

Screening bone marrow biopsy / aspirate is required for all participants and may be obtained up to about 120 days prior to the start of protocol therapy. Repeat bone marrow biopsy / aspirate is required on day cycle 4 day 1 (±14-day scheduling window) as per standard of care guidelines. Bone marrow biopsy / aspirate may also be done at any time at the treating investigator’s discretion.
### 11.3 Response Criteria

#### Table 12: Response Definition Following Treatment of CLL Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>Complete Remission (CR)¹</th>
<th>Partial Remission (PR)²</th>
<th>Stable Disease (SD)³</th>
<th>Progressive Disease (PD)⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lymph nodes</td>
<td>None ≥ 1.5 cm</td>
<td>Decrease ≥ 50% (from baseline)⁵</td>
<td>Change of -49% to +49%</td>
<td>Increase ≥ 50% from baseline or from response</td>
</tr>
<tr>
<td></td>
<td>Liver and/or spleen size⁶</td>
<td>Spleen size &lt; 13 cm; liver size normal</td>
<td>Decrease ≥ 50% (from baseline)</td>
<td>Change of -49% to +49%</td>
<td>Increase ≥ 50% from baseline or from response</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms</td>
<td>None</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Circulating lymphocyte count</td>
<td>Normal</td>
<td>Decrease ≥ 50% from baseline</td>
<td>Change of -49% to +49%</td>
<td>Increase ≥ 50% from Baseline</td>
</tr>
<tr>
<td>B</td>
<td>Platelet count</td>
<td>≥ 100 × 10⁹/L</td>
<td>≥ 100 × 10⁹/L or increase ≥ 50% over baseline</td>
<td>Change of -49% to +49%</td>
<td>Decrease of ≥ 50% from baseline secondary to CLL</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
<td>≥ 11.0 g/dL (untransfused and without erythropoietin)</td>
<td>≥ 11 g/dL or increase ≥ 50% over baseline</td>
<td>Increase &lt; 11.0 g/dL or &lt; 50% over baseline, or decrease &lt; 2 g/dL</td>
<td>Decrease of ≥2 g/dL from baseline secondary to CLL</td>
</tr>
<tr>
<td></td>
<td>Marrow</td>
<td>Normocellular, no CLL cells, no B-lymphoid nodules</td>
<td>Presence of CLL cells, or of B-lymphoid nodules, or not done</td>
<td>No change in marrow infiltrate</td>
<td>Increase of CLL cells by ≥ 50% on successive biopsies</td>
</tr>
</tbody>
</table>

1. For CR, all criteria have to be met from groups A and B.
2. For PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve.
3. For SD, all of the criteria have to be met.
4. For PD, at least 1 of the criteria of group A or group B has to be met.
5. Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
6. Spleen size is considered normal if < 13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in accordance with local standard of care guidelines.

### 11.4 Definitions

**Treatment Failure:** Responses that should be considered clinically beneficial include CR and PR; all others (e.g., stable disease, non-response, PD, death from any cause) should be rated as a treatment failure.
Overall Survival (OS): Defined as the time from first treatment day to death due to any cause, or censored at date last known alive.

Progression-Free Survival (PFS): Defined as the time from first treatment day to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Event-Free Survival (EFS): Defined as the interval between the first treatment day to the first sign of disease progression or start of a new treatment or withdrawal from the trial because of toxicity or death (whichever occurs first).

Time to Next Treatment (TTNT): Defined as the interval between the first treatment day until the patient starts an alternative therapy for progressive CLL.

Relapse: Defined as evidence of disease progression in a patient who has previously achieved the above criteria of a CR or PR for ≥ 6 months.

Refractory Disease: Defined as treatment failure or as progression within 6 months from the last dose of therapy.

Minimal Residual Disease (MRD)-Negative: Blood or marrow with < 1 CLL cell per 10,000 leukocytes assessed by at least four-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay.

Complete Remission with incomplete marrow recovery (CRi): Some patients fulfill all the criteria for a CR, but have a persistent anemia, thrombocytopenia or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi). The marrow evaluation should be performed with scrutiny and not show any clonal disease infiltrate.

11.5 Response Review

Confirmation of scan results will be performed centrally by the Tumor Imaging Metrics Core (TIMC) at DF/HCC.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method
The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.2 Primary Endpoint

- The highest risk tumor lysis syndrome (TLS) group among patients with newly diagnosed or relapsed/refractory CLL who are able to safely tolerate an accelerated, daily venetoclax dose ramp-up

13.3 Secondary Endpoints

- The safety and tolerability of an accelerated, daily venetoclax dose ramp-up
- The best ORR, defined as partial response and complete response according to the 2018 IW-CLL criteria, rate of complete response (CR), the duration of response (DOR) among patients who have achieved a PR or CR, defined as the time from first response to progression or last follow-up, progression free survival (PFS), defined as the time from treatment start to progression, death or last follow-up, whichever comes first, overall survival (OS), defined as time from treatment start to death or last follow-up
MRD negativity, determined by 4-color flow cytometry with a sensitivity of $10^{-4}$

### 13.4 Exploratory Endpoints

- The rate of uMRD in as determined by next generation sequencing (ClonoSeq)
- The association of overall mitochondrial priming, dependency on specific anti-apoptotic BCL-2 family members, and protein expression with efficacy and toxicity, including risk of TLS

### 13.5 Sample Size, Accrual Rate and Study Duration

This study will utilize a continuous monitoring design. Patients will be separated into two cohorts. **Cohort A** will include patients at low risk for TLS. **Cohort B** will consist of patients with both median and high risk for TLS. The first 5 participants will be from cohort A. If the regimen is not tolerated in these first 5 patients using the stopping rules below, no further enrollment will occur in the study. If these first 5 participants tolerate the accelerated ramp-up, cohorts A and B will subsequently enroll simultaneously. Patients will be observed for signs and symptoms consistent with laboratory and clinical TLS (refer to Section 5.5). A maximum sample size of 20 patients will enroll in each cohort as described in Section 5.

**For each cohort A and B (if accrued) the same stopping rule will be implemented.**

Sequential Pocock-type stopping boundary will be used to monitor TLS rate.$^{20}$ The accrual will be halted if excessive numbers of TLS events are seen, that is, if the number of TLSs is equal to or exceeds $b_n$ out of $n$ patients (see table below). The probability of crossing the boundary is at most 0.05 when the rate of TLS is equal to the acceptable rate of 0.1. **Calculations were performed in R using toxbdry function in Clinfun library.**

The trial will be stopped if the number of laboratory TLS events is equal to or exceeds $b_n$ out of $n$ patients with completed follow-up.

<table>
<thead>
<tr>
<th>Number of Patients, $n$</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boundary, $b_n$</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

In the table below we show the probability of stopping for different values of true underlying laboratory TLS rate:

<table>
<thead>
<tr>
<th>True rate</th>
<th>Probability of stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>0.3</td>
<td>0.68</td>
</tr>
<tr>
<td>0.4</td>
<td>0.91</td>
</tr>
</tbody>
</table>
If the true underlying probability of laboratory TLS is greater than 0.4, the accelerated ramp-up would be considered intolerable. The current continuous monitoring design results in a probability of early stopping of 0.9 if the probability of laboratory TLS is over 0.4.

For clinical TLS, we will assume that acceptable rate is below 0.2. The trial will be stopped if the number of clinical TLS is equal to or exceeds $b_n$ out of $n$ patients with completed follow-up.

| Number of Patients, $n$ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Boundary, $b_n$         | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   | 2   |

The table below shows probability of stopping for different values of true underlying clinical TLS rate.

<table>
<thead>
<tr>
<th>True rate</th>
<th>0.01</th>
<th>0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of stopping</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True rate</th>
<th>0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of stopping</td>
<td>0.32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True rate</th>
<th>0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of stopping</td>
<td>0.64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True rate</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of stopping</td>
<td>0.94</td>
</tr>
</tbody>
</table>

The laboratory and clinical TLS will be monitored simultaneously, and enrollment in each cohort will be stopped if either laboratory or clinical TLS events exceed the boundaries.

Toxicity rate in each cohort will be estimated together with 90% confidence intervals. The regimen will be considered potentially tolerable and worth of further investigation if 5 or less patients out of 20 experience lab TLS and 1 or less patients experience clinical TLS. These counts correspond to the upper limit of 90% CI of 0.45 and 0.22 for lab TLS and clinical TLS respectively.

13.6 Analysis of Primary Endpoints

- The highest risk TLS group that is able to safely tolerate an accelerated venetoclax ramp up will be determined as described in Section 5 and 13.5.

13.7 Analysis of Secondary Endpoints

- The safety and tolerability of an accelerated, daily venetoclax dose ramp-up will be assessed descriptively
- In the highest risk group cohort after expansion rates of laboratory and clinical TLS will be estimated along with 95% exact binomial CIs.
- The best ORR, defined as partial response and complete response according to the 2018 IW-CLL criteria, rate of complete response (CR), the duration of response (DOR) among patients who have achieved a PR or CR, defined as the time from first response to progression or last follow-up, progression free survival (PFS), defined as the time from
treatment start to progression, death or last follow-up, whichever comes first, overall survival (OS), defined as time from treatment start to death or last follow-up. ORR will be estimated along with a 95% confidence interval. DOR, PFS, and OS will be estimated using Kaplan-Meier methodology.

- MRD negativity will be determined by 4-color flow cytometry with a sensitivity of $10^{-4}$. The rate of MRD negativity will be estimated along with a 95% confidence interval.

13.8 Analysis of Exploratory Endpoints

- The rate of uMRD in the bone marrow as determined by next generation sequencing will be reported as a percentage.
- The association of overall mitochondrial priming, dependency on specific anti-apoptotic BCL-2 family members, and protein expression with efficacy and toxicity, including risk of TLS will be assessed using the Wilcoxon rank test.

13.9 Reporting and Exclusions

13.9.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment with drug on study.

13.9.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study who receive at least one dose of drug on study must be assessed for safety and response to therapy, even if there are major protocol therapy deviations.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.
REFERENCES

17. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or


# APPENDIX A PERFORMANCE STATUS CRITERIA

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status Scale</th>
<th>KPS Performance Status Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100 Normal, no complaints, no evidence of disease.</td>
</tr>
<tr>
<td></td>
<td>90 Able to carry on normal activity; minor signs or symptoms of disease.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).</td>
<td>80 Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td></td>
<td>70 Cares for self, unable to carry on normal activity or to do active work.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>60 Requires occasional assistance, but is able to care for most of his/her needs.</td>
</tr>
<tr>
<td></td>
<td>50 Requires considerable assistance and frequent medical care.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
<td>40 Disabled, requires special care and assistance.</td>
</tr>
<tr>
<td></td>
<td>30 Severely disabled, hospitalization indicated. Death not imminent.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>20 Very sick, hospitalization indicated. Death not imminent.</td>
</tr>
<tr>
<td></td>
<td>10 Moribund, fatal processes progressing rapidly.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
<td>0 Dead.</td>
</tr>
</tbody>
</table>
### Table 17: Grading Scale For Hematological Toxicity in CLL Studies

<table>
<thead>
<tr>
<th>Grade</th>
<th>Decrease in platelets(^3) or hemoglobin(^4) (nadir) from baseline value, %</th>
<th>Absolute neutrophil count (nadir)(^5) (\times 10^9)/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change to 10</td>
<td>(\geq 2)</td>
</tr>
<tr>
<td>1</td>
<td>11 – 24</td>
<td>(\geq 1.5) and &lt; 2</td>
</tr>
<tr>
<td>2</td>
<td>25 – 49</td>
<td>(\geq 1) and &lt; 1.5</td>
</tr>
<tr>
<td>3</td>
<td>50 – 74</td>
<td>(\geq 0.5) and &lt; 1</td>
</tr>
<tr>
<td>4</td>
<td>(\geq 75)</td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>

1. Refer to iwCLL 2018 Criteria\(^{15}\)
2. 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 baseline will be recorded as grade 5.
3. Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20 \(\times 10^9\)/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20 \(\times 10^9\)/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
4. Hb levels must be below normal levels for grades 1-4. 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.
5. If the absolute neutrophil count (ANC) reaches <1 \(\times 10^9\)/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 \(\times 10^9\)/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity but should be documented.