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Sponsor Protocol #: *IST-145-15*

TITLE: A Phase I/II Study of Duvelisib and Venetoclax in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or Patients with Richter's Syndrome

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NCI-Supplied Agent(s): *N/A*
Other Agent(s): Venetoclax (ABT-199/GDC-0199, commercial), Duvelisib (IPI-145, Secura Bio, Inc.)

IND #: 137998
IND Sponsor: Matthew S. Davids, MD, MMSc

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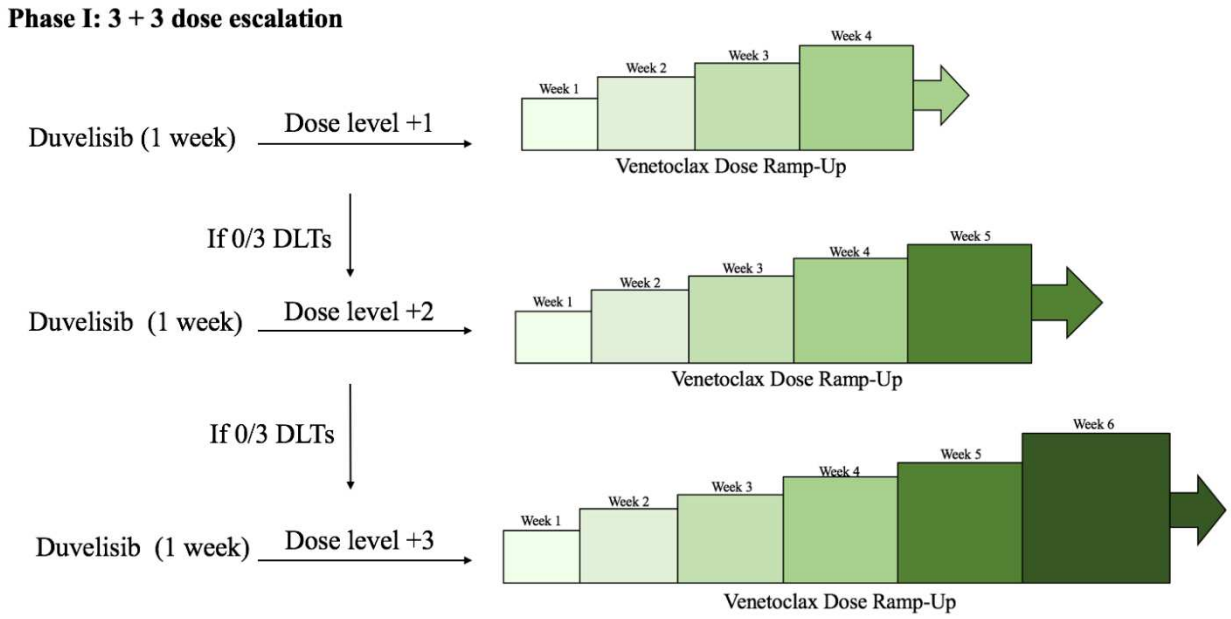
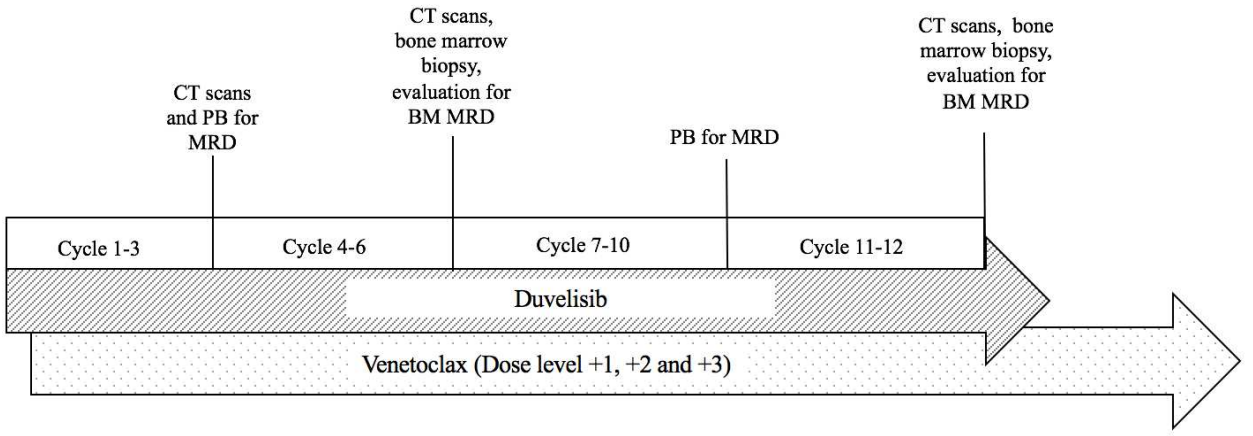
SCHEMA

Phase I Dose Escalation

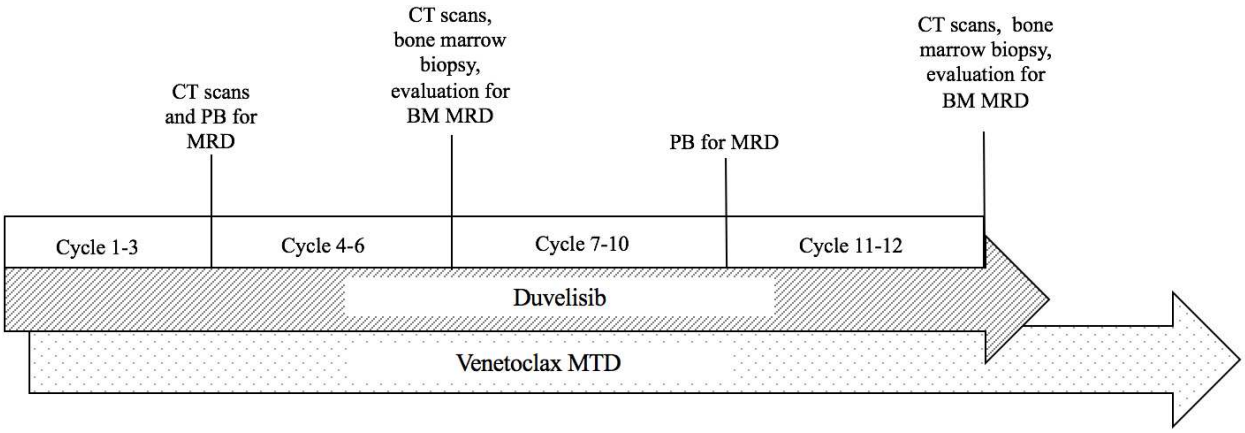




Phase II

CLL/SLL Cohort

Stage I: Enroll 12 CLL/SLL patients



Stage II: If at least 2 CLL/SLL patients achieve a complete response (CR) as defined by the IWCLL 2008 criteria after one year, an additional 23 patients will be enrolled in the second stage.

RS Cohort

Twenty patients with RS will be enrolled to a separate phase II cohort and treated with the same regimen as above for the phase II CLL/SLL Cohort.

SYNOPSIS

Title of Study: A Phase I/II Study of Duvelisib and Venetoclax in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, or patients with Richter's Syndrome
Principal Investigator: Matthew S. Davids, MD, MMSc
Study Center(s): This study will be conducted within the Dana-Farber/Harvard Cancer Center (Dana-Farber Cancer Institute and Massachusetts General Hospital. Collaborator includes Dr. Jacob Soumerai (MGH).
Rationale: Venetoclax, a potent, selective inhibitor of BCL-2, was approved by the U.S. Food and Drug Administration (FDA) in 2016 for the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL) with deletion 17p (del(17p)). Venetoclax has since been established as an effective therapeutic option for patients with traditionally difficult to treat disease. While venetoclax has demonstrated impressive clinical results, complete response (CR) rates range from only 10-20% as monotherapy, and responses are not durable for many patients. In the initial phase I trial, 35% of patients progressed within 15 months of initiating therapy. Based on experience with chemoimmunotherapy, achieving a CR with minimal residual disease (MRD) negativity is highly beneficial both in terms of remission duration and overall survival (OS). Novel therapeutic strategies, especially those utilizing combination approaches, are urgently needed, as they have the potential to deepen responses and thus improve outcomes for patients with relapsed/refractory CLL. Duvelisib, an oral, reversible and selective small molecule dual inhibitor of PI3K-δ and PI3K-γ, has emerged as a promising therapeutic option for patients with CLL. Preclinical studies have shown that duvelisib inhibits B-cell receptor (BCR) signaling, reduces chemotaxis, and inhibits cytokine mediated CLL cell proliferation. PI3K-γ inhibition also inhibits the tumor-promoting effects of T-cells and myeloid cells in the microenvironment, providing the potential for enhanced anti-tumor effect as compared to PI3K-δ inhibition alone. At concentrations achieved at a dose of 25 mg BID, duvelisib results in near complete inhibition of PI3K-δ and fifty percent inhibition of PI3K-γ. Early phase clinical trials have shown overall response rates in relapsed/refractory CLL in the 80% range with a manageable toxicity profile at this dose, making this a suitable partner for combination studies. Duvelisib was FDA-approved in 2018 for patients with relapsed/refractory CLL after 2 or more prior therapies. As venetoclax and duvelisib target pathways fundamental to CLL biology and have distinct mechanisms of action, they offer great promise as a combination therapy for the treatment of patients with CLL. Preclinical data further supports this combination, as duvelisib therapy has been shown to upregulate BCL-2 transcript and protein expression levels and enhance the ability of venetoclax to induce apoptosis in *ex vivo* human CLL cells. BH3 profiling has also

previously shown that inhibition of PI3K enhances the apoptotic threshold of CLL cells and sensitivity to BCL-2 inhibition.

Study Concept:
In this phase I/II trial, we combine duvelisib and venetoclax in patients with relapsed/refractory CLL, small lymphocytic lymphoma (SLL), or Richter's Syndrome (RS). We aim to determine the maximum tolerated dose (MTD) of venetoclax to be used in combination with duvelisib and the safety of combination therapy. We will also monitor for MRD. Patients achieving MRD negativity have the option to discontinue therapy after at least one year of treatment, which has the potential to reduce the toxicities associated with indefinite treatment, improve adherence to therapy, and significantly reduce costs.

In correlative laboratory studies, we will utilize BH3 profiling, a functional assay that determines the apoptotic threshold of a cell, to determine whether duvelisib primes cells for death or enhances their reliance on BCL-2 for survival. This has the potential to predict response and identify patients likely to benefit from combination therapy. We can also use this tool to identify whether the dependence on other anti-apoptotic proteins, such as MCL-1 or BCL-XL, confers resistance to therapy. Given the effects of PI3K inhibition on T-cells and myeloid cells in the microenvironment, we also plan to use cytometry by time-of-flight (CyTOF) to identify the effect of duvelisib on immune subsets and determine how this impacts response to therapy as well as toxicity.

Primary Objectives:

Phase I:

- Determine the dose limiting toxicities (DLTs), and the maximum tolerated dose (MTD) as well as the recommended phase II dose for this combination regimen of duvelisib plus venetoclax for patients with relapsed or refractory CLL/SLL

Phase II:

- Determine the rate of complete response (CR) of duvelisib in combination with the MTD of venetoclax, as defined by the IWCLL 2008 criteria for CLL/SLL or Lugano 2014 Criteria for RS

Secondary Objectives:

Phase I:

- Evaluate pharmacokinetics of both duvelisib and venetoclax in patients with CLL/SLL and with RS

Phase II:

- Evaluate preliminary efficacy, including objective response rate (ORR), duration of response (DOR) among patients who have achieved a partial response (PR) or CR, progression free survival (PFS), and OS in patients treated with combined duvelisib and venetoclax
- Determine the rate of MRD negativity (MRD-negative CR) in the bone marrow after six months and one year of combination therapy

- Determine the association of FISH abnormalities, *TP53*, *NOTCH1*, or *SF3B1*mutations, complex karyotype, and *IGHV* mutational status with ORR, CR rate, and PFS
- Evaluate pharmacokinetics of both duvelisib and venetoclax in patients with RS

Exploratory Objectives:

- Use both standard (performed prior to initiation of therapy and following one week of duvelisib monotherapy) and dynamic BH3 profiling to determine whether duvelisib therapy enhances mitochondrial priming and how this correlates with response
- Use BH3 profiling (performed prior to initiation of therapy, following one week of duvelisib monotherapy, and after three and six months of combination therapy) to determine whether dependency of anti-apoptotic proteins other than BCL-2 (i.e. MCL-1 and BCL-XL) predicts resistance to therapy
- Use CyTOF to identify how duvelisib monotherapy and duvelisib and venetoclax combination therapy impacts immune cell subtypes, in particular the ratio of regulatory to conventional T cells, and how this correlates with response and toxicity
- Determine change in lymph node size following one week of duvelisib monotherapy
- Determine change in quality of life score using quality of life survey (appendix F) after one week of duvelisib monotherapy

Study Design: This is an open-label, multicenter, phase I/II study of duvelisib in combination with venetoclax for patients with relapsed/refractory CLL/SLL or patients with Richter's Syndrome (RS) of any disease status

Phase I:

In the phase I study, patients will start with 25 mg BID of duvelisib for seven days. A traditional 3 + 3 design will be used to accrue patients to one of three doses of venetoclax, which will start on day 8 and will be given in combination with duvelisib. The starting dose level of venetoclax will be 100 mg daily (dose level +1) with escalation to 200 mg daily (dose level +2) and to 400 mg daily (dose level +3). De-escalation to 50 mg daily (dose level -1) will be performed if unexpected toxicity is observed.

At each dose level, patients will undergo a weekly dose ramp-up of venetoclax starting with a dose of 10 mg (given the potential for drug-drug interactions), and subsequently ramp-up to the eventual cohort dose. Patients in the initial dosing cohorts will stop at a lower dose of venetoclax than the approved dose of 400 mg. Patients will be admitted for each dose of venetoclax during the dose ramp-up for close monitoring for tumor lysis syndrome (TLS). Patients will continue combination therapy for up to one year. Once the MTD of venetoclax in combination with duvelisib is determined, patients assigned to lower dose levels in the phase I trial will also have the option to escalate their venetoclax dose to the MTD.

Phase II:

The phase II study will include two stages. We will start by enrolling 12 CLL/SLL patients who will receive 25 mg BID of duvelisib followed by venetoclax. If 2 CLL/SLL patients

achieve a CR after one year of therapy, an additional 23 CLL/SLL patients will be enrolled in the second stage. A separate cohort of 20 patients with Richter's Syndrome will be enrolled in parallel with the CLL/SLL cohort in a one stage design.

Since no TLS was observed with the 10 mg starting dose of venetoclax in phase I, patients in the phase II portion of the study start will have the option to start with 10 or 20 mg of venetoclax as per the standard of care and will follow a standard dose ramp-up to the MTD. Patients who are low- or medium risk for TLS and wish to be treated all in the outpatient setting will have to start at 10 mg and then the following week go up to 20 mg, and then complete the rest of the usual ramp-up to 50 mg, 100 mg, 200 mg, and 400 mg.
High risk patients will all be hospitalized for the initial dose ramp-ups, and will have the option to start at 10 or 20 mg. If they start at 10 mg, they will need to be hospitalized for the first 3 dose ramp-ups (10 mg, 20 mg, and 50 mg), or first 2 dose ramp-ups (20 and 50mg) if they start at 20 mg. When venetoclax dosing is performed as an outpatient, TLS labs should be checked pre-dose, approximately 6-8 hours after first dose and approximately 24 hours after treatment.

Accelerated ramp up for RS patients: Given the potential for rapidly progressive RS, these patients will also have the option to undergo an accelerated venetoclax ramp-up in the inpatient setting modeled after another study of venetoclax plus chemotherapy that was recently reported (Davids et al., ICML, 2019). In that study, venetoclax was safely ramped up in a daily fashion for 20 RS patients, who were monitored closely in the inpatient setting, with no evidence of tumor lysis syndrome. The venetoclax is dosed at 20mg for day 1, and if no TLS is observed on labs done 6-8 hours and 24 hours later, then the dose is ramped up to 50mg on day 2, 100mg on day 3, 200mg on day 4, and 400mg on day 5 if the daily labs done 6-8 hours and 24 hours later continue to show no TLS. If laboratory TLS does occur, the next day's dose will be held until there is improvement in the TLS, at which point escalation to the next dose may occur

Study visits will occur weekly through cycles 1-2, once per cycle during cycles 3-7, every 2 cycles from cycle 8-13, then every 3 cycles up to cycle 60, and then every 6 cycles thereafter until discontinuation of therapy. Patients will be treated with duvelisib plus venetoclax combination therapy for up to one year (12 cycles), followed by venetoclax monotherapy until the time of disease progression without clinical benefit, death, unacceptable toxicity, withdrawal of consent.

Additionally, if after at least one year of combination treatment, a patient achieves a complete remission (CR) or complete remission with incomplete count recovery (CRi) with MRD-negativity in the bone marrow, they will have the option to discontinue therapy. Those that come off treatment for this reason will be monitored for disease recurrence with peripheral blood MRD testing by flow cytometry approximately every 3 months. Patients who have detectable recurrence (at minimum, confirmed by two successive peripheral blood MRD positive assessments) in the peripheral blood will have the option to restart venetoclax. If they do not achieve MRD negativity or have evidence of disease progression after reaching

full dose venetoclax monotherapy, they will also have the option to add duvelisib and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability.

CT scans (or PET/CT for Richter's participants) will occur at C4, C7, C13. After this first year, scans can be done every 6 cycles thereafter, or at the investigator's discretion. Bone marrow biopsies and aspirates will be mandatory at study entry (unless within screening window), at the C7D1, C13D1, and C25D1 re-staging visits and as clinically indicated thereafter. Patients will be evaluated for MRD negativity in the peripheral blood approximately every 3 months and with each bone marrow biopsy (other than the baseline biopsy). MRD testing will be performed by 4-color flow cytometry with a sensitivity of 10^{-4} and when possible by next generation sequencing.

Patients who achieve CR or best response and are candidates for allogeneic transplant can elect to go off study to undergo transplant.

Baseline Labs:

- CBC with differential
- Comprehensive metabolic panel
- Amylase and lipase
- Testing to rule out active Hep B, Hep C, CMV and HIV infection
- Serum pregnancy test (pre-menopausal female patients only)
- FISH and karyotype cytogenetic analysis
- *IGHV* and *TP53* mutational status of all participants- Additional somatic mutation testing for *NOTCH1* and, *SF3B1* will be done for Dana-Farber CLL/SLL patients only.

Instrumental Tests:

- CT scans (or PET/CT scans for RS patients) prior to cycle 4, 7, and 13 and every 6 cycles thereafter at the investigator's discretion
- Bone marrow biopsy and aspirate prior to cycle 7, 13 and 25 and as clinically indicated thereafter
- MRD testing in the bone marrow prior to cycle 7, 13 and 25 and any time a clinically indicated bone marrow biopsy is performed thereafter
- MRD testing in the peripheral blood will occur approximately every 3 cycles during treatment up to Cycle 60, and every 6 cycles thereafter- This will also be tested approximately every 3 months during active follow up for routine disease monitoring

Sample Size:

We anticipate that approximately 12 CLL/SLL patients will be enrolled in the phase I study, using the traditional 3+3 design as described above.

For the phase II study, a Simon's two-stage design will be employed with 12 CLL/SLL patients accrued to the first stage. All patients will be followed for up to one year. If at least 2 patients achieve a CR then an additional 23 patients will be accrued to the second stage. Patients who receive the MTD of venetoclax in the phase I portion of the trial can also be counted in the analysis of the phase II portion of the trial.

A separate cohort of 20 patients with Richter's Syndrome will be enrolled in parallel with the CLL/SLL cohort in a one stage design.

Key Eligibility Criteria (*please see protocol section 3 for complete list*):

Inclusion Criteria:

- Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma requiring therapy, as per IW-CLL 2008 criteria OR biopsy confirmed Richter's Syndrome (RS)
- Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy (CLL/SLL patients only)
- ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)
- Adequate hepatic function defined as:
    - Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN), bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
- Adequate renal function as defined by:
    - Serum creatinine ≤1.5 x ULN or creatinine clearance ≥ 50 mL/min using a 24-hour urine collection
- Patients must meet the following hematologic criteria at screening, unless they have significant bone marrow involvement of CLL confirmed on biopsy:
    - Absolute neutrophil count ≥500 cells/mm^3 (0.5 x 10^9/L). Growth factor is allowed in order to achieve this
    - Platelet count ≥25,000 cells/mm^3 (25 x 10^9/L) independent of transfusion within 7 days of screening

Exclusion Criteria:

- Previous treatment with venetoclax or duvelisib (prior venetoclax allowed for RS patients and for CLL/SLL patients if they have been off venetoclax therapy for at least one year prior to enrollment)
- 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:
    - For patients on targeted therapies, a washout of at least five half-lives is required
    - Patients who experience clinical deterioration may start therapy after a shorter

washout period with prior approval by the PI
    - Corticosteroid therapy (prednisone or equivalent ≤20 mg daily) is allowed
- Confirmed central nervous system involvement
- Allogeneic hematologic stem cell transplant within 6 months of starting study or active graft vs. host disease (GVHD) requiring treatment or prophylaxis
- Active malignancy other than CLL/SLL or Richter's Syndrome requiring ongoing therapy, with the exception of hormonal therapy
- Any active systemic infection requiring IV antibiotics or other uncontrolled, active infections
- Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening
- Administration of live or live attenuated vaccine within 6 weeks of initiation of therapy
- Human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)
- Major surgery within 4 weeks of first dose of study drug
- Currently active gastrointestinal disease, including colitis, inflammatory bowel disease and diarrhea requiring therapy
- 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, acute coronary syndrome, stroke, or sustained ventricular arrhythmia within 6 months prior to initiation of therapy
- Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety
- Use of Coumadin for anticoagulation (other anticoagulants permitted)
- Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A (see Appendix D)
- Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine)
- History of chronic liver disease or veno-occlusive disease/sinusoidal obstruction syndrome
- History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
- Active abuse of alcohol or illicit drugs

Intervention and Mode of Delivery:
Duvelisib, 25 mg BID, oral
Venetoclax, up to 400 mg daily, oral

Regulatory and Feasibility Issues: Patients must have access to commercially available venetoclax. Secura Bio, Inc. will provide duvelisib at no cost to the participant.

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1. OBJECTIVES

1.1 Study Design

This is an open-label, multicenter, phase I/II study of duvelisib in combination with venetoclax for patients with relapsed/refractory CLL or SLL or Richter's Syndrome.

Phase I
The phase I portion of the trial will determine the dose, schedule, safety and tolerability of duvelisib in combination with venetoclax. Patients will start with 25 mg BID of duvelisib for seven days. A traditional 3 + 3 design will be used to accrue patients to one of three doses of venetoclax, which will start on day 8. The starting dose level of venetoclax will be 100 mg daily (dose level +1) with escalation to 200 mg daily (dose level +2) and to 400 mg daily (dose level +3). De-escalation to 50 mg daily (dose level -1) will be performed if unexpected toxicity is observed. At each dose level, patients start with 10 mg of venetoclax followed by a weekly dose ramp-up, with patients in the initial dosing cohorts stopping at a lower dose of venetoclax than the approved dose of 400 mg.

Phase II
The phase II study will occur in two stages in order to determine the rate of complete response (CR) of duvelisib in combination with the MTD of venetoclax. Patients will be treated with duvelisib plus venetoclax for up to one year followed by venetoclax monotherapy until the time of disease progression without clinical benefit, death, unacceptable toxicity, or withdrawal of consent.

Additionally, if after at least one year of treatment, a patient achieves a complete remission (CR) or complete remission with incomplete count recovery (CRi) with MRD-negativity in the bone marrow, they will have the option to discontinue therapy. Those that come off treatment for this reason will be monitored for disease recurrence with peripheral blood MRD testing by flow cytometry approximately every 3 months. Patients who have detectable recurrence (at minimum, confirmed by two successive peripheral blood MRD positive assessments) in the peripheral blood will have the option to restart venetoclax. If they do not achieve MRD negativity or have disease progression with venetoclax monotherapy after reaching full dose venetoclax, they have the option to add duvelisib and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability.

Patients will be regularly monitored for minimal residual disease (MRD) throughout the trial.

1.2 Primary Objectives

Phase I

- Determine the dose limiting toxicities (DLT), maximum tolerated dose (MTD) as well as the recommended phase II dose and safety profile for this combination regimen of duvelisib plus venetoclax for patients with relapsed or refractory CLL/SLL

Phase II:

- Determine the best rate of complete response (CR) or complete response with incomplete count recovery (CRi) of duvelisib in combination with the MTD of venetoclax as defined by the IWCLL 2008 criteria for CLL/SLL or Lugano 2014 criteria for RS.

1.3 Secondary Objectives

Phase 1

- Evaluate pharmacokinetics of both duvelisib and venetoclax in CLL/SLL and RS

Phase II

- Evaluate preliminary efficacy, including the best objective response rate (ORR), duration of response (DOR) among patients who have achieved a partial response (PR) or CR, progression free survival (PFS), and overall survival (OS) in patients treated with combined duvelisib and venetoclax
- Determine the rate of minimal residual disease (MRD-negative CR) in the bone marrow at six months, one year and two years, and rate of best MRD-negative CR/CRi in the bone marrow
- Determine the association of FISH abnormalities, *TP53*, *NOTCH1*, or *SF3B1* mutations, and *IGHV* mutational status with ORR and CR rate

Exploratory Objectives:

- Use both standard (performed prior to initiation of therapy and following one week of duvelisib monotherapy) and dynamic BH3 profiling to determine whether duvelisib therapy enhances mitochondrial priming and how this correlates with response
- Use BH3 profiling (performed prior to initiation of therapy, following one week of duvelisib monotherapy, and after three and six months of combination therapy) to determine whether BCL-2 dependency predicts response to therapy or risk of tumor lysis syndrome. Alternatively, we will determine whether dependency of anti-apoptotic proteins other than BCL-2 (i.e., MCL-1 and BCL-XL) predicts resistance to therapy
- Use Cytometry by Time of Flight (CyTOF) to identify how duvelisib monotherapy and duvelisib and venetoclax combination therapy impacts immune cell subtypes, in particular the ratio of regulatory to conventional T cells
- Determine change in lymph node size following one week of duvelisib monotherapy
- Determine change in quality of life score using quality of life survey (appendix F) after one week of duvelisib monotherapy

2. BACKGROUND:

2.1 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the western world, with approximately 19,000 new cases diagnosed in the United States each year.[1] 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, a deeper insight into the molecular and genetic underpinnings of CLL have helped to elucidate these differences in outcomes and have paved the way for a pharmacologic revolution, with the development of a variety of highly effective and well-tolerated novel targeted agents. Although this has led to an expansion in therapeutic options for patients unable to tolerate traditional chemoimmunotherapy (CIT) and for patients with relapsed/refractory disease or high-risk biology, complete response (CR) rates remain low and responses are not durable in a large subset of patients on novel agent monotherapy. Novel therapeutic combination strategies are urgently needed to deepen responses and improve outcomes.

Among the novel targeted agents available for patients with relapsed/refractory disease and high-risk biology are Bruton's tyrosine kinase inhibitors, such as ibrutinib. Ibrutinib is an oral, covalent inhibitor of BTK, a key component in B-cell signaling. The first phase Ib-II trial of ibrutinib for patients with relapsed/refractory CLL and symptomatic older patients with treatment naïve CLL demonstrated high response rates and an acceptable safety profile.[2,3] Patients with relapsed/refractory CLL showed an 86% overall response rate (ORR) and 10% CR rate with a median progression free survival (PFS) of 52 months. While patients with deletion 17p (del(17p)) had high response rates, responses were less durable, with a median PFS of 26 months. The confirmatory phase III trial, RESONATE, also demonstrated an improvement in ORR, PFS, and overall survival (OS) of ibrutinib monotherapy compared to ofatumumab in patients with relapsed CLL, leading to full FDA approval of ibrutinib for this population.[4,5]

Although patients have demonstrated excellent responses to ibrutinib, the effects are not durable for many patients, especially for those with high-risk features such as del(17p). For patients who relapse after ibrutinib, the survival is poor, with median overall survival ranging from 3 months to 23 months in one study.[6] Other patients are not able to tolerate ibrutinib given associated side effects such as atrial fibrillation and bleeding risk.[7,8] Novel therapeutic options for these patients are urgently needed.

2.2 Richter's Syndrome

Although the course for most CLL patients is at least initially an indolent one, it is estimated that between 1% to 11% CLL patients transform to an aggressive lymphoma.[9] The most common transformation event, known as Richter's syndrome (RS), involves CLL transforming into diffuse large B cell lymphoma (DLBCL).[10]

Overall, the prognosis for patients with RS is poor, though response to therapy depends on

whether the disease is clonally related to the antecedent CLL. Patients with clonally unrelated RS have a median survival estimated at 62 months[11]; however, about 80% of patients have clonally-related Richter's, and the median overall survival for these patients ranges from 8 to 14 months depending on the study.[9]

Based largely on extrapolation of data from *de novo* DLBCL, the approach to RS treatment has historically been to use anthracycline containing chemotherapy, most commonly the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen. The efficacy of this approach has been evaluated in small phase 2 studies such as the German CLL2G trial, which included 15 patients with RS, and the CR rate was only 7%.[14] Recently, data were published by the CLL group at Ohio State University on the use of a dose adjusted infusional regimen of rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone (da-R-EPOCH) in 46 patients with RS.[15] The CR rate of 20% was modest, and the durability of response was short. As such, novel approaches to treating Richter's Syndrome are urgently needed.

2.3 Venetoclax

Venetoclax is an oral, potent, selective inhibitor of BCL-2, a key mediator of the intrinsic pathway of apoptosis. BCL-2 inhibits cell death by binding to pro-death, BCL-2 family proteins that activate apoptosis at the level of the mitochondria.[19] CLL cells express high levels of BCL-2 and are dependent on it for their survival, making BCL-2 an attractive therapeutic target.[20,21] Preclinical studies have demonstrated that venetoclax selectively binds BCL-2 with subnanomolar affinity (Ki<0.01 nM) and rapidly induces apoptosis in human CLL cells.[22] Venetoclax also has a lower affinity for other anti-apoptotic BCL-2 family proteins, like BCL-XL and BCL-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to BCL-2, respectively) and therefore has a different safety profile than prior dual BCL-2/BCL-XL inhibitors, which led to dose-limiting thrombocytopenia due to inhibition of BCL-XL. Venetoclax yields an improved therapeutic index by maintaining efficacy against tumor cells while avoiding dose-limiting thrombocytopenia.

In the first-in-human, phase I trial in CLL, venetoclax was well-tolerated and active at all doses studied.[16] 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. The most prominent 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 and weekly ramp-up to a target dose for each cohort, 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. Other toxicities associated with venetoclax, such as neutropenia and gastrointestinal adverse events, were manageable.

In the initial phase I trial, the ORR, including both the dose-escalation and expansion cohorts, was 79%, with a 20% CR rate. Overall, 5% of patients achieved minimal residual disease (MRD) negativity by 4-color flow cytometry in the peripheral blood, though analysis was not uniformly available. Of note, response rates among patients with del(17p) were similar to the overall cohort, with a 71% ORR and 16% CR rate. Patients with other high-risk features, including unmutated *IGHV*, refractoriness to fludarabine, and bulky disease similarly had excellent responses to venetoclax.

The follow-up landmark, phase II study included 107 patients with del(17p) CLL.[17] An ORR of 79.4% was achieved, with a CR rate of 10%. In a subset of 45 patients evaluated for MRD in peripheral blood, 18 had no evidence of detectable disease. At the time of the analysis, the median duration of overall response, event free survival, time to progression, PFS and OS had not been reached. The estimated 12-month PFS and OS were 72% and 86.7%, respectively. The results of this study led to accelerated approval of venetoclax by the FDA for relapsed or refractory del(17p) CLL. More recently venetoclax has also been tested in patients who relapsed after or were refractory to ibrutinib or idelalisib, a group recently appreciated to have a particularly poor prognosis. Although the sample size in this study is small, there was a less than 5% CR rate.[23]

Venetoclax has since been studied in combination with rituximab. The initial phase Ib trial demonstrated that this combination was well tolerated, efficacious, and associated with a high degree of MRD negativity.[24] This prompted the phase III MURANO trial, a randomized trial of venetoclax plus rituximab versus BR for patients with relapsed/refractory CLL, which demonstrated a 2-year PFS of 84.9% with venetoclax plus rituximab as compared to 36.3% with BR, leading to FDA approval in 2018 of venetoclax in combination with rituximab in CLL patients after one prior line of therapy, independent of del(17p) status.[25]

While the results of venetoclax monotherapy are promising, CR rates range from only 5-20%, and a large subset of patients did not have durable responses, especially those with complex karyotype and/or del(17p).[16,26] In the phase I study, 35% of patients progressed with 15 months of initiating therapy.[16] Similarly, a phase II trial of patients who were refractory to or relapsed after ibrutinib therapy, showed a median PFS of 22 months.[23] Based on experience with chemoimmunotherapy, achieving CR with MRD negativity is highly beneficial both in terms of remission duration and OS. The use of combination therapy has the potential to deepen responses for this difficult to treat population and thus improve outcomes for patients for relapsed/refractory or high-risk CLL.

For additional information regarding the pharmacology, metabolism, toxicology, and pharmacokinetics, please refer to the venetoclax package insert.

2.4 Duvelisib

Another key target in CLL is phosphatidylinositol-3-kinase (PI3K). PI3K is a heterodimeric lipid kinase composed of both a regulatory and catalytic subunit, that serves as a key component of B-cell receptor (BCR) signaling, which is constituently activated in CLL.[27-29] Of the four PI3K isoforms, PI3K-δ and PI3K-γ, are preferentially expressed in normal and malignant cells of hematopoietic lineage and have distinct and complementary roles in leukocyte signaling, differentiation, activation and chemotaxis.[29,30] Inhibition of the PI3K-δ isoform with idelalisib, for example, is able to de-adhere CLL from the stroma and increase their susceptibility to apoptosis.[31,32] Idelalisib has also shown clinical activity in patients with CLL, with an ORR of 72% and a median PFS of 15.8 months, and is FDA-approved in combination with rituximab for relapsed/refractory CLL.[33]

Duvelisib, an oral, reversible and selective small molecule dual inhibitor of PI3K-δ (K_d= 23pM) and PI3K-γ (K_d=243 pM), has also emerged as a promising therapy for patients with CLL. Preclinical studies have shown that duvelisib inhibits BCR signaling, reduces chemotaxis, and inhibits cytokine mediated proliferation.[34] PI3K-γ inhibition also inhibits the tumor-promoting effects of T-cell and myeloid cells in the microenvironment, providing the potential for enhanced anti-tumor effect as compared to PI3K-δ inhibition alone.[35]

The initial phase I study for duvelisib monotherapy enrolled patients with a variety of hematologic malignancies, including those with CLL.[36,37] In 55 patients with CLL, the most common adverse events were cytopenias (neutropenia 31%, thrombocytopenia 11%), febrile neutropenia (15%), and pneumonia (11%).[38] Grade 3 ALT/AST increase occurred in 5% of patients and no grade 4 elevations were seen.[37] There were initial concerns regarding infection risk, thus prompting the addition of mandatory infection prophylaxis. This trial demonstrated a maximum tolerated dose of 75 mg twice per day, though patients with CLL responded to lower doses of 25 mg twice per day, thus this lower dose was chosen for the follow-up phase II trial.[36] Even at 25 mg, there was complete suppression of PI3K-δ (>1C_{90}) and partial inhibition of PI3K-γ (≥IC_{50}). Of patients with baseline CT scans, 83% had a >50% in adenopathy. The best ORR by IW-CLL criteria for patients with CLL was 55%. Patients with del(17p) had similar response rates.

A follow-up phase II trial, DYNAMO, included patients with follicular lymphoma (FL), small lymphocytic leukemia (SLL) and marginal zone lymphoma (MZL). The ORR in the SLL cohort was 68%. The phase III randomized trial of duvelisib vs. ofatumumab (DUO) was designed to seek regulatory approval for duvelisib. The study is currently being analyzed but top-line data reported an improvement in PFS of duvelisib as compared to ofatumumab in patients with R/R CLL, with rates of 13.3 and 9.9 months, respectively, leading to recent FDA approval in September 2018.[39]

For additional information regarding the pharmacology, metabolism, toxicology, and pharmacokinetics, please refer to the duvelisib investigator brochure.

2.5 Rationale for Duvelisib and Venetoclax Combination Therapy

As venetoclax and duvelisib target pathways fundamental to CLL biology and have distinct mechanisms of action, they offer promise as a combination therapy for the treatment of patients with CLL and RS. Preclinical data further support this combination, as duvelisib therapy has been shown to upregulate BCL-2 transcript levels and protein expression levels and enhance the ability of venetoclax to induce apoptosis in *ex vivo* human CLL cells.[35] BH3 profiling has also previously shown that inhibition of PI3K enhances the apoptotic threshold of CLL cells and sensitivity to BCL-2 inhibition.[32] As PI3K inhibition results in decreased CLL cell adhesion, it has the potential to decrease the protective effects of stromal cells and increases the CLL cells' susceptibility to apoptosis. Although duvelisib had minimal activity in aggressive non-Hodgkin lymphomas in the phase I study, there may be synergy when used in combination with venetoclax in this population.[40] In DLBCL, it has also been shown that PI3K inhibition is synergistic with venetoclax in subtypes of DLBCL.[41]

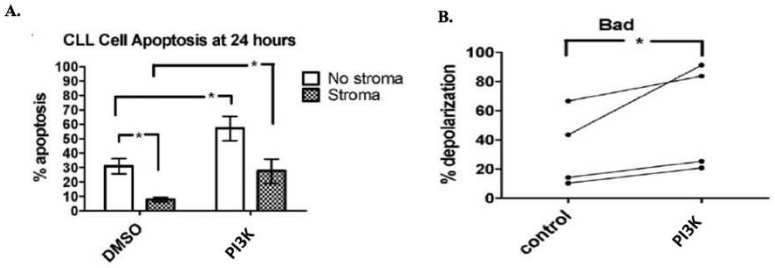


Figure 1. (A) Treatment with a PI3K inhibitor (PI3K) demonstrates an ability to kill CLL cells even in the presence of stroma. (B) PI3K inhibition increases cytochrome release in response to the Bad peptide, suggesting increased BCL-2 dependency following PI3K inhibition (Davids et al., 2012).

This trial provides the unique opportunity to combine agents with known activity in CLL with the goal of inducing higher rates of MRD-negative CR. Patients who achieve MRD negativity can discontinue therapy after a minimum of one year of treatment with close monitoring of recurrent disease, thus providing the opportunity to avoid the toxicities associated with indefinite treatment and significantly reduce costs. This strategy has already been employed in other studies. For example, in a phase II trial of venetoclax plus rituximab, 13 patients who had responded to therapy discontinued all treatment.[17] Among the 11 patients with MRD-negative CR, all remained progression free off treatment, with some patients off therapy for greater than one year.[17] Numerous ongoing trials in CLL are using MRD status as a decision point to guide treatment duration.

While duvelisib and venetoclax have distinct mechanisms of action, they have potential for significant drug-drug interactions, given their simultaneous effects on CYP3A4. We will therefore initially add venetoclax to duvelisib at a lower dose than used in the initial phase I clinical trials and monitor closely for toxicity.

2.6 Rationale for inclusion of Richter's Syndrome patients

In addition to the studies in CLL, venetoclax monotherapy has also been studied in a small number of patients with RS, where 3/7 patients (43%) achieved a partial response, including one patient who remains in remission on treatment now for over 18 months.[18] Venetoclax generally had a favorable toxicity profile in these RS patients that looked similar to its toxicity profile in CLL/SLL. Direct evidence for the efficacy of PI3K-inhibitors such as duvelisib in RS remains anecdotal. However, an interesting line of indirect evidence for the utility of the PI3Ki in RS comes from the large, randomized phase 3 trials of duvelisib and an older PI3Ki idelalisib, where a very low incidence of RS was observed (Flinn et al., Blood, 2018 and Furman et al., NEJM, 2015). It has been hypothesized that the immune-stimulating properties of PI3K inhibition may enhance anti-tumor immune surveillance, thereby eliminating early Richter's clones that may emerge on treatment. Additional prospective clinical studies of PI3Ki as a component of RS therapy are warranted, and given the known single agent activity of venetoclax in RS and the potential for synergy with duvelisib based on the preclinical data of this combination in CLL, we now plan to explore this combination in a separate exploratory cohort in this trial.

2.7 Correlative Studies Background

BH3 Profiling:

This study 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.[42] 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.[32] 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.[43] Building on these initial studies, we will incorporate BH3 profiling into this trial to determine whether *in vivo* treatment with duvelisib enhances mitochondrial priming and or BCL-2 dependency and whether this correlates with response to combination therapy with venetoclax. We will also use BH3 profiling to determine whether dependency of anti-apoptotic proteins other than BCL-2 (i.e., MCL-1 and BCL-XL) predicts resistance to therapy. In a similar fashion, we will utilize dynamic BH3 profiling to determine whether short incubations of CLL cells with duvelisib *ex vivo*, enhances mitochondrial priming or BCL-2 dependency, and if these results correlate with clinical response.[44]

Cytometry by Time of Flight (CyTOF):

Mass cytometry or cytometry by time-of-flight (CyTOF) is a technology for multiparameter single cell analysis that uses heavy metal ions as antibody labels, thus overcoming many of the limitations of fluorescence-based flow cytometry.[45] Previous studies have demonstrated that treatment of CLL with PI3K inhibitors alters immune subsets, including the percentage of regulatory T-cells, which is associated with development of toxicity.[46] As duvelisib is known to have effects on tumor-promoting effects of T-cell and myeloid cells in the microenvironment, we aim to characterize these changes and correlate our findings with both response to therapy (ORR) as well as toxicity. We will plan to use a panel of monoclonal antibodies targeting 35 markers, including 26 surface membrane and 9 intracellular markers. The Wilcoxon matched-pairs signed rank test will be used to compare percentages of T cell subsets obtained from CyTOF at various time points.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Unless otherwise specified, laboratory tests required for eligibility must be completed within 28 days prior to start of protocol therapy. Baseline tumor measurements by CT scan must be performed within approximately 4 weeks (28 days) of starting study treatment. Bone marrow biopsy within approximately 12 weeks (90 days) prior to study treatment will be acceptable if there has not been a significant change to the anti-cancer therapy given since the test was performed.

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

Inclusion:

3.1.1 Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma per IW-CLL 2008[34] 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 10^9/L)
- Massive (≥6 cm below the left costal margin), OR progressive, OR symptomatic splenomegaly
- Massive nodes (at least 10 cm longest diameter), OR 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 (also see Exclusion Criteria, Section 3.2)
- Documented constitutional symptoms, defined as 1 or more of the following disease related symptoms or signs:
  - evidence of infection
  - night sweats for more than 1 month prior to screening without evidence of infection

OR

- Biopsy proven transformation to diffuse large B cell lymphoma (DLBCL), consistent with Richter's Syndrome

3.1.2 Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy (CLL/SLL patients only)
- If Richter's Syndrome, this criterion is not applicable

3.1.3 Age greater than 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:
- Absolute neutrophil count ≥500 cells/mm^3 (0.5 x 10^9/L). Growth factor is allowed in order to achieve this
- Platelet count ≥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:
- Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x local upper limit of normal (ULN), bilirubin ≤1.5 x local ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

3.1.7 Adequate renal function as defined as:
- Serum creatinine ≤1.5 times the local upper limit of normal or creatinine clearance ≥ 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,for the duration of study participation, and for 3 months after the last dose of duvelisib. Male subjects must also refrain from donating sperm during their participation during the study and for 3 months after the last dose of duvelisib. Effective methods of contraception include:

- True abstinence: When this is in line with the preferred and usual lifestyle of the subject.
  - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal <u>are not</u> effective methods of contraception.
- Sterilization
  - Female subject or female partner of male subject: When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to starting treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been

confirmed by follow up hormone level assessment would they be eligible to begin treatment
    - Male subject or male partner of female subject: (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Hormonal methods of contraception associated with inhibition of ovulation: oral, implantable, injectable, intravaginal, or transdermal contraception

3.1.9 Negative serum human chorionic gonadotropin (hCG) pregnancy test within 7 days before first dose of study intervention if the subject is a woman of childbearing potential.

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

3.2 Exclusion Criteria

3.2.1 Previous treatment with venetoclax or duvelisib (prior venetoclax allowed for RS patients and for CLL/SLL patients if they have been off venetoclax therapy for at least one year prior to enrollment)

3.2.2 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:
    - For patients on targeted therapies, a washout of least five half-lives is required
    - Patients who experience clinical deterioration may start therapy after a shorter washout period with prior approval by the PI
    - Corticosteroid therapy (prednisone or equivalent $\leq$20 mg daily) is allowed

3.2.3 Confirmed central nervous system involvement

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

3.2.5 Administration of live or live attenuated vaccine within 6 weeks of initiation of therapy

3.2.6 Unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster (VZV) at screening

3.2.7 Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine)

3.2.8 Active malignancy other than CLL/SLL or RS requiring therapy with the exception of hormonal therapy, non-melanoma skin cancer or carcinoma in situ of the cervix, bladder cancer, or prostate cancer not requiring treatment. Subjects with previous malignancies are eligible if they have been disease-free for 2 years or more.

3.2.9 Any active systemic infection requiring IV antibiotics or uncontrolled, active infections

3.2.10 Active Human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)

- Subjects with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCV Ab] will be excluded
- Subjects with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) to be eligible, must receive prophylaxis with entecavir (or equivalent) concomitant with duvelisib treatment, and must be periodically monitored for HBV reactivation by institutional guidelines
- Investigators who believe that a positive HBcAb is false due to passive immunization from previous immunoglobulin infusion therapy should consider the risk-benefit for the patient given the potential for reactivation

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

3.2.12 Currently active gastrointestinal disease, including colitis, inflammatory bowel disease and diarrhea requiring therapy

3.2.13 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, acute coronary syndrome, stroke, or sustained ventricular arrhythmia within 6 months of first dose of study drug

3.2.14 Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk

3.2.15 Use of Coumadin for anticoagulation (other anticoagulants permitted)

3.2.16 Lactating or pregnant

3.2.17 Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A (see Appendix D) . 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 duvelisib.

3.2.18 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

3.2.19 Unable to swallow capsules or malabsorption syndrome, 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

3.2.20 History of chronic liver disease or veno-occlusive disease/sinusoidal obstruction syndrome

3.2.21 History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function

3.2.22 Active abuse of alcohol or illicit drug use

3.2.23 Known hypersensitivity to duvelisib and/or its excipients

3.2.24 History of tuberculosis treatment within the 2 years prior to initiation of therapy

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 Overall 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.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the lead site project manager. All sites should call the project manager to verify dose level and or slot availabilities.

Following registration, participants should begin protocol therapy as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall 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.

4.4 Registration Process for Other Investigative Sites

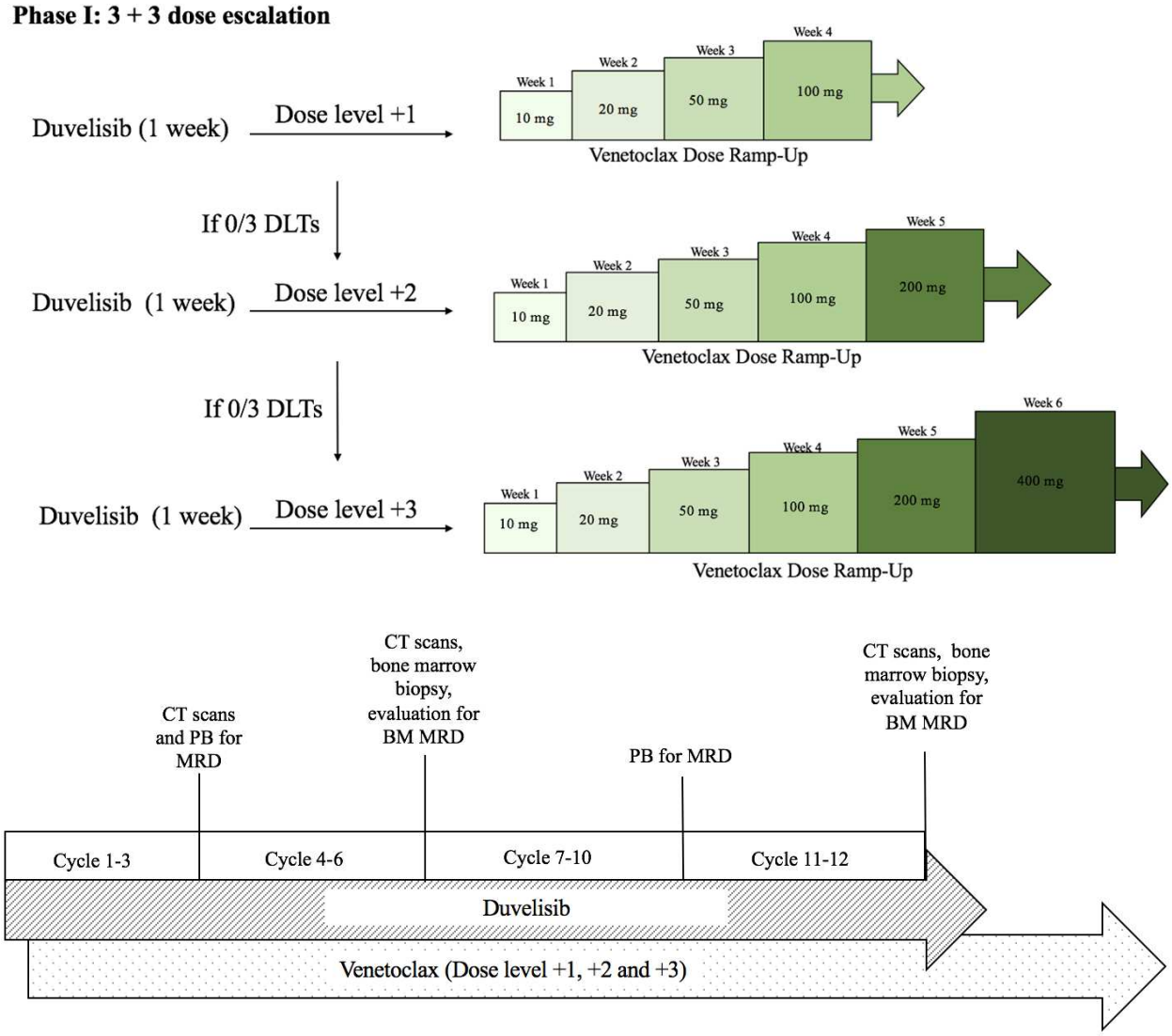
To register a participant, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the lead site project manager.

- Copy of relevant medical records that support the items on the eligibility checklist (with PMI redacted)
- Participant consent form signed by both the consenting physician investigator, and the participant
- HIPAA authorization form (if applicable)
- Completed eligibility checklist

The participating site will e-mail the lead site project manager to verify eligibility. The project manager will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The lead site project manager will email the participant study number, and if applicable the dose treatment level, to the participating site. The lead site may also contact the participating site and verbally confirm registration.

5. TREATMENT PLAN

Figure 2: Phase I dosing algorithm



In the phase I portion of the study, patients will start with 25 mg BID of duvelisib for seven days. A traditional 3 + 3 design will be used to accrue patients to one of three dose levels of venetoclax, which will start on day 8 and will be given in combination with duvelisib. The starting dose level of venetoclax will be 100 mg daily (dose level +1) with escalation to 200 mg daily (dose level +2) and to 400 mg daily (dose level +3). De-escalation to 50 mg daily (dose level -1) will be performed if unexpected toxicity is observed. Patients will be admitted for initial dosing at the initial dose and at each dose escalation of venetoclax during the dose ramp-up for close monitoring for tumor lysis syndrome (TLS).

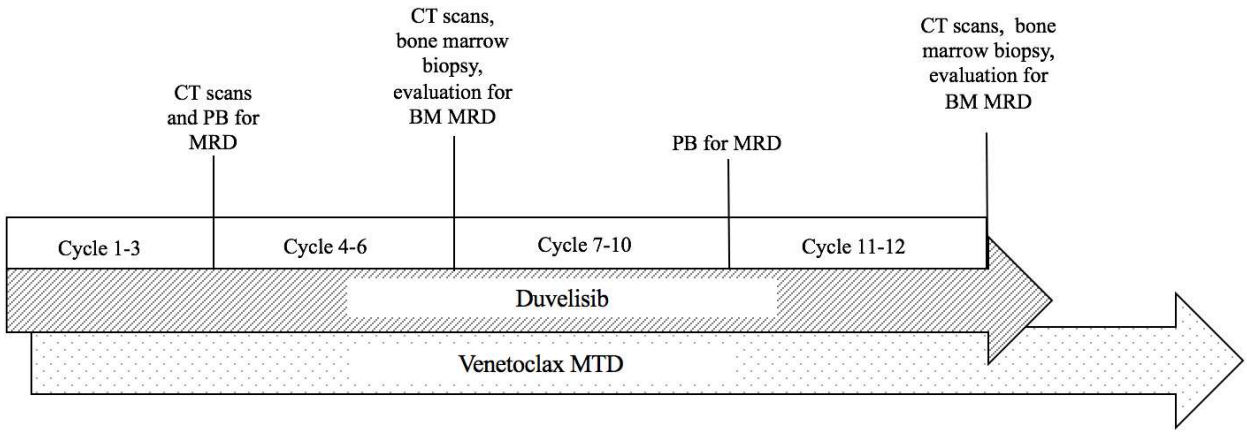
At each dose level, patients be treated with 10 mg of venetoclax for one week, followed by a weekly dose ramp-up of venetoclax as per the label, with patients in the initial dosing cohort

stopping at a lower dose of venetoclax than the approved dose of 400 mg. Patients will continue combination therapy for a total of one year, followed by venetoclax monotherapy until the time of disease progression without clinical benefit, death, unacceptable toxicity, withdrawal of consent, or physician/patient discussion of discontinuation based on objective disease response.

Once the MTD of venetoclax in combination with duvelisib is determined, 3 additional patients will be accrued at that dose level who will start with venetoclax 20 mg and have a dose ramp up identical to the other patients in that cohort. Also, patients assigned to lower dose levels in the phase I portion of the trial will have the option to escalate their venetoclax dose to the MTD.

Phase II:

Figure 3: Phase II Dosing algorithm



The phase II portion of the study will be designed in two stages. Patients will undergo a dose-ramp up venetoclax as described in the phase I trial, with the exception that since there was no evidence of TLS in patients at 10 mg during phase I, participants in phase II will have the option of starting their dose ramp up at 20 mg of venetoclax for one week, followed by a weekly dose ramp-up to 400 mg daily. Patients who wish to start at 20 mg venetoclax will be required to do so inpatient for the first 2 dose ramp-ups (at 20 mg and 50 mg) and can then do the remaining ramp-ups (i.e. to 100, 200, and 400 mg) as an outpatient.

Patients who are low- or medium risk for TLS and wish to be treated all in the outpatient setting will have to start at 10 mg and then the following week go up to 20 mg, and then complete the rest of the usual ramp-up to 50 mg, 100 mg, 200 mg, and 400 mg.

High risk patients will be hospitalized for the initial dose ramp-ups, but will have the option to start at 10 or 20 mg. If they start at 10 mg then they will need to be hospitalized for the first 3 dose ramp-ups (10 mg, 20 mg, and 50 mg), or for the first two dose ramp ups (20mg and 50mg) if they start at 20 mg.

Accelerated ramp up for RS patients:

Given the potential for rapidly progressive RS, these RS patients will also have the option to undergo an accelerated venetoclax ramp-up in the inpatient setting modeled after another study of venetoclax plus chemotherapy that was recently reported (Davids et al., ICML, 2019). In that study, venetoclax was safely ramped up in a daily fashion for 20 RS patients, who were monitored closely in the inpatient setting, with no evidence of tumor lysis syndrome. The venetoclax is dosed at 20 mg for day 1, and if no TLS is observed on labs done 6-8 hours and 24 hours later, then the dose is ramped up to 50 mg on day 2, 100 mg on day 3, 200 mg on day 4, and 400 mg on day 5 if the daily labs done 6-8 hours and 24 hours later continue to show no TLS. If laboratory TLS does occur, the next day's dose will be held until there is improvement in the TLS, at which point escalation to the next dose may occur

Study visits will occur weekly through cycles 1-2, once per cycle during cycles 3-7, every two cycles from cycle 7-13, and every 3 cycles thereafter through cycle 60. After cycle 60, patients will return for study visits every six cycles until they are removed from treatment. Patients will be treated with duvelisib plus venetoclax for up to one year followed by venetoclax monotherapy until disease progression without clinical benefit, death, unacceptable toxicity, withdrawal of consent, physician/patient discussion of discontinuation based on objective disease response, or they elect to go on a new CLL or Richter's directed therapy.
CT of the neck, abdomen, pelvis and neck (CLL) or full body PET/CT (Richter's) scans will be mandatory at C4D1, C7D1, C13D1, and then at the discretion of the treating investigator or approximately every six cycles thereafter. Bone marrow biopsy will be mandatory at study entry and at the C7D1, C13D1, and C25D1 re-staging visits. Subsequent bone marrow biopsies will be performed as clinically indicated thereafter at the discretion of the treating investigator.

Patients will be evaluated for MRD negativity in the peripheral blood approximately every three months and with each bone marrow biopsy (except the baseline biopsy).MRD testing will be performed by 4-color flow cytometry with a sensitivity of 10^{-4} and when possible also by ClonoSEQ (Adaptive), a next generation sequencing technology.

If after at least one year of treatment, a patient achieves a complete remission (CR) or complete remission with incomplete count recovery (CRi) with MRD-negativity in the marrow, they will have the option to discontinue venetoclax. Patients with a PR with MRD-negativity will have the option of discontinuing venetoclax after 24 months of treatment. Those that come off treatment for this reason will be monitored for disease recurrence with peripheral blood MRD testing by flow cytometry approximately every 3 months. Patients who have detectable recurrence (at minimum, confirmed by two successive peripheral blood MRD positive assessments) in the peripheral blood will have the option to restart venetoclax.

In the event that patients need to restart venetoclax due to disease recurrence, they will be re-staged. If they have MRD-detectable disease but no other evidence of clinical disease progression, venetoclax can be resumed at 400 mg daily in the outpatient setting with TLS monitoring 6-8 and 24 hours after the initial dose. Patients with evidence of clinical disease progression on the re-staging evaluation will be treated with a venetoclax dose ramp up as per the label, starting with 20 mg daily and escalating to 400 mg daily. Prophylaxis against and

treatment of TLS will be performed as during initial therapy. Patients who do not achieve MRD negativity or have disease progression after reaching full dose venetoclax monotherapy have the option to add duvelisib at the highest dose they had previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability. Patients who achieve maximal response and are allo transplant candidates can elect to go off study to move on to transplant.

Participants who elect to come off therapy at the time of complete response must have received at least one year of treatment on study.

Those that discontinue duvelisib during combination therapy may continue to receive venetoclax monotherapy.

5.1 Treatment Regimen

5.1.1 **Duvelisib**:

Duvelisib will be administered twice daily, with 28 consecutive days defined as a treatment cycle (up to 49 days for cycle 1), for up to a total of 12 cycles. Treatment will be administered on an outpatient basis with the exception of doses given while inpatient for venetoclax ramp up/dose escalation. Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1.2 **Venetoclax**:

Venetoclax will be administered daily, with 28 consecutive days defined as a treatment cycle (up to 42 days for cycle 1) until the time of disease progression without clinical benefit, death, unacceptable toxicity, withdrawal of consent, or physician/patient discussion of discontinuation based on objective disease response, or they elect to go on a new CLL or Richter's directed therapy. The first dose of venetoclax will be given on day 8 of cycle 1 at a starting dose of 10 mg. All patients will be admitted for administration of the initial dose of venetoclax at each dose escalation. Patients will be started on allopurinol and IV hydration for TLS prophylaxis. TLS laboratories will be checked approximately 4, 8, 12, and 24 hours post venetoclax dose. Pre-dose laboratory values will be used as baseline to assess for potential electrolyte abnormalities following venetoclax. Patients can be discharged if no evidence of laboratory TLS 24 hours after dosing, according to the Cairo-Bishop criteria for TLS. If laboratory or clinical TLS is seen, as defined by Cairo-Bishop criteria, patients will be managed as per appendix C. Patients will be admitted weekly for each dose escalation (10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg) for up to six weeks (42 days) depending on the target dose level. The same rules and TLS laboratory evaluations will be applied for each dose escalation, with the potential to escalate to 100 mg (dose level +1), 200 mg (dose level +2), and 400 mg (dose level +3).

Phase II-
Patients will undergo a dose-ramp up venetoclax as described in the phase I trial, with the exception that since there was no evidence of TLS in patients at 10 mg during phase I, participants in phase II will have the option of starting their dose ramp up at 20 mg of venetoclax for one week, followed by a weekly dose ramp-up to 400 mg daily. Patients who wish to start at 20 mg venetoclax will be required to do so inpatient for the first 2 dose ramp-ups (at 20 mg and 50 mg) and can then do the remaining ramp-ups (i.e. to 100, 200, and 400 mg) as an outpatient.

Patients who are low- or medium risk for TLS and wish to be treated all in the outpatient setting will have to start at 10 mg and then the following week go up to 20 mg, and then complete the rest of the usual ramp-up to 50 mg, 100 mg, 200 mg, and 400 mg.

High risk patients will be hospitalized for the initial dose ramp-ups, but will have the option to start at 10 or 20 mg. If they start at 10 mg then they will need to be hospitalized for the first 3 dose ramp-ups (10 mg, 20 mg, and 50 mg), or for the first two dose ramp ups (20mg and 50mg) if they start at 20 mg.

Inpatient:
When venetoclax dosing is performed as an inpatient, TLS labs must be performed STAT at least at the following time points: pre-dose (within 4 hours before venetoclax administration), and approximately 4, 8, 12, and 24 hours after the first dose of venetoclax and each subsequent dose escalation. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.

Outpatient:
When venetoclax dosing is performed as an outpatient, TLS labs should be checked pre-dose, approximately 6-8 hours after first dose and approximately 24 hours after treatment.

Accelerated ramp up for RS patients: Given the potential for rapidly progressive RS, these RS patients will also have the option to undergo an accelerated venetoclax ramp-up in the inpatient setting modeled after another study of venetoclax plus chemotherapy that was recently reported (Davids et al., ICML, 2019). In that study, venetoclax was safely ramped up in a daily fashion for 20 RS patients, who were monitored closely in the inpatient setting, with no evidence of tumor lysis syndrome. The venetoclax is dosed at 20 mg for day 1, and if no TLS is observed on labs done 6-8 hours and 24 hours later, then the dose is ramped up to 50 mg on day 2, 100 mg on day 3, 200 mg on day 4, and 400 mg on day 5 if the daily labs done 6-8 hours and 24 hours later continue to show no TLS. If laboratory TLS does occur, the next day's dose will be held until there is improvement in the TLS, at which point escalation to the next dose may occur

Subjects should take venetoclax within approximately 30 minutes after the completion of breakfast or the subject's first meal of the day. Subjects may not consume: grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or

starfruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

The participant will maintain a medication diary of each dose of medication. The medication diary should be returned to clinic staff at the end of each cycle or visit period (every 2, 3 or 6 cycles as outlined in the study calendar). If the patient has not taken their duvelisib dose within 4 hours and venetoclax dose within 8 hours of the recommended time, they will be instructed to skip their dose.

Administration of venetoclax and duvelisib may be in any order.

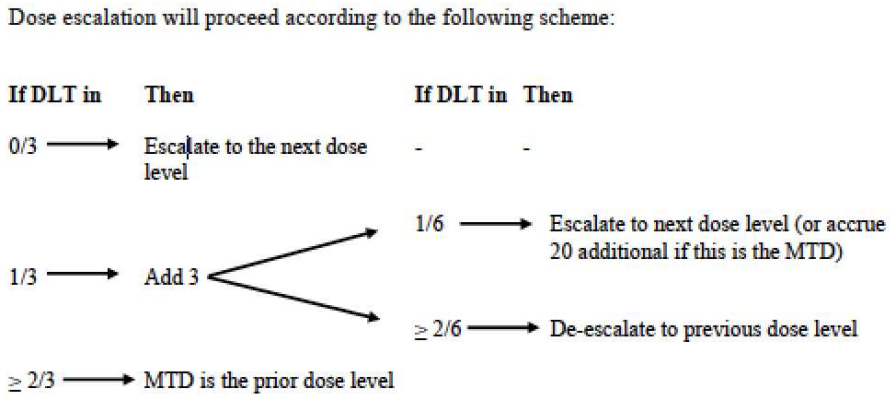
5.1.2.1 **Phase I:**

Table 1: Dose Escalation Schedule of Duvelisib and Venetoclax

Dose Escalation Schedule		
Dose Level	**Dose***	
	Duvelisib	***Venetoclax***
Level -1	25 mg BID	50 mg daily
Level +1(Starting Dose)	25 mg BID	100 mg daily
Level +2	25 mg BID	200 mg daily
Level +3	25 mg BID	400 mg daily

In the Phase I portion of the trial, we aim to determine the maximum tolerated dose (MTD) of venetoclax when given in combination with duvelisib. A standard 3+3 dose escalation design will be employed (Figure 4). Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable.

Figure 4: 3+3 dose escalation for the phase I trial:



The MTD is defined as the highest dose studied for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the NCI Common Toxicity.

Once the MTD of venetoclax in combination with duvelisib is determined, patients assigned to lower dose levels of venetoclax will have the option of escalating their venetoclax dose to the MTD.

5.1.2.2 **Phase II:**

Patients in the phase II portion of the trial will also begin duvelisib on day 1 and add venetoclax on day 8. Please refer to section **5.1.2** for full venetoclax dose ramp up instructions. Patients will continue combination therapy for up to 12 cycles followed by venetoclax monotherapy until unacceptable toxicity, patient withdrawal, disease progression without clinical benefit, physician decision, physician/patient discussion of treatment discontinuation based on objective disease response, or death. Those patients who achieve CR/CRi with undetectable MRD in the bone marrow after 1 year of combination therapy have the option to discontinue study therapy and be monitored with the option to resume venetoclax monotherapy if at least 2 peripheral blood MRD tests come back as detectable. If they do not achieve MRD negativity or have evidence of disease progression after reaching full dose venetoclax monotherapy, they have the option to add duvelisib at the highest dose they previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability.

Patients in the RS cohort will be treated similarly to those in the phase II CLL/SLL cohort with one week of duvelisib monotherapy prior to adding venetoclax. RS patients will also start with 20 mg of venetoclax with weekly ramp-up to 400 mg similar to the CLL/SLL cohort. However, given the potential for rapidly progressive RS, these RS patients will also have the option to undergo an accelerated venetoclax ramp-up modeled after another study of venetoclax plus chemotherapy that was recently reported (Davids et al., ICML, 2019). In that study, venetoclax was safely ramped up in a daily fashion for RS patients, who were monitored closely in the

inpatient setting. The venetoclax is dosed at 20 mg for day 1, and if no TLS is observed on labs done 6-8 hours and 24 hours later, then the dose is ramped up to 50 mg on day 2, 100 mg on day 3, 200 mg on day 4, and 400 mg on day 5 if the daily labs done 6-8 hours and 24 hours later continue to show no TLS. If laboratory TLS does occur, the next day's dose will be held until there is improvement in the TLS, at which point escalation to the next dose may occur. If a treating investigator wishes to do this accelerated ramp-up, written approval must be obtained from the Overall PI (or delegate) prior to initiating venetoclax therapy.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1:

Participants must meet all the inclusion criteria, have none of the exclusion criteria prior to treatment with the exception that patient's laboratory evaluations on C1D1 do not need to meet eligibility criteria again provided that they did meet criteria at screening and any changes in the patient's condition or labs do not in the opinion of the investigator pose significant risk to the patient. Participants must be registered to the protocol prior to initiating therapy.

5.2.2 Ramp-up cycles Day 1 of combination duvelisib and venetoclax therapy:

- ANC must be ≥ 500/mm^3 (growth factor support allowed), unless they have significant bone marrow involvement of CLL confirmed on pretreatment biopsy
- Platelet count must be ≥ 20K (transfusion support allowed), unless they have significant bone marrow involvement of CLL confirmed on pretreatment biopsy
- Serum creatinine must be ≤1.5 times the upper limit of normal or creatinine clearance must be ≥ 50 mL/min using a 24-hour urine collection
- All non-hematologic toxicities must have resolved to ≤ Grade 2, or to the patient's baseline condition
- No evidence of active tumor lysis syndrome

5.2.3 Combination cycles of duvelisib and venetoclax therapy and venetoclax monotherapy (maintenance) cycles

The following treatment parameters must be met at visits when a new cycle is being started:

- ANC must be ≥ 500/mm^3, unless they have significant bone marrow involvement of CLL confirmed on pretreatment biopsy (growth factor support allowed)

- Platelet count must be ≥ 20K, unless they have significant bone marrow involvement of CLL confirmed on pretreatment biopsy (transfusion support allowed)

- All non-hematologic toxicities must have resolved to ≤ Grade 2, or to the patient's baseline condition

5.3 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicity (DLT) is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. DLT refers to toxicities experienced at any time during the first cycle of study treatment, defined as the following:

- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of any duration (ANC<1.0 x 10^9/L and fever ≥38.5°F)
- Grade ≥3 thrombocytopenia with clinically significant bleeding
- Grade ≥4 infection by NCI-CTCAE criteria
- Any grade 3 or greater non-hematologic toxicity with the following exceptions:
  - Grade 3 or greater nausea/vomiting/diarrhea that persists for 7 days or less
  - Grade 3 asymptomatic laboratory abnormalities that improve to grade 2 or less within 3 days
- Any grade ≥ 3 diarrhea or vomiting or diarrhea that requires tube feeding, total parenteral nutrition, or requires or prolongs hospitalization
- Inability to receive Day 1 therapy of Cycle 2 after a delay in treatment of up to 21 days due to continued drug related toxicity from the prior cycle
- Severe cutaneous reaction (grade 3 or greater)
- Grade 4 elevation in ALT and/or AST or grade ≥ 3 elevation in ALT and/or AST occurring in the context of a Grade ≥ 2 elevation in bilirubin
- Grade 5 treatment-related adverse events

All toxicities will be considered relevant to determining DLTs and to reporting unless the event can clearly be determined to be unrelated to the study drug(s).

The DLT observation period is considered the period from the first dose of combination therapy through the completion of cycle 1. In the phase I study, if a patient comes off study due to a reason other than a DLT (e.g. disease progression) prior to the end of the DLT observation period, that patient can be replaced.

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

5.3.1 **Safety Rules and Data Safety and Monitoring Trigger for Enrollment Pause**

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. This information can also be found in Appendix E addressed in more detail.

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; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; 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

5.4 General Concomitant Medication and Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, hematopoietic growth factors, analgesics, and anti-emetics when appropriate. Local institutional standard of care may also be followed.

5.4.1 Tumor Lysis Syndrome (TLS) Prophylaxis:

Tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in patients receiving venetoclax, necessitating TLS prophylaxis. The risk of TLS is highest during initiation of venetoclax.

- All patients should be started on an oral uric acid reducer (such as allopurinol 300 mg/day) prior to initial study therapy administration (ideally at least 72 hours prior when possible) and continued until each subject has completed a week at their highest dose level of venetoclax, unless known allergy.
- Patients should remain well hydrated

The following is recommended for prophylaxis in patients being admitted for TLS observation.

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) prior to initial study therapy administration (ideally at least 72 hours prior when possible) and continued until each subject has completed a week at their highest dose level of

venetoclax. Patients with an allergy to allopurinol and thought to be at high risk for TLS, should receive a prophylactic dose of rasburicase prior to administration of venetoclax.

- IV hydration should be started the night before the first dose of 10 mg (during Phase II, before 10mg or 20mg as indicated), with a target of approximately 1.5 – 2 L/day, or as clinically appropriate, and continued for at least 24 hours after administration of venetoclax.
- Nephrology (or other acute dialysis service) consultation should be considered prior to dosing per institutional standards at the investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS.
- Telemetry should also be considered.
- Rasburicase (given at a flat dose of 6 mg IV x 1) must be administered per institutional guidelines for subjects with elevated uric acid level at baseline (> ULN) as prophylaxis prior to the initial dose of venetoclax. For subjects with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase [G6PD] deficiency), the TLS risk mitigation plan must be reviewed with the Overall PI.
- Chemistry laboratory tests must be performed STAT at least at the following time points: pre-dose (within 4 hours before venetoclax administration), and approximately 4, 8, 12, and 24 hours after the first dose of venetoclax at 10 mg and each subsequent dose escalation. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- If any laboratory changes in potassium, uric acid, phosphate, calcium, lactate dehydrogenase, or creatinine are observed within the first 24 hours after initiation of dosing, see Appendix C (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for additional laboratory assessments and management guidelines.
- Patients without evidence of TLS can be discharged 24 hours following venetoclax administration

5.4.2 Treatment of TLS:

All subjects meeting criteria of laboratory TLS or ≥ grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix B) should receive vigorous intravenous hydration, aggressive electrolyte management, and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. See Section 6, Dose Modification, for additional instructions.

5.4.3 Monitoring for skin reactions:

Patients will be closely monitored for the development of a skin rash while being treated with duvelisib. Patients will also be informed to call their provider with any evidence of rash.

5.4.4 Prophylactic Antibiotics:

Prophylaxis for Pneumocystis jiroveci pneumonia (PCP) with Bactrim or equivalent, and anti-herpetic viral prophylaxis with acyclovir or equivalent is mandated beginning with cycle one and continuing for the duration of the participant's treatment on study.

5.4.5 CMV Monitoring:

Based on data from the duvelisib phase I study in CLL, subjects taking duvelisib might be at an increased risk of cytomegalovirus (CMV) reactivation. Clinically significant CMV infection can generally be avoided by close monitoring and institution of anti-CMV therapy at time of positive viral load detection. Therefore, all subjects on study will have mandatory CMV viral measurement at study entry and monthly thereafter while on duvelisib therapy. Subjects whose CMV viral load becomes positive will be started on treatment dose valganciclovir and the CMV viral load will be checked weekly until it becomes undetectable. At that point, dosing of valganciclovir can be changed to the prophylactic dose for the remainder of the study. The subject should continue to undergo weekly CMV viral load surveillance for four consecutive negative tests and can then return to monthly testing thereafter. Alternative anti-herpetic viral prophylaxis should be stopped during valganciclovir dosing. Testing at outside laboratories will be allowed during months that the patient is not scheduled for clinic visits.

5.4.6 Medications of Food that Inhibit or Induce CYP3A4/5:

In vitro data also indicate that oxidative metabolism may play an important role in the elimination of duvelisib and venetoclax, with CYP3A4/5 identified as the primary enzymes for metabolism. As duvelisib and venetoclax are moderate inhibitors of CYP3A4/5, there is potential for drug-drug interactions and increased exposures. Preliminary data from a drug-drug interaction study with ketoconazole (a potent CYP3A4/5 inhibitor) indicate exposure to duvelisib increased approximately 4- fold in the presence of ketoconazole. For this reason, the concomitant use of drugs or foods that are strong or moderate inhibitors or inducers of CYP3A are not allowed for 7 days prior to the first dose of duvelisib. Additionally, the use of these drugs and foods are not allowed during study treatment. Appendix D provides a list of medications known to be strong or moderate inhibitors or inducers of CYP3A. Please note that Appendix D is not a comprehensive list of all medications which may modulate CYP3A4/5 activity. The Principal Investigator should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity. The concomitant use of weak inhibitors may be allowed in selected circumstances after consultation with the Principal Investigator.

5.5 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), treatment may continue until one of the following criteria applies:

- Disease progression without clinical benefit
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Physician discretion
- After at least one year of treatment, if a patient achieves a complete remission (CR) or complete remission with incomplete count recovery (CRi) with MRD-negativity in the bone marrow, they will have the option to discontinue therapy and transition to active disease monitoring with the option to restart venetoclax if they experience disease recurrence as evidenced by at least two instances of MRD-detectability or clinical disease progression. If patients do not achieve MRD negativity or have evidence of disease progression after reaching full dose venetoclax monotherapy, they have the option to add duvelisib at the highest dose they previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability
- If after 24 months of treatment (Cycle 25 restage) a patient achieves a PR with MRD negativity in the bone marrow, they will have the option to discontinue therapy and transition to active disease monitoring with the option to restart venetoclax if they experience disease recurrence as evidenced by at least two instances of MRD-detectability or clinical disease progression in the opinion of the investigator. If patients do not achieve MRD negativity or have evidence of disease progression after reaching full dose venetoclax monotherapy, they have the option to add duvelisib at the highest dose they previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability
- 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 (treatment) 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, they will remain on study in active follow up for up to one year or until withdrawal of consent, initiation of other CLL or Richter's directed therapy, or death. They will then be followed for survival indefinitely.

When a participant is off of the study completely (no longer in follow up or being followed for survival), the relevant Off-Treatment/Off-Study information will be relayed to the lead site study team, and updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, *Dr. Matthew Davids* at *617-632-3352, pager 57215.*

5.6 Duration of Follow Up and Active Disease Monitoring

Disease Monitoring:
Participants who elect to discontinue treatment after having achieved MRD negative CR or CRi (or MRD- PR after C25) will be followed every 3 months (+/- 14 days) for active disease monitoring. Subjects are allowed to alternate visits with a local team so that they only need to be seen at the trial site every 6 months. They will be monitored until they resume treatment with venetoclax (if they show signs of progression by MRD positivity or clinical manifestations) or are removed from active disease monitoring for other reasons such as withdrawal of consent, removal from monitoring by treating investigator, lost to follow up, elect to go on to other CLL/RS directed therapy, or death.

Assessments for Active Disease Monitoring:

- History and physical
- CBC differential and platelet count
- Serum Chemistry Panel including magnesium, uric acid, phosphorus and LDH
- CT or PET CT scan and response assessment as clinically indicated
    - De-identified scans must continue to be sent to the lead site to be centrally read for response
- Bone marrow biopsy and aspirate as clinically indicated and MRD sent for analysis
- MRD assessment in the peripheral blood every 3 months, or at minimum every 6 months

Follow Up:
Those who are removed from treatment for reasons <u>other</u> than MRD negativity will be followed every 3 months for up to one year (+/- 14 days). During active follow up (not those who are in active disease monitoring) participants will be offered the opportunity to have follow up visits at their treating institution every 6 months (versus every 3) to minimize travel burden if they choose, so long as they are being clinically followed by a hematologist/oncology team locally every other visit, <u>and</u> relevant clinical information is being conveyed to the lead site for follow up data entry purposes.

Assessments for those who discontinue treatment for reasons <u>other</u> than MRD negative CR/Cri or PR after C25 :

- History and physical
- CBC differential and platelet count
- Serum Chemistry Panel including magnesium, uric acid, phosphorus and LDH
- CT or PET CT scan and response assessment as clinically indicated
- Bone marrow biopsy and aspirate as clinically indicated

After the active disease monitoring and follow up periods are complete, survival follow up data will be collected indefinitely unless one of the following occurs:

- Death
- Lost to survival follow up
- Withdrawal of consent

Survival status may be collected by phone, email, or other traditional data collection methods indefinitely.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

5.7 Resuming Treatment after Discontinuation

If a patient elects to discontinue therapy and is currently in active follow up, and the participant exhibits MRD positivity at least two times in the peripheral blood or exhibits clinical disease progression in the opinion of the investigator, the participant may resume venetoclax monotherapy.

If patients do not achieve MRD negativity or has evidence of disease progression after reaching full dose venetoclax monotherapy, they have the option to add duvelisib at the highest dose they previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability.

A re-staging bone marrow evaluation (aspirate, core, FISH, cytogenetics, flow/MRD, pathology) and CT scan (or PET/CT if RS) is required prior to re-initiation of venetoclax. If there is no clinical evidence of disease and only MRD detectable disease, venetoclax can be resumed at 400 mg in the outpatient setting with TLS lab monitoring 6-8 hours and 24 hours after the initial dose. If there is clinical evidence of disease, ramp up per package insert of venetoclax to the dose the participant received during their last cycle on treatment is required. The participant will have the opportunity to increase their dose of venetoclax to the MTD if tolerated after discussion with the treating investigator. Study visit frequency will coincide with where the participant left off while they were on treatment. For example, if discontinuation occurred at the end of Cycle

37, the participant would resume a q3 month assessment schedule after the appropriate ramp up cycle

5.8 Criteria for Taking a Participant Off Study (No longer being followed for Survival).

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- The study will no longer be collecting this data, and is considered complete

Participants may be followed for survival after completing the follow up portion of the study by phone, email, or other traditional data collection methods indefinitely.
The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

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. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Duvelisib:

Participants will be monitored continuously for toxicity while on study therapy. Non-hematologic toxicity will be assessed using the NCI-CTCAE Version 5.0. Hematologic toxicity will be assessed by 2008 IW-CLL criteria (see Appendix H) for both CLL and RS patients.[47]

If a patient has an adverse event of particular severity (see Table 3) **at least possibly related to duvelisib,** then dose modifications can be made according to Table 2. There should be no attempt to make up for doses omitted due to toxicity.

Table 2: Dose levels of duvelisib

Dose Level	Duvelisib Dose
-2	25 mg every other day
-1	25 mg daily
+1	25 mg BID

All duvelisib dose reductions should be discussed with the principal investigator. Duvelisib dosing may be withheld up to 28 days for toxicity.

If dosing is withheld for >28 days for toxicities that are related to duvelisib this will result in discontinuation of duvelisib treatment on the study. In these cases, patients can continue on venetoclax monotherapy.

In cases where duvelisib has been held >28 days, duvelisib may be resumed after discussion with the overall PI in cases where toxicity is thought to be due to a cause other than duvelisib. Any participant who requires > 2 dose reductions for the same toxicity will be discontinued from active treatment on the study.

Patients who have a dose reduction due to toxicity may be eligible for a dose increase back to the dose level prior to the reduction (i.e., the starting dose or dose of previous reduction if patient was dose reduced more than one level) if the following criteria are met:

1. Patient has tolerated the lower treatment dose for 2 or more treatment cycles
2. Patient has recovered to baseline levels from the toxicity which caused the dose reduction
3. Toxicity was not drug-induced colitis or pneumonitis

Table 3: Recommended Management/Next Dose for Duvelisib

Event	Recommended Management/Next Dose for Duvelisib
≤ Grade 1 Hematologic or Non-Hematologic	Continue current dose
Grade 2 Hematologic or Non-Hematologic	Continue at current dose. If dose reduction considered, contact the principal investigator
Grade 3 Hematologic or Non-Hematologic (non-DLT)	Continue at current dose. If dose reduction considered, contact the principal investigator
Grade 3 Hematologic (DLT)	First occurrence: Withhold and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; re-initiate therapy at current dose if duration ≤ 10 days. If duration >10 days, re-initiate therapy at one dose level lower. Second occurrence: Withhold and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; re-initiate therapy at one dose level lower. Third occurrence: Discontinue patient from study drug
Grade 3 Non-hematologic (DLT)	First occurrence: Withhold until return to grade 1 or baseline level; re-initiate therapy at 25 mg daily. Second occurrence: Withhold until return to grade 1 or baseline level; re-initiate therapy at 25 mg every other day. Third occurrence: Discontinue patient from study drug Exceptions: Patients with pneumonitis and skin reactions will discontinue active treatment on protocol
Grade 4 Non-hematologic (DLT) other than asymptomatic lab abnormalities	Discontinue patient from the study
Grade 4 Hematologic (DLT or non-DLT)	First occurrence: Withhold and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; re-initiate therapy at current dose if duration ≤ 10 days. If duration >10 days, re-initiate therapy at one dose level lower.

Event	Recommended Management/Next Dose for Duvelisib
	Second occurrence: Withhold and provide growth factor or transfusion support if indicated until return to grade 2 or baseline level; re-initiate therapy at one dose level lower. Third occurrence: Discontinue patient from study drug

6.1.1 Management Guidelines for Hepatotoxicity:

For Grade 2 ALT/AST elevation (> 3 to 5 X ULN), maintain duvelisib dose and monitor at least weekly until return to < 3 X ULN. For Grade 3 ALT/AST elevation (> 5 to 20 X ULN), withhold duvelisib and monitor at least weekly until return to < 3 X ULN. Resume duvelisib at the same dose (first occurrence) or at a reduced dose for subsequent occurrences. For grade 4 ALT/AST elevation (> 20 X ULN), discontinue duvelisib.

6.1.2 Management Guidelines for Diarrhea and Colitis:

Severe and/or serious diarrhea has been observed in subjects with hematologic malignancies receiving duvelisib. In some cases, diarrhea preceded a diagnosis of colitis. For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e., up to 6 stools per day over baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents, continue duvelisib at the current dose, and monitor the patient at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold duvelisib and initiate supportive therapy with enteric acting steroids. Upon resolution of the diarrhea, consider restarting duvelisib at a reduced dose. For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or with severe diarrhea (Grade 3) (i.e., > 6 stools per day over baseline), withhold duvelisib and initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy when applicable, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart duvelisib at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue duvelisib. Discontinue duvelisib for life-threatening diarrhea or colitis.

6.1.3 Skin Rash:

For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue duvelisib at the current dose, initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids, and monitor the patient closely. Withhold duvelisib for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or antihistamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart duvelisib at a reduced dose. Discontinue duvelisib if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous

reactions, discontinue duvelisb. In patients with SJS, TEN, or DRESS of any grade, discontinue duvelisib.

6.1.4 Treatment Related Lymphocytosis:

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of duvelisib, in which inhibition of PI3K-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood. Upon initiation of duvelisib monotherapy, a rapid, but transient increase in lymphocyte count (i.e., ≥50% increase from baseline and above absolute count 5000/μL), often associated with reduction of lymphadenopathy, has been observed in the majority of patients with relapsed/refractory CLL/SLL. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered an adverse event or progressive disease in the absence of other clinical findings. Lymphocytosis occurs typically during the first few weeks of duvelisib monotherapy and resolves within a median of 6 months.

6.2 Venetoclax:

The cohort doses for venetoclax in the phase I trial after intra-patient dose ramp-up are 100 mg QD (dose level +1), 200 mg (dose level +2) and 400 mg (dose level +3). If known venetoclax toxicities such as TLS, diarrhea, or neutropenia are observed, dose reductions can occur by 50% at a time to as low as 50 mg (dose level -1).

In the phase II trial, patients will ramp up to the MTD of venetoclax determined in the phase I trial. If known venetoclax toxicities such as TLS, diarrhea, or neutropenia are observed, dose reductions can occur by 50% at a time to as low as 50 mg.

Venetoclax dosing may be withheld for up to 28 days for toxicity. Doses withheld for >28 days will result in discontinuation from venetoclax treatment on the study. In these cases, patients can continue with duvelisib monotherapy for up to 12 total cycles.

In cases where venetoclax has been held >28 days, venetoclax may be resumed after discussion with the overall PI in cases where toxicity is thought to be due to a cause other than venetoclax. Any patient who requires > 3 dose reductions for the same toxicity will be discontinued from active treatment on the study.

Table 4: Dose Levels of Venetoclax for the Phase I Trial

Dose Level	Venetoclax Dose
-1	50 mg daily
+1	100 mg daily
+2	200 mg daily
+3	400 mg daily

6.2.1 Tumor Lysis Syndrome:

If any significant laboratory changes consistent with TLS are observed within the first 24 hours after initiation of dosing, see Appendix C (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]), for additional laboratory assessments and management guidelines.

6.2.2 Management of Other Toxicities:

If a patient has an adverse event assessed as **at least possibly related to venetoclax,** then dose modifications can be made according to the recommendations in the tables below.

The following tables provide recommended guidelines for venetoclax dose reduction based on specific toxicities. Management not consistent with these guidelines should be discussed with the PI.

Table 5. Recommended Management of Non-hematologic toxicities for Venetoclax

Event	**Recommended Management/Next Dose for Venetoclax**
≤ Grade 1	Continue current dose
Grade 2	Hold until grade ≤ 1. Resume at same dose level
Grade 3	Hold until grade ≤ 1 or baseline. Resume at one dose level lower if indicated
Grade 4 (other than asymptomatic lab abnormalities)	Discontinue active treatment on protocol

Table 6: Recommended Management of Diarrhea for Venetoclax

Event	**Recommended Management**
Diarrhea	Loperamide: Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Table 7: Recommended Management of Thrombocytopenia for Venetoclax

Event	**Recommended Management/Next Dose for Venetoclax**
Thrombocytopenia	
Grade 1, 2 or 3	No change in dose
Grade 4	Hold until ≤ Grade 3. First occurrence: Resume venetoclax at the same dose.

	Second occurrence: If occurs within 28 days, the venetoclax dose should be reduced by 50%. Third occurrence: If occurs within 28 days, the venetoclax dose should be reduced by 50%. Fourth occurrence: Discontinue patient from study drug

Table 8: Recommended Management of Neutropenia for Venetoclax

Event	**Recommended Management/Next Dose for Venetoclax**
Neutropenia	
Grade 1 or 2	No change in dose
Grade 3	Hold until ≤ Grade 2. If previously growth factor responsive administer growth factor and resume dosing as long as growth factor is administered. If not previously growth factor responsive, resume at one dose level lower, if indicated.
Grade 4	Hold until ≤ Grade 2. If previously growth factor responsive administer growth factor and resume dosing at current dose once ≤ Grade 3. If not previously growth factor responsive, resume at one dose level lower, if indicated.
At any time during the study, if the subject presents with febrile neutropenia, venetoclax dosing should be interrupted until resolution of the fever or infection. At the first occurrence, venetoclax may be re-initiated at the same dose. At a second or later occurrence, consideration should be given to venetoclax dose reduction.	
Growth factor support with filgrastim or pegfilgrastim may be utilized as necessary throughout the study and does not require holding venetoclax.	

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following list of reported and/or potential adverse events (AEs) and the characteristics of an observed AE will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Definitions:

7.1.1 Adverse Event:

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

These include the following:

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

7.1.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scale found in the revised NCI Common Terminology Criteria for Adverse Events CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- 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.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the subheading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **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.

7.2 Serious Adverse Event:

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

- Results in death (i.e., the AE actually causes or leads to death)
- Is life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to duvelisib plus venetoclax
- Important medical events that may not result in death, are not immediately life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Overdose of either drug involved in the clinical trial

7.3 Adverse Event List for Venetoclax:

In the phase I trial of venetoclax for patients with relapsed/refractory CLL, the most common AEs with were grade 1 and 2 and included diarrhea (52%), upper respiratory tract infection (48%), nausea (47%), fatigue (40%), and cough (30%). Neutropenia was the most common grade 3 or 4 AE, occurring in 41% of patients. Serious adverse events included febrile neutropenia (6%), pneumonia (4%), upper respiratory tract infection (3%) and immune thrombocytopenia (3%). Dose limiting toxicities were rare and included TLS, muscle spasms, neutropenia, thrombocytopenia and vomiting.[16,48]

7.3.1 Common AEs Associated with Venetoclax

7.3.1.1 *Tumor Lysis Syndrome (TLS)*

TLS, including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL patients with high tumor burden when treated with venetoclax. Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 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 further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Blood chemistries must be monitored closely and abnormalities must be managed promptly. Dosing can be interrupted if needed and more intensive measures (intravenous hydration, frequent monitoring, hospitalization) can be employed as overall risk increases. Concomitant use of venetoclax with strong or moderate CYP3A inhibitors and P-gp inhibitors increases venetoclax exposure and may increase the risk of TLS.

7.3.1.2 *Neutropenia*

Neutropenia is an important identified risk for venetoclax, specifically in CLL. Clinical data from oncology studies suggest that neutropenia was observed among subjects who received venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in the protocol. Granulocyte colony stimulating factors can be used concomitantly with venetoclax for supportive measures.

7.3.1.3 *Infections*

Infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies and are similar across all indications. Infections are closely monitored in the venetoclax program across all indications. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (e.g., National Comprehensive Cancer Network guidelines [NCCN] for oncology subjects). In CLL patients, serious infections are potential risks. Upper respiratory tract infections are very common while pneumonia and urinary tract infections are commonly reported. **Additional guidance for the investigator regarding venetoclax use:**

On the basis of nonclinical data and previous experience with BCL-2 inhibitors, as well as the available preliminary data in the venetoclax clinical oncology program, the following guidance is provided for the investigator.

7.3.1.4 *Contraindications*

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated (Appendix D).

7.3.1.5 *Reproductive System Effects*
Based on nonclinical studies, there is a potential for decreased spermatogenesis. Non-reversible depletion of testicular germ cells has been observed in dogs at all doses tested after 4 weeks of dosing. In the oncology studies, male subjects should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

7.3.1.6 *Treatment-Emergent Malignancies (Second Primary Malignancies)*
Events of second primary malignancies have been reported across the oncology program. No pattern has been observed.

7.3.1.7 *Food Effect*
Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal.

7.3.2 **Special Patient Populations**

7.3.2.1 *Pregnancy*
Although no potential risks have been identified in nonclinical studies, the effect of BCL-2 inhibition on pregnancy has not been fully characterized. Venetoclax resulted in increased post implantation loss and decreased fetal body weights were observed in the mouse embryofetal development study at the highest dosage administered. Venetoclax was not teratogenic, and there were no other effects on development or fertility. Two pregnancies have been reported in the program, including 1 pregnancy of a partner. Venetoclax should not be administered to pregnant women. Female subjects enrolled in clinical studies with single agent venetoclax must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test. Female subjects enrolled in clinical studies with venetoclax must agree to use contraception from initial study drug administration until 30 days after the last dose of study drug. Venetoclax must be discontinued if a female subject becomes pregnant. Male subjects enrolled in clinical studies with single agent venetoclax must agree to use contraception from initial study drug administration until 30 days after the last dose of study drug. For clinical studies with venetoclax in combination with other agents, use of contraception may be longer.

7.3.2.2 *Nursing Mothers*
It is not known whether venetoclax is excreted in human milk. Hence, until further data become available, venetoclax should not be administered to nursing mothers.

7.3.2.3 *Children*
Safety and effectiveness in pediatric patients under 18 years of age have not been established; therefore, venetoclax should not be administered to this patient population.

7.3.2.4 *Geriatric Patients*
Venetoclax has been administered to elderly subjects (> 65 years) across the oncology program. The available data do not demonstrate any additional safety concerns when administrating venetoclax in the elderly population.

7.3.3 **Concomitant Use with Other Medications and Overdose**
Venetoclax should not be used with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) at initiation and during ramp-up phase. Venetoclax dose should be reduced by at least 50% in the presence of moderate CYP3A4 inhibitors if concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil) cannot be avoided. These patients also require close monitoring for venetoclax toxicities. Strong CYP3A inducers (i.e.., carbamazepine, phenytoin, rifampin, St. John's wort), or moderate CYP3A inducers (i.e., bosentan, efavirenz, etavirine) should be avoided.

Venetoclax should be administered using caution with weak inhibitors or inducers of CYP3A, substrates or inhibitors of P-gp, BCRP, or OATP1B1/B3. If venetoclax is co-administered with warfarin, the international normalized ratio (INR) should be monitored closely. A list of common medications that should either not be used or should be used with caution with venetoclax can be found in Appendix D.
Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following the last dose of study treatment.

7.3.3.1 *Overdose*
Dosing with venetoclax may vary with indication, with the maximum evaluated dose for venetoclax being 1200 mg. Please refer to the protocol for the maximum dose that may be allowed. In the event of an adverse event of overdose, appropriate supportive treatment should be initiated according to the subject's clinical signs and symptoms. A detailed discussion of venetoclax toxicology, metabolism, pharmacology and safety can be found in the Investigator's Brochure.

7.4 Adverse Event List for Duvelisib:

In the phase I trial of duvelisib for the treatment of relapsed/refractory (R/R) CLL/SLL, all 55 subjects experienced a treatment emergent adverse event (TEAE). The most frequently occurring TEAEs in R/R CLL/SLL subjects were: diarrhea (47.3%); fatigue (38.2%); neutropenia and cough (each 36.4%); anemia and pyrexia (each 32.7%); upper respiratory tract infection (29.1%); AST increased (27.3%); pneumonia, ALT increased, nausea, decreased appetite, neutrophil count decreased, and arthralgia (each 25.5%); and dyspnea (23.6%).

Treatment-emergent serious adverse events (TESAEs) occurred in 36 (65.5%) R/R CLL/SLL subjects. TESAEs occurring in 2 or more subjects with R/R CLL/SLL were: pneumonia and febrile neutropenia (each 16.4%); disease progression and pneumonitis (each 7.3%); fatigue,

colitis, and diarrhea (each 5.5%); and pyrexia, constipation, stomatitis, pneumonia pseudomonas aeruginosa, sepsis, and hypercalcemia (each 3.6%).

As of 19 July 2017, 98 patients with CLL/SLL have enrolled in the IPI-145-12 study, an open-label phase 3 extension study for subjects who experienced disease progression in the phase 3 trial comparing duvelisib to ofatumumab. Of these, 89 subjects have received duvelisib 25 mg BID. For the subjects who have received duvelisib, the median exposure is 31.0 weeks (range 2.0 to 126.7 weeks).

Of 85 of 89 (95.5%) subjects who received duvelisib had a treatment emergent adverse event (TEAE); of these,70 subjects (78.7%) experienced a TEAE assessed as related to duvelisib. TEAEs that occurred in ≥10% subjects included diarrhea (38.2%); neutropenia (24.7%); pyrexia (22.5%); rash (21.3%); colitis, vomiting, asthenia, pneumonia, and cough (each 11.2%); and nausea and decreased appetite (each 10.1%). TEAEs assessed as related to duvelisib that occurred in ≥ 10% subjects included diarrhea (32.6%), neutropenia (16.9%), and rash (14.6%).

Seventy-two subjects (80.9%) experienced at least 1 TEAE Grade 3 or higher, of which 30 (46.2%) were assessed as related to duvelisib. Grade 3 or higher TEAE that occurred in ≥5% of subjects were neutropenia (22.5%), diarrhea (16.9%), pneumonia, (10.1%), colitis (9.0%), lipase increased (6.7%), and thrombocytopenia (5.0%). The only grade 3 or higher TEAEs assessed as related to duvelisib that occurred in ≥5% of subjects were diarrhea (15.7%), neutropenia (13.5%), colitis (9.0%), and lipase increased (6.7%).

7.4.1 **Additional guidance for the investigator regarding duvelisib use:**

7.4.1.1 *Reproductive effects:*

Based on embryo-fetal toxicity observed in preliminary studies in rats and rabbits, duvelisib may have effects on the embryo or fetus when administered to pregnant women. There are no available human data informing the drug-associated risk. In a preliminary rat developmental toxicity study, a decrease in fetal body weight in the absence of maternal toxicity was observed at a free exposure 43-fold greater than the free exposure at the intended commercial dose of 25 mg BID. Higher exposures in rats and rabbits resulted in embryotoxicity (early resorption) in the presence of maternal toxicity. Duvelisib was not teratogenic and did not cause adverse developmental effects in pivotal studies at free exposures in the rabbit and rat that were 30- to 40-fold greater than the free exposure at the intended commercial dose. Please refer to individual protocols for specific instructions regarding eligibility and additional contraindications, contraception, and pregnancy reporting. Testicular degeneration/atrophy was present in male rats in the 28-day and 13-week studies, with evidence of reversibility (13-week study). Sexual immaturity of animals in the monkey studies precluded the interpretation of any potential toxicological effects in the testes. There are no clinical data assessing the effect of duvelisib on spermatogenesis. Based on the effects observed in rats, duvelisib may impair fertility in men. The exposure margin identified between the intended commercial dose of 25 mg BID and the plasma exposure at which this finding was considered adverse (50 mg/kg/day, 28-day study) was

21-fold when duvelisib protein binding differences between human and rat are taken into account.

7.4.1.2 *Effect of food:*
In 2 studies in healthy subjects (the first study using the clinical trial formulation and the second using the market-image formulation), concomitant administration of a high fat meal resulted in a minimal change in the bioavailability of duvelisib. On average, C_{max} decreased by 10% in the first study and 37% in the second; median t_{max} was slightly delayed from 1 hour (fasted) to 3 hours (fed) in the first study and 4 hours (fed) in the second. However, overall exposure, as assessed by $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$, increased by 8%-9% in the first study and decreased 2%-6% in the second study. These data indicate that duvelisib may be administered without regard to meals. Please refer to individual study protocols for specific instructions related to fasting or fed status in relation to collection of PK or other clinical samples.

7.4.1.3 *Concomitant use with other agents:*
CYP3A4 has been identified as the primary contributor to the metabolism of duvelisib. In Study IPI-145-01, exposure to duvelisib increased approximately 4-fold in the presence of the strong CYP3A inhibitor ketoconazole, and decreased approximately 80% in the presence of rifampin, a CYP3A inducer. For these reasons, the concomitant use of drugs or foods that are strong inhibitors or inducers of CYP3A is not allowed during treatment with duvelisib.
In vitro studies in human liver microsomes demonstrated that duvelisib and its primary metabolite IPI-656 are reversible inhibitors of CYP3A4 and CYP2C8 and mechanism-based inhibitors of CYP3A4.

Coadministration of duvelisib (25 mg BID for 5 days) with MDZ (a sensitive CYP3A substrate) resulted in an approximate 4-fold increase in MDZ systemic exposure (AUC) compared to administration of MDZ alone. Systemic exposure to other medications that are substrates for CYP3A4 may be increased in subjects receiving duvelisib. Caution should be used if duvelisib is administered concomitantly with drugs that are substrates for CYP3A, particularly those with a narrow therapeutic range. Drugs that are substrates for CYP3A should be used only if medically necessary and therapeutic alternatives are not available.

Based on plasma concentrations following administration of 25 mg BID, duvelisib is not expected to increase the exposure of medications metabolized via CYP2C8; however, a clinical study with a CYP2C8 substrate has not been conducted. Medications that are metabolized via CYP2C8 may be used as medically indicated but with caution.

7.5 Expedited Adverse Event Reporting

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

If the participant goes on to another SLL/CLL or RS directed therapy before the 30-day period, the reporting period ends when they begin new treatment.

7.5.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

External (Non-DF/HCC) sites will send their report to the lead site project manager and Overall PI for review and submission to the appropriate entities according to DFCI IRB policies and procedures in reporting adverse events.

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.
- **CTCAE Grade 4 Events –** Report all events that are *Unexpected*. Events that are *Expected* and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB.
    - Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.
- **ALL CTCAE Grade 5 Events.**

When assessing expectedness, investigators should consult the investigator's brochure, package insert, and the most current version of the informed consent form.

7.5.3 External Site Adverse Event Reporting Guidelines

In addition to following the SAE reporting requirements for DFCI and Secura Bio, other participating investigative sites will report SAEs to their respective IRB per the local IRB's policies and procedures.

For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution must abide by the reporting requirements set by the DF/HCC. Criteria for reporting to DFCI listed in section 7.5.3. The lead site will report external site SAEs to the DFCI IRB on the external site's behalf after review and approval by the overall PI.

This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected 4 toxicities and grade 5 (death) regardless of study phase or attribution.

7.6 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI 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.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.8 Expedited Reporting to Hospital Risk Management

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

8. PHARMACEUTICAL INFORMATION

8.1 Duvelisib

8.1.1 Description

Duvelisib is a potent oral inhibitor of the delta- and gamma-isoforms of PI3K. Duvelisib is rapidly absorbed following oral administration, with maximal concentrations occurring approximately 0.5 to 2 hours after dosing. Exposure (AUC) increased proportionally with doses through 75 mg PO BID. The half-life was 7 hours, regardless of dose. The mean pre-dose steady state plasma concentration following 25 mg BID was 425 ng/mL, indicating suppression of PI3K-delta (IC90=361 ng/mL) and PI3K-gamma (IC_{50}=429 ng/mL) throughout the dosing interval. Pharmacodynamic studies confirmed rapid, profound and sustained inhibition of AKT phosphorylation by duvelisib in CLL cells, as well as decreased levels of chemokines such as CCL3 and CCL4, which are important for

lymphocyte trafficking. The MTD of duvelisib as monotherapy for CLL has been determined to be 75 mg BID, but the recommended phase 2 dose is 25 mg bid, which was chosen as the optimal balance of safety and efficacy.

8.1.2 **Form:**

Duvelisib is supplied as 25 mg (size 2 white hard) gelatin capsules for oral delivery. Patients in this study will receive 25 mg BID as initial dosing.

8.1.3 **Storage and Stability**

Duvelisib must be stored at room temperature (15 to 30°C) and protected from light.

If a temperature excursion is experienced at any investigational site/institution beyond the stated storage parameters, the site must report the excursion and associated details to the lead site project manager as soon as the excursion is identified.

8.1.4 **Compatibility**

NA

8.1.5 **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.

Caution is required when handling duvelisib. Pharmacists should follow standard procedure for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, provide treatment as necessary for physical exposure (skin washing) or inhalation (move to fresh air) and seek medical advice as necessary.

When duvelisib capsules are distributed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash their hands thoroughly. If someone who is not enrolled in a clinical trial involving duvelisib swallows a capsule or inhales drug powder from a broken capsule of duvelisib, they should contact the relevant Principal Investigator to determine whether safety monitoring is necessary. Capsules should always be stored in the container provided to the study subject.

8.1.6 **Availability**

Duvelisib is an investigational agent and will be supplied by Secura Bio, Inc.

8.1.7 **Preparation**

Duvelisib will be supplied to the clinical trial site as open-label medication. Capsules are packaged in thermoform blister cards with peel and push child-resistant lidding. The label attached to each blister card will include, at a minimum, a statement limiting its use for investigational study only.

8.1.8 **Administration**

Duvelisib is administered orally as a capsule formulation as a fixed dose in mg and should be administered using the minimal number of capsules necessary.

8.1.9 **Ordering**

The DF/HCC pharmacy will order duvelisib from an investigational stock directly from Secura Bio, Inc. who will be providing the study drug.

External (Non-DF/HCC) investigative sites will be provided with a study specific drug order form by the lead site project manager once all necessary documents are collected, and the site is otherwise approved to enroll participants on the study.

The drug will be provided at no cost to the participant.

If necessary, the drug may be shipped to the participant's home from the investigative site pharmacy without specific approval from the overall PI. The shipment must be sent via traceable carrier, and confirmation of receipt must be filed in the participant's study file

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of duvelisib using a drug accountability form that is compliant with local and federal guidelines.

Additionally, a designated study team member will complete drug accountability/reconciliation based on the participant actual drug return versus the anticipated drug return and document the findings according to local and federal regulations and guidance.

8.1.11 **Destruction and Return**

After full drug accountability and reconciliation, all unused duvelisib will be destroyed according to local site procedures and policies. Destruction will be documented in the Drug Accountability Record Form. If any study drug is lost or damaged, the disposition

of the study drug should be documented. Patients should be instructed to bring all unused duvelisib to each study visit. The study site should count all capsules that the patient returns, and should take account for missed doses, doses reduced due to missing or lost capsules, etc., before dispensing new study drug to the patient. Any patient who does not take the prescribed dose should be requested to return the remaining drug to the clinical trial site for accountability.

8.2 Venetoclax

8.2.1 **Description:**

Venetoclax (ABT-199/GDC-0199) is a novel, orally bioavailable, small-molecule BCL-2 family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity (Ki < 0.010 nM) to antiapoptotic protein BCL-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like BCL-XL and BCL-w (> 4,800-fold and > 24,500-fold lower affinity than to Bcl-2, respectively).

In vitro studies have shown that venetoclax was metabolized primarily by CYP3A4/5. Interaction of venetoclax with co-administered CYP3A inhibitors or inducers may cause an increase or decrease in the exposure of venetoclax. In vivo, venetoclax was also demonstrated to be metabolized by CYP3A4/5. Venetoclax is also substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. Renal contribution to the elimination of venetoclax is negligible, with < 0.1% of the dose being recovered in urine. Based on in vitro results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (IC50 > 30 μM); and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7. Following co-administration of a single dose of venetoclax with warfarin, R- and S-warfarin Cmax and AUC∞ increased by approximately 18% to 28%. Relatively low variability was observed in warfarin PK.

The venetoclax formulation currently used in clinical studies is a tablet formulation with strengths of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of venetoclax by 3- to 4-fold. Preliminary pharmacokinetic results indicated that the absorption of venetoclax after the oral dosing was relatively slow. Venetoclax plasma concentrations peaked at approximately 5 to 8 hours after dosing. Mean harmonic terminal phase half-life from 17 to 41 hours and the mean oral clearance was approximately 13 L/hr after a single dose. Preliminary data did not suggest apparent pharmacokinetics differences among subjects with CLL/SLL, NHL, Multiple Myeloma (MM), Acute Myeloid Leukemia (AML), or SLE. The combined data from subjects with CLL/SLL and NHL suggested that venetoclax exposure was approximately dose proportional across the 150 to 800 mg dose levels at steady state. Additional information about venetoclax is available in the package insert.

8.2.2 **Form:**

Venetoclax tablets are film coated and are available in strengths of 10 mg, 50 mg, or 100 mg. Venetoclax will be packaged in high density polyethylene (HDPE) plastic bottles. Each bottle will be labeled per local regulatory requirements. Labels must remain affixed to the bottle.

8.2.3 **Storage and Compatibility:**

Venetoclax must be stored at 15° to 25°C (59° to 77°F) per package insert

Compatibility:

N/A

8.2.4 **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 agent in a self-contained and protective environment.

8.2.5 **Availability:**

Patients are required to have access to a commercial supply of venetoclax.

8.2.6 **Preparation**

N/A

8.2.7 **Administration:**

Oral. Patients should take venetoclax tablets with a meal and water at approximately the same time each day, preferably about 30 minutes after breakfast. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

8.2.8 **Ordering**

Supplies of venetoclax will be procured through the participant's insurance via commercial supply through an appropriate specialty pharmacy.

8.2.9 **Accountability:**

Venetoclax is commercially sourced therefore, no drug accountability records are required.

8.2.10 **Destruction and Return:**

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

While the goal of the correlative studies is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to either practical reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc). Therefore, depending on the results obtained during the study, sample collection/analysis may be omitted at the discretion of the PI.

Samples collected on this study may be used for future research studies, including genetic research. Samples may also become part of a biobank, a biorepository that accepts, processes, stores and distributes biospecimens and associated data for use in research and clinical care.

9.1 BH3 Profiling:

BH3 profiling is a functional assay that detects the proximity of cells to the threshold of apoptosis (i.e. priming) through interrogation of BCL-2 family members. To perform a BH3 profile, we add individual peptides, which bind to the BH3-only region of anti-apoptotic proteins, to gently permeabilized malignant cells. We then use Fluorescence-activated cell sorting (FACS) to measure the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release. Previous trials at our institution have suggested that this technique may be useful as an effective predictor of response in CLL.[43]

We hypothesize that patients whose cells undergo significant depolarization to the BIM BH3 peptide (primed) will have superior clinical response to duvelisib plus venetoclax as compared to patients whose cells undergo minimal BIM BH3 depolarization (unprimed). These assessments will be made on circulating CLL cells from the peripheral blood drawn from patients at baseline and after three and six months of combination therapy.

If we have bone marrow aspirates available, we will also perform BH3 profiling to see whether the level of priming in CLL cells from these tissues is a better predictor of response than peripheral blood CLL cells.

After 1 week of duvelisib monotherapy on cycle 1 day 8 (prior to receiving venetoclax), we will obtain another peripheral blood sample. We will compare the BH3 profile of this steady-state sample to a baseline sample, which will allow us to assess the short term change in apoptotic priming induced by in vivo duvelisib as a single agent.

Lastly, peripheral blood will be collected from subjects at the time of disease progression, and the BH3 profile of these samples will be compared to subjects' baseline. By measuring the cytochrome c loss in response to other BH3 peptides, such as BAD, MS-1 and HRK, it will be possible to determine whether dependencies on anti-apoptotic proteins other than BCL-2 predicts

resistance to therapy. We can also determine whether BCL-2 dependency predicts response to therapy or risk of tumor lysis syndrome.

We will simultaneously perform dynamic BH3 profiling, in which CLL cells will be treated with duvelisib *ex-vivo*, prior to traditional BH3 profiling. This will also allow us to see the change in mitochondrial priming as well as changes in anti-apoptotic dependencies following treatment with duvelisib.

All peripheral blood samples will promptly be delivered to the laboratory of Dr. Jennifer Brown, where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be batched and later transported to the laboratory of Dr. Matthew Davids, where the BH3 profiling assays will be performed.

CLL Center, J. Brown lab
Dana Farber Cancer Institute
1 Jimmy Fund Way SM 648
Boston, 02115

M. Davids Lab
Dana Farber Cancer Institute
440 Brookline Ave
Mayer-540
Boston, 02215

9.2 Cytometry by Time of Flight (CyTOF):

We will obtain samples prior to therapy, after one week of duvelisib monotherapy (cycle 1, day 8) and after three and six months of combination therapy. We will plan to use a panel of monoclonal antibodies targeting 35 markers, including 26 surface membrane and 9 intracellular markers. The Wilcoxon matched-pairs signed rank test will be used to compare percentages of T-cell subsets, NK cells, and monocytes obtained from CyTOF at various time points. As duvelisib is known alter the tumor-promoting effects of T-cell and myeloid cells in the microenvironment, we aim to characterize these changes and correlate our findings with both response to therapy (ORR), complete response (CR) rate as well as toxicity. In particular we will assess how changes in the ratio of regulatory to conventional T cells correlates with immune-mediated toxicities, as has been observed with other PI3K inhibitors.[46]

9.3 Minimal Residual Disease (MRD):

All participants will be assessed for minimal residual disease (MRD) on both blood and bone marrow throughout the course of the study. Such patients who have fewer than 0.01% (10^{-4}) CLL cell percentage of leukocytes in the bone marrow, as assessed by four-color flow cytometry will be considered to be MRD negative.

9.3.1 **Adaptive Sequencing Studies**

Depending on sample and funding availability, additional testing may also be performed at Adaptive Biotechnologies in Seattle, WA for MRD testing by their NGS platform known as ClonoSEQ. 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

9.3.2 **Mayo Clinic Minimal Residual Disease/ Flow Cytometry**

Bone marrow and blood samples will be collected for minimal residual disease analysis by Mayo Clinic Genetics by flow cytometry as part of standard of care required disease monitoring per the study calendar in section 10, and also in Table 9.

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.

Source	Collection Container	Catalog ID	Shipment Conditions*
Blood	1 x 6 ml Lavender Tube	CLLMV	Ambient

Bone Marrow Aspirate	1 x 6 ml Lavender Tube	CLLMV	Ambient

* Sent same day, first overnight

9.4 Exome sequencing of tumor cells

Whole-exome capture libraries will be constructed from 100ng of tumor and normal DNA followed by shearing, end repair, phosphorylation and ligation to barcoded sequencing adapters. The DNA will be size-selected to exonic hybrid capture using SureSelect v2 Exome bait (Agilent, CA). Samples will be multiplexed and sequenced on Illumina HiSeq flowcells with the goal of an average depth of coverage of 100x. The resulting data will be analyzed with the current Illumina pipeline, which generates data files (BAM files). The details of the current analysis pipeline are published elsewhere. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm. Indels and translocations are determined by the algorithms IndelLocator and dRanger, respectively. The MutSig algorithm identifies genes in which the observed mutations are inconsistent with what would be expected at random. To accurately assess the significance of mutations, MutSig takes into account several covariates, which influence the background mutation model. These include the expression level of genes (for which published gene expression data of MM samples can be used), and other gene characteristics observed empirically to co-vary with mutation rate: local relative replication time, and open vs. closed chromatin status. Focal as well as arm-level copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm.

The DNA library will be prepared at the Brown Lab, and then sequencing will be done at the following external lab:
Broad Institute Genomics Services
320 Charles Street
Cambridge, MA 02141

Sequencing data will then be provided back to Brown and Davids Lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

9.4.1 RNA sequencing of tumor cells

For RNA Sequencing, poly-A selection and cDNA synthesis will be performed, followed by library preparation, sequencing (76bp or 101bp paired reads), and sample identification with quality control. We will perform library construction using a non-strand specific Illumina TruSeq Protocol and sequence coverage to 100M total reads. Analysis will be performed as described in the preliminary data and in previous studies.

The RNA library will be prepared at the Brown Lab, and then sequencing will be done at the following external lab:

Broad Institute Genomics Services
320 Charles Street
Cambridge, MA 02141

Sequencing data will then be provided back to Brown and Davids lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned

9.5 Pharmacokinetic (PK) Testing (Phase I) :

In the phase I study, PK testing for duvelisib will be performed at baseline, 0.5, 1, 2, 4, 6, 8, 10, , and 24 hours following the initial dose of duvelisib on Day 1. PK testing will be performed at baseline, 0.5, 1, 2, 4, 6, 8, 10, and 24 hours following the initial venetoclax dosing on Day 8 to analyze both duvelisib and venetoclax PK. The 10-hour post dose PK is strongly encouraged, but optional. PK analysis for both drugs will be performed at pre-dose, 1 and 4 hours in subsequent weeks to assess steady-state levels prior to cycle 2 at each venetoclax dose escalation.

	Cycle 1 Day 1 (duvelisib)	Cycle 1 Day 8 (duvelisib + venetoclax)	Cycle 1 On days of venetoclax dose escalation
Pre-dose (-2 hrs)	X	X	X
0.5h post dose (± 5 mins)	X	X	
1h post dose (± 5 mins)	X	X	X
2h post dose (± 5 mins)	X	X	
4h post dose (± 15 mins)	X	X	X
6h post dose (± 15 mins)	X	X	
8h post dose (± 15 mins)	X	X	
10h post dose (± 15 mins) (optional)	X	X	
24h post dose (± 15 mins)	X	X	

Blood will be collected in vacutainers (4.0 ml BD Vacutainer® K2 EDTA Purple Top) at above mentioned time points and centrifuged (within 30 minutes) at a standard speed and time in a refrigerated centrifuge to process the plasma. The processed plasma will be divided and transferred into two cryotubes (primary and secondary; 2X1.8 mL white cryotubes) using transfer pipette. The cryotubes will be stored at -80°C freezer until shipment to bioanalytical laboratory.

Duvelisib and Venetoclax PK analyses will be performed at:
inVentiv Health
2500 Einstein Street,
Quebec, Quebec, G1P 0A2
CANADA

9.6 Jennifer Brown Lab Sample Collection and Shipping Instructions

9.6.1 **DF/HCC Local Samples:** DFCI patient samples will be hand-delivered to the Brown lab. Other DF/HCC sites may send samples via preferred courier service, or hand delivery to the lab.

9.6.2 **External Investigative Site Sample Preparation and Shipment:**

Once fresh samples (blood and bone marrow aspirate) are collected, the vacutainers will be refrigerated and stored per instructions below. There is no required processing for any of the samples by the participating site prior to shipment.

1. Package tubes at room temperature and wrap in a liberal amount of paper towel around the tubes to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage.
2. Place wrapped specimen in a biohazard labeled Ziploc bag or sealable bag with a fridge pack and securely close.
3. Wrap bubble wrap around the bag and place in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples.
4. Complete the shipping requisition form using the address listed below. Prepare the package for shipping, applying packing tape as needed.
5. Ship the package using FedEx or UPS next day or overnight delivery the same day the sample was collected.
6. Only ship Monday-Thursday and avoid shipping before a holiday as the lab does not receive packages on Saturday or on holidays.
7. With each shipment, please include the following:
    a. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form and retain a copy for site record maintenance. **A sample requisition form will be provided by the lead site for use in sample shipment inventory.**

b. An electronic copy (Word or pdf) of the sample requisition must also be sent via email and include the tracking number of the package. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

8. Please email the Lead Site Research Project Manager to notify of an incoming shipment at least 48 hours prior to a shipment
9. Samples may be shipped **via overnight air to:**

Stacey Fernandes, Principal Research Technician
CLL Center, J. Brown lab
Dana Farber Cancer Institute
1 Jimmy Fund Way, SM 648
Boston, MA 02115, U.S.A.
617-632-5828 (phone)

Please retain a copy of both the Fed-Ex or UPS tracking number, and of the completed requisition form for each sample sent.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks (28 days) prior to patient registration with the exception of the required bone marrow biopsy, which can be done within 12 weeks (90 days) prior to registration if no significant intervening treatment has occurred since the biopsy. Treatment should begin as soon as possible after registration. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments and correlative lab draws must be performed prior to administration of any study agent. Study assessments and agents should be administered within +/- 3 days of the protocol-specified date during the dose ramp up period, +/- 7 days during the rest of the combination portion, and +/- 14 days after the completion of the combination portion (Cycle 12), unless otherwise noted.

For venetoclax ramp-up instructions, please refer to section 5.1.2.

If after at least one year of treatment, a patient achieves a complete remission (CR) or complete remission with incomplete count recovery (CRi) with MRD-negativity in the peripheral blood and bone marrow, they will have the option to discontinue venetoclax in favor of active disease monitoring in follow up. If after at least two years of treatment (Cycle 25 restage), a participant achieves a partial remission (PR) with MRD-negativity in the bone marrow, they will have the option to discontinue venetoclax in favor of active disease monitoring.

In the event that the participants who have discontinued treatment in favor of disease monitoring have recurrent disease as defined by MRD testing ($>10^{-4}$) in at least two MRD assessments they can restart venetoclax. Patients will be treated with a dose ramp up as per the label, starting with 20 mg daily and escalating to 400 mg daily. Prophylaxis against and treatment of TLS will be performed as during initiation of venetoclax therapy. If patients do not achieve MRD negativity after reaching full dose venetoclax monotherapy, they have the option to add duvelisib at the highest dose they previously tolerated and continue it until MRD negativity is achieved on two successive peripheral blood MRD assessments or indefinitely depending on tolerability.

Table 9: Study Calendar:

Cycle = 28 days (except for cycle 1 which will vary in length)	**Screening****	**Cycle 1** (+-3 Days)					**Cycle 2** (+-7 Days)				**Cycles 3-6** (+-7 Days)	**Cycles 7+ (*2 cycles +/- 7d until C13, then q3 cycles +/-14d through cycle 60, then q6 months +/- 14 days***	**End of Treatment[12]**	**Active Follow Up (q3 months +/- 14 days) and Disease Monitoring [14,16]**	**Survival Status**
Procedure / Days	**-28-0**	Day 1[1]	Day 2	Day 8[2]	Day 15[3]	Day 22 Day 29 Day 36 Day 43	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1			
Informed consent	X														
Duvelisib		X	X	X	X	X	X	X	X	X	X	X (through cycle 12)			
Venetoclax				X	X	X	X	X	X	X	X	X			
Survival Status															X
PK assessments (phase I study only)		X	X	X	X	X									
History and Physical Exam + Vital signs[17]	X	X		X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test	X*														
Physical Exam Lymph node measurements		X[17]		X[17]											
Quality of life survey (appendix F)		X		X											
Concurrent Medications	X	X		X	X	X	X	X	X	X	X	X	X		
Urinalysis	X														
BM aspirate/biopsy[5,6]	X[4]										X	X	X	X	
SPEP + Immunoglobulins[7]	X										X	X			

Cycle = 28 days (except for cycle 1 which will vary in length)	**Screening****	**Cycle 1** (+-3 Days)					**Cycle 2** (+-7 Days)				**Cycles 3-6** (+-7 Days)	***Cycles 7+ (2 cycles +/- 7d until C13, then q3 cycles +/-14d through cycle 60, then q6 months +/- 14 days***	**End of Treatment[12]**	**Active Follow Up (q3 months +/- 14 days) and Disease Monitoring [14,16]**	**Survival Status**
Procedure / Days	**-28-0**	Day 1[1]	Day 2	Day 8[2]	Day 15[3]	Day 22 Day 29 Day 36 Day 43	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1			
ECOG performance status	X						X				X	X	X	X	
EKG	X[18]														
Serology: SARS CoV2-,HIV, HCV, HBV[20]	X														
CT or PET/CT scan and Response Assessment[8,9]	X										X	X	X	X	
Hematology (CBC with differential and platelets)	X	X		X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry (CMP, magnesium, uric acid, phosphate, LDH, amylase and lipase)[15]	X	X		X	X	X	X	X	X	X	X	X	X	X	
CMV viral load[11]	X						X				X	X			
PT/PTT/INR	X														
FISH, *TP53*, *NOTCH1*, *SF3B1*, and *IGHV* testing[10]	X														
Correlative studies**	X[13]	X[13]		X			X				X	X	X	X	
Adverse Event Evaluation	X	X		X	X	X	X	X	X	X	X	X	X		
MRD assessment[14]											X	X	X	X	

[1] During cycle 1, patients will start with duvelisib alone on days 1-7. Dose ramp up of venetoclax will begin on C1D8. Please refer to section 5.1.2 for admission requirement, TLS monitoring, and inpatient versus outpatient dosing of venetoclax and ramp up instructions.

[2] C1D8 patients will initiate venetoclax ramp up and continue duvelisib

[3] Please refer to section 5 for venetoclax ramp-up dosing per arm.

[4] Unilateral bone marrow aspirate and/or biopsy required within 12 weeks (90 days) prior to C1D1.

[5] Bone marrow biopsy and aspirate will be mandatory at study entry and at C7D1 (+-7 days), C13D1 (+-7 days), and C25D1 (+-14 days). Bone marrow biopsies will be at the discretion of the treating investigator thereafter. MRD will be tested in the bone marrow each time a standard of care or clinically indicated biopsy is performed both during venetoclax maintenance and during active follow up through the Mayo Clinic Lab. Please refer to Section 9 and Table 10 for additional details on schedule and ordering instructions.

[6] Marrow sample requested for correlative studies if bone marrow is done as standard of care, or part of protocol schedule.

[7] SPEP required at baseline and then at Cycles 3, 6, 9, 13 and every 3 cycles thereafter only if M protein detected at baseline; If no M protein detected at baseline, IgG, IgA, IgM to be checked Cycles 3, 6, 9, 13 and every 3 cycles thereafter (B2M only at baseline, C6 and C13).

[8] C4D1, C7D1, and C13D1 (+/- 7 days for each). De-identified scans (Initials, assigned patient number, study number, date of scan, and timepoint must be included) will be sent to the DFCI/Lead site project manager to then send for analysis by the Tumor Imaging Metrics Core- Scans may also be uploaded to the TIMC portal by local radiology

[9] After Cycle 13, CT (Chest, Neck, Abdomen and Pelvis) or PET/CT (Richter's Patients) scans may occur just prior to every 6 cycles (+/- 14 days), or per investigator discretion. De-identified scans (Initials, assigned patient number, study number, date of scan, and timepoint must be included) will be sent to the DFCI/Lead site project manager to then send for analysis by the Tumor Imaging Metrics Core- Scans may also be uploaded to the TIMC portal by local radiology- For instructions on sending scans to Dana-Farber for central review, please refer to section 11.1.3

[10] FISH for both CLL/SLL are to be done locally- *IGHV, TP53* testing can be performed locally or externally via Mayo Clinic Laboratories; If ordering through Mayo Clinic Laboratories, please refer to section 9 and table 10. – *SF3B1* and *NOTCH1* to be ordered for DFCI patients only.

[11] CMV viral load testing should be performed at the time of screening and monthly thereafter in patients while on duvelisib. Local testing is permitted.

[12] End of treatment visit should occur at the next study visit following a completed cycle after study drug was administered and include adverse event monitoring for 30 days following drug discontinuation (visit window +/-14 days). End of treatment due to MRD-CR or MRD- PR does not require labs or exam to be repeated after the C13 or C25 restaging unless clinically indicated.

[13] Baseline correlative studies may be obtained either at the screening visit or prior to study drug administration on C1D1.

* Within 3 days of Cycle 1 Day 1

** Please see section 5.2 for requirements for treatment and Table 10 for full correlative and send out sample collection schedule

[14] MRD will be evaluated in the bone marrow prior to cycle 7, 13, and 25 (+/-7 days) and any time a clinically indicated bone marrow procedure is done thereafter- MRD assessments will also be performed in the peripheral blood prior to cycle 4, 7, 11, 13, 16, 19, 22, 25 and every three cycles up to Cycle 60, then every 6 cycles thereafter- MRD of the blood will be assessed every 3 months or every 6 months at minimum during follow up/active disease monitoring. Please refer to section 9 and Table 10 for directions on ordering, collection, and shipping of samples to Mayo Clinic Laboratories

[15] Amylase and lipase required only while on duvelisib

[16] Please refer to section 5.6 for more specific follow up and active disease monitoring requirements

[17] Includes history and physical exam (with standard review of systems) in addition to blood pressure, pulse rate, and temperature- On Cycle 1 Day 1 and Cycle 1 Day 8, the physical exam will also include measurement and assessments of palpable lymph nodes

[18] Local EKG machine; single test

[19] Participants will be followed for survival status indefinitely after active follow up unless they have withdrawn consent, died, or are lost to follow up

[20] SARS- COV2, Hepatitis B ,C, and HIV serologies: HBV surface antigen, HBV surface antibody, HBV core antibody: if HBV core antibody is positive, must have a negative HBV viral load to enroll. HCV antibody: if positive, must have negative HCV viral load to enroll. HIV 1/2 antibody: must have negative result to enroll. SARS-COV2 must have negative PCR to enroll.

Table 10: Correlative and Required Send out Sample Schedule:

Sample Time Point	Container [2]	Sample Type	Shipping Method[1,8]	Recipient[3,6]
Baseline or C1D1 Predose	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6ml Green	Bone Marrow Aspirate	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	MUTATIONS	Peripheral Blood	Ambient	Mayo Clinic or Local Assay
	1x Oragene Kit	Saliva[2]	Ambient	Brown Lab
C1D8 Predose	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
C2D1	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
C4D1	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD
	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
C7D1, C13D1, C25D1	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6ml Green	Bone marrow Aspirate		
	1x6ml Lavender	Bone marrow Aspirate	Ambient	Mayo Clinic MRD
	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD

C11D1	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD
C16D1	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD
C19D1	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
Clinically Indicated[5]	1x6ml Green	Bone marrow Aspirate	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6mL Lavender	Bone Marrow Aspirate	Ambient	Mayo Clinic MRD
Confirmation of Complete Response	6x 6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6ml Green[4]	Bone Marrow Aspirate	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6mL Lavender[5]	Bone Marrow Aspirate	Ambient	Mayo Clinic MRD
	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD
End of Treatment or Suspected Progression **<u>OR</u>** **Prior to Resuming Venetoclax after Discontinuation**	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6ml Green	Bone Marrow Aspirate	Hand-delivered or Fridge pack overnight shipping	Brown Lab
	1x6mL Lavender	Bone Marrow Aspirate	Hand-delivered or Fridge pack overnight shipping	Mayo Clinic MRD

Every 3 Cycles from C25D1 through C60[6]	1x6ml Lavender	Peripheral Blood	Ambient	Mayo Clinic MRD
Every 6 Cycles from Cycle 25 onward[7]	6x6mL Green 1x6ml Red	Peripheral Blood	Hand-delivered or Fridge pack overnight shipping	Brown Lab
Active Disease Monitoring Every 3 months	1x6ml Lavender[6]	Peripheral Blood	Ambient	Mayo Clinic MRD

[1]Local samples from DFCI, MGH, or BIDMC will be refrigerated and hand-delivered as soon as possible same day to Dr. Jennifer Brown's lab- For external investigative sites, shipping instructions are in section 9. Samples are to be shipped to the Brown lab by overnight, trackable shipping on fridge packs
[2]Green=Sodium Heparin Tube; Red= No additive; Purple = K2EDTA; Oragene saliva collection kit provided by lead site and can be collected at any time before or during the trial
[3] Requisition form for Mayo Labs and for Jennifer Brown lab provided by the lead site project manager
[4] Only required in patients who had a positive marrow at baseline
[5] After C25 (both patients on treatment or in active follow up) bone marrow aspirate samples will be collected each time a bone marrow biopsy is done as part of routine standard of care or the investigator's discretion
[6] MRD testing of the peripheral blood will be sent to Mayo Clinic Laboratory just prior to cycles 4, 7, 11, 13, 16, 19, 22, 25 and every three cycles until cycle 60, then at minimum q6 cycles thereafter – During active follow up, MRD of the blood should be tested q3 months or at minimum, q6 months for up to one year.
[7] Correlative samples requested for all patients who remain on study past cycle 25, i.e. 30, 36, 42, 48, 54, and 60 to be sent to Brown Lab at DFCI.
[8] Both blood and aspirate MRD samples are to be sent ambient, priority overnight to Mayo Clinic Laboratories at the address listed in section 9.3.2
[9] Please refer to section 5.6 for full details on active disease monitoring and follow up

11. MEASUREMENT OF EFFECT

11.1 Definitions:

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for DLT: All participants who complete the first cycle of combination therapy will be evaluable for DLT from the time of their first treatment. Any patient who experiences a DLT after receiving at least one dose of combination study treatment will also be considered evaluable for DLT. In the phase I portion of the study, if a patient comes off study due to a reason other than a DLT (e.g. disease progression) prior to the end of the DLT observation period, that patient can be replaced.

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.2 Methods for Evaluation of Measurable Disease:

All baseline evaluations should be performed as closely as possible to the beginning of treatment.

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: 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.

Conventional CT: 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. Although CT scan is the preferred imaging modality for this study, MRI or PET/CT will also be considered acceptable. Images of the Chest, Neck, Abdomen and Pelvis are required at each timepoint listed in the study calendar.

PET/CT: For patients with Richter's Syndrome, PET/CT evaluation is preferred over contrast CT, though the latter can be used if necessary.

11.3 Response Criteria

Response and progression will be evaluated in this study using the 2008 IW-CLL criteria for CLL (Hallek et al., 2008) or for RS by Lugano criteria (Cheson et al., 2014).

If a bone marrow biopsy was done to confirm a response, sites may use the blood MRD results within 2 months of the biopsy to confirm that MRD status.

11.3.1 **2008 IW-CLL Criteria (CLL/SLL patients only)**

11.3.1.1 **Complete Remission (CR):**

- Evaluation of Non-Target Lesions CR requires all of the following criteria: Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x10^9/L (4,000/μL). The presence of minimal residual disease (MRD) after therapy should be assessed. The sensitivity of the method used to evaluate for MRD should be reported.
- Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. A CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.
- No hepatomegaly or splenomegaly by physical examination. A CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.
- Absence of constitutional symptoms.
- Blood counts above the following values: Neutrophils more than 1.5 x 10^9/L (1,500/μL) without need for exogenous growth factors, Platelets more than 100 x 10^9/L (100,000/μL) without need for exogenous growth factors, Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.
- Bone marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

11.3.1.2 **Complete Response with incomplete marrow recovery (CRi):**

- Complete response as defined above, but without normal blood counts.

11.3.1.3 **Minimal Residual Disease:**

- Patients with CR or CRi or patients with PR with resolution of lymphocytosis will be assessed for minimal residual disease (MRD) at every three months. Such patients who have fewer than 0.01% (10^{-4}) CLL cell percentage of leukocytes in the bone marrow, as assessed by four-color flow cytometry, will be considered to be MRD negative.

11.3.1.4 **Partial Response (PR):**

- A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.
- Reduction in lymphadenopathy as defined by the following:
  - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
  - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more
- The blood count should show one of the following results: Neutrophils more than 1.5 x 10^9/L (1,500/μL) without need for exogenous growth factors, Platelet counts greater than 100 x 10^9/L (100,000/μL) or 50% improvement over baseline without need for exogenous growth factors, Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

11.3.1.5 **Nodular Partial Response (nPR):**

- All criteria for CR are met, but lymphoid nodules can be found in the bone marrow biopsy. Note, if flow cytometry and immunohistochemistry are negative for a clonal B-cell population then these patients can be considered as CR or CRi.

11.3.1.6 **Partial Response with Lymphocytosis (PR-L):**

- Evidence of a radiographic PR but persistent lymphocytosis with >5,000 B-lymphocytes per μL where the absolute lymphocyte count has not decreased by 50% or more compared to baseline are considered to have a PR with lymphocytosis.

11.3.1.7 **Progressive Disease:**

- Progressive disease during or after therapy is characterized by at least one of the following:
  - Lymphadenopathy: Progression of lymphadenopathy is often discovered by physical examination and should be recorded. For CT scans used to

confirm progression or relapse of lymphadenopathy, progression is defined as:
    - An increase by 50% or more in greatest determined diameter of any previous site.
    - An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
  - An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter (Note: because of the well-described lymphocyte redistribution phenomenon, any increase in lymphocyte count during duvelisib monotherapy or any increase during combination therapy in the setting of improvement of lymph nodes or cytopenias will not be considered disease progression)
  - Transformation to a more aggressive histology (i.e., Richter syndrome). This diagnosis must be established by lymph node biopsy.
- Occurrence of cytopenias (neutropenia, anemia, or thrombocytopenia) due to CLL.
    - During therapy, cytopenias cannot be used to define disease progression.
    - After therapy, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if marrow biopsy demonstrates an infiltrate of clonal CLL cells.

11.3.1.8 **Stable Disease:** Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease.

11.3.1.9 **Treatment Failure:** Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, progressive disease, or death from any cause) should be rated as a treatment failure.

11.3.1.10 **Relapse:** Relapse is defined as a patient who has previously achieved the above criteria of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression.

11.3.1.11 **Refractory Disease:** Refractory disease is defined as treatment failure or disease progression within 6 months to the last anti-leukemic therapy.

11.3.2 **2014 Lugano Criteria (Richter's Patients Only):**

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[*] with or without a residual mass on 5PS[‡]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra-lymphatic sites	Score 4 or 5[‡] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from

Response and Site	PET-CT–Based Response	CT-Based Response
		baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

- Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

- ↵* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
- ↵† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

11.3.3 **Progression free Survival**

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

Overall Survival: Overall Survival (OS) is defined as the time registration to death due to any cause, or censored at date last known alive.

11.3.4 **Central Radiology Interpretation**

All scans will be reviewed centrally by the Tumor Imaging Metrics Core (TIMC) either by submission through their secure portal, or by mailing de-identified (only including subject number, trial number, date of scan, timepoint, and site contact information).

Radiographic responses will then be communicated to the investigative sites for entry in to the EDC.

Scans will be uploaded to the secure file transfer portal at:
https://transfer.partners.org/courier/web/1000@/wmLogin.html

External Site Access:
External collaborators must be invited to use the system. Please email the study lead if a new staff member needs access to this portal.

1. If you used the old system, type in your email address, click Next, then select the "forgot password" link to reset your password
2. If you're new, please ask your MGB collaborator to send you an email from https://transferkw.partners.org
3. Email Tumor Imaging Metrics Core help desk (tumormetrics@partners.org) and provide two email addresses for account registration (a primary and a backup)
4. TIMC will send an invite via the Partners Healthcare Secure File Sharing service
5. Click the link in the email to accept the invitation and register your account
    a. *Invitations will expire after 7 days*
    b. Check Spam and Junk email folders for invite if not received in Inbox
6. Create a password
7. Click Register

Send Files
1. Create a desktop folder
2. Copy DICOM data from CD into the desktop folder

   a. Remove any image viewers as this will interfere with data upload to the local analysis software
3. Right click folder > Send To > Compressed (zipped) folder
1. Log in to the system: https://transferkw.partners.org
4. Select Send File tab
5. Enter tumormetrics@partners.org into the To field
6. Enter a subject into the Subject field
7. Select Choose File > browse the desktop for the zipped file
8. Add patient initials, trial number, and any notes pertaining to the scan or assessment in the body of the email
   a. Do not include any protected health information (PHI) in the email subject line
9. Select notification preferences from the Additional Options field (optional)
10. Click 'Mark as secure (fingerprint)'
11. Click Send
12. Click OK after receiving confirmation that the files have been sent
13. **Notify the lead site PM that a file has been uploaded, so that an order can be placed for the scan to be read.**

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 in accordance with DF/HCC SOPs.

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 clinical specialists with experience in oncology and who have no direct relationship with the study. 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 or more often if required to review toxicity and accrual data. 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 with 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.

12.3 Multicenter Guidelines:

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Agreements Language: N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Phase I Study: Evaluation of Toxicity

Primary Endpoint: The primary endpoint in the phase I study is the dose limiting toxicity (DLT), and the maximum tolerated dose (MTD) as well as the recommended phase II dose for this combination regimen of duvelisib plus venetoclax.

A standard 3+3 dose escalation design will be employed with three dose levels of venetoclax. Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable. A dose-limiting toxicity (DLT) is defined as per section 5.3, and the DLT observation period is the first cycle of combination treatment.

The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. The maximum tolerated dose (MTD) is defined as the highest dose level where a DLT occurs within at most one out of six patients treated. The escalation scheme is as follows:

(1) If none of the initial three patients in a cohort experiences a DLT, then a new cohort of three patients will be treated at the next higher dose level.

(2) If one of the three patients in a cohort experiences a DLT, then up to three additional patients will be treated at the same dose. Escalation will continue if only one of the six patients experiences DLT.

(3) If two or more patients in a cohort experience DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered the MTD.

(4) If only three patients were treated at a dose level under consideration as the MTD, then up to three additional patients will be accrued. If no more than one of the six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD. If two or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

The MTD is defined as the highest dose studied for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the NCI Common Toxicity Criteria. Patients will be continued to be followed for one year for evidence of late toxicity.

Table 10: Below gives the probabilities of dose escalation based on true DLT risk in the 3+3 design.

True DLT rate:	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

escalation									

In the phase I study, if a patient comes off study due to a reason other than a DLT (e.g. disease progression) prior to the end of the DLT observation period, that patient can be replaced.

Phase II Study (CLL/SLL patients):

Treatment Efficacy

The primary endpoint for the phase II study is the rate of complete response (CR) at 12 months according to 2008 IW-CLL criteria. The CR rate will be obtained for all patients at 12 months and will be reported as a percentage of total patients.

Evaluation of Toxicity in Phase II

We will closely monitor treatment-related toxicity for all participants. Participants in the phase II portion of the study who meet DLT criteria during the first cycle of combination treatment as specified in section 5.3 will be analyzed by the following method:

Sequential Pocock-type stopping boundaries will be used to monitor the unexpected toxicity rate (Ivanova et al., 2005). Accrual will be halted and the Data Safety Monitoring Committee consulted if excessive numbers of unexpected toxicities are seen, that is, if the number of toxicities is equal to or exceeds b_n out of n patients who received at least one dose of combination therapy (see table 11). For example, if 6 or more out of the first 20 patients (≥40%) experience unacceptable toxicities the study will be stopped; or if 8 or more out of the first 30 patients (≥26%) experience unacceptable toxicities the study will be stopped. With these rules, the probability of early stopping the trial if the true rate of toxicity is ≤10% does not exceed 0.05, if the true toxicity rate is 30% the probability of early stopping is 0.865 (table 12).

Table 11: The trial will be stopped if the number of toxicities is equal to or exceeds b_n out of n patients evaluable for toxicity.

Number of Patients, *n*	Boundary, b_n
1	-
2	2
3	3
4	3
5	3
6	3
7	4
8	4
9	4
10	4
11	5
12	5
13	5
14	5
15	5
16	6
17	6
18	6
19	6
20	6
21	6
22	7
23	7
24	7
25	7
26	7
27	7
28	8
29	8
30	8
31	8
32	8
33	8
34	9
35	9

Table 12: Probabilities of early stopping at different true but unobserved toxicity rates.

Toxicity Rate	0.10	0.20	0.30	0.40	0.50	0.60
Probability of early stopping	0.048	0.436	0.865	0.988	0.999	1.00

Phase II Study (Richter's Syndrome Cohort):

In a previous study with a commonly used chemoimmunotherapy regimen for RS, dose-adjusted EPOCH-R, the CR rate was 20%.[15] We base this as the null hypothesis. With the addition of

venetoclax, we hypothesize that the CR rate will be 45% or higher. Twenty patients will be enrolled and if 7 or more patients achieve CR we will regard the treatment efficacious. Conversely, if 6 or fewer patients achieve CR, we will regard the treatment inefficacious. With this design, the probability of concluding the treatment efficacious is 0.87 if the true but unknown response rate is 45% and 0.09 if the true rate is 20%. This decision rule is calculated using the exact binomial method. Table 1 below shows the operating characteristics of this design.

Table 1. Operating Characteristics

	True but Unknown CR Rate					
	20%	25%	30%	35%	40%	45%
Prob(≥7 CR in 20)	0.09	0.21	0.39	0.58	0.75	0.87

13.2 Sample Size, Accrual Rate and Study Duration

We anticipate approximately 12 CLL/SLL patients will be enrolled in the phase I study, using the traditional 3+3 design as described above.

For the phase II study, a Simon two-stage design will be employed whereby a 10% complete response (CR) rate is considered not promising, a 30% complete response rate is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively.[23] In the first stage of this design, 12 CLL/SLL patients will be accrued. All patients will be followed for up to one year. If at least 2 patients achieve CR then an additional 23 CLL/SLL patients will be accrued to the second stage. If 0 or 1 patients achieve CR the study will be terminated and declared negative. The probability of early stopping based on an optimal Simon's two stage design is 65%. At the end of the trial, if 6 or more patients respond out of a total of 35 patients, then this combination will be considered worthy of further investigation. This design yields at least a 0.90 probability of a positive result if the true response rate is at least 30% and yields a 0.90 probability of a negative result if the true response rate is 10%.

Of note, all patients in the phase I study will be evaluated for response and can be counted in efficacy evaluations in stage 1 of the phase II portion of the trial. An exploratory analysis will also be performed to estimate the rate of CR with confidence intervals in the 29 patients treated at the venetoclax MTD.

For the Richter's Syndrome Cohort, we plan to accrue 20 additional patients. Given the poor prognosis and lack of a standard of care for this population, we will not have an early stopping rule for this cohort based on efficacy or toxicity.

13.3 Analysis of Secondary Endpoints

Phase I Study:

Secondary endpoints in the phase I trial include PK assessments. Pharmacokinetic parameters including half-life, C_{max}, AUC, volume of distribution, and clearance will be determined using non-compartmental methods. Standard descriptive statistics (mean, standard deviation, median, range) will be presented on all parameters. These analyses will be performed in all patients accrued to the phase I component of the trial.

Phase II Study:

Secondary endpoints in the phase II trial include, response assessments including ORR, defined as partial response and complete response or complete response with incomplete count recovery according to the 2008 IW-CLL or Lugano 2014 criteria the duration of response (DOR) among patients who have achieved a PR or CR/CRi, 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} and a complete response in the bone marrow at 6 and 12 months, and the association FISH abnormalities, *TP53*, *NOTCH1*, or *SF3B1*mutations, and *IGHV* mutational status with ORR and CR rate.

ORR (defined as proportion of patients who achieve a complete and partial response) will be estimated along with a 95% confidence interval, and rate of best response and MRD will be calculated. For patients who respond to treatment (complete or partial response), duration of response will be calculated from the date of response to the date of progression of disease. Patients still responding at date of last follow-up will be censored. PFS will be calculated as the time from start of treatment to the date of progression, death or last follow-up. OS will be calculated as the time from the start of treatment to the date of death or last follow-up. OS, PFS and DOR will be calculated using Kaplan-Meier methodology. The rate of MRD negativity and pathologic CR/CRi will be estimated along with a 95% confidence interval. The association between baseline characteristics (such as FISH abnormalities, *TP53*, *NOTCH1*, or *SF3B1*mutations, and *IGHV* mutational status) and response will be assessed using Fisher's exact test.

Exploratory endpoints:

Associations between the change in mitochondrial priming at baseline as compared to at the time of duvelisib monotherapy and between baseline and combination therapy and ORR will be assessed using Wilcoxon rank test. Associations between change in the percentage of cytochrome c release in response to the Bad, HRK and MS-1 peptides and ORR will be assessed using the Wilcoxon rank test. We will determine whether the percentage of regulatory T-cells, NK cells or monocytes at the start of therapy, after one week of duvelisib monotherapy, and after three months of combination therapy correlates with ORR, CR rate or toxicity using the Wilcoxon rank test.

The average change in lymph node diameter measured on day 1 and day 8 will be measured on physical exam and recorded in the medical record.

We will also measure the change in total score using the quality of life (QoL) questionnaire in appendix F.

13.4 Reporting and Exclusions

Participants who never start combination therapy will be excluded from analysis in both the phase I and phase II study

13.4.1 Evaluation of Toxicity

All participants who receive at least one dose of combination therapy (duvelisib and venetoclax) will be evaluable for toxicity from the time of their first treatment.

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.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: CAIRO –BISHOP DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

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

Table 2. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

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

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

* Not directly or probably attributable to therapeutic agent.

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

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

APPENDIX C: MANAGEMENT OF TUMOR LYSIS SYNDROME

Abnormality	Management Recommendations
Hyperkalemia (Including Rapidly Rising Potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1 (or higher dose as needed) • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT until improvement observed.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (6 mg IV x 1 or as per institutional standard). o If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (6 mg IV x 1 or as per institutional standard). o When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

APPENDIX D: LIST OF EXCLUDED OR CAUTIONARY MEDICATIONS:

PRESCRIPTION MEDICATIONS - INHIBITORS OF CYP3A4 **Copyright EBM Consult** www.ebmconsult.com			
Drug Class	**Weak 3A4 Inhibitors** (≥1.25 to < 2-fold ↑AUC) or (Clearance ↓ by 20-50%)	**Moderate 3A4 Inhibitors** (≥2 to < 5-fold ↑ AUC) or (Clearance ↓ by 50-80%)	**Strong 3A4 Inhibitors** (≥5-fold ↑ AUC) or (Clearance ↓ by >80%)
Antiarrhythmics		Amiodarone*	
Antibiotics		Erythromycin	Clarithromycin Telithromycin
Antidepressants			Nefazodone
Antifungals		Fluconazole Miconazole*	Itraconazole Ketoconazole
Calcium Channel Blockers		Diltiazem Verapamil	
H2 Receptor Antagonist	Cimetidine		
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)		Delavirdine	
Protease Inhibitors		Amprenavir Fosamprenavir	Atazanavir Darunavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir
Other		Conivaptan Grapefruit juice Cat's claw (*Uncaria tomentosa*)* *Echinacea angustifolia* Wild cherry (*Trifolium pratense*) Chamomile (*Matricaria chamomilla*) Licorice (*Glycyrrhiza glabra*)	

Note: The referenced change in area under the curve (AUC) and/or change in clearance of either midazolam (Versed; a specific substrate of CYP3A4) or a known sensitive CYP3A4 substrate. The use of an (*) reflects opinion of editorial board based on clinical experience since no data available with midazolam or other sensitive substrate.

APPENDIX E: PATIENT WALLET CARD

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial using the experimental agent **_____.** This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, and pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	_____ interacts with a specific liver enzyme called **CYP_____**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____**.**

APPENDIX F: DRUG DIARY

PATIENT INSTRUCTIONS: Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking. Both duvelisib and venetoclax should be kept in the provided bottles. You can take the medications in any order. Store drugs at room temperature.

Duvelisib:

- Unless otherwise instructed by our study physician, duvelisib should be taken by mouth twice per day, once in the morning and once in the evening. Duvelisib can be taken with or without food.
- Do not split or crush tablets or empty into any food or drink for oral ingestion. Tablets must be swallowed whole.
- If you vomit after taking duvelisib, do NOT take another dose. Please note any vomiting in the Comments section of the diary on the next page.
- Do not consume grapefruit, grapefruit juice or Seville oranges while taking duvelisib. Do not take fish oil or vitamin E supplements. Consult your doctor before making any changes to medications or supplements.
- If a dose is missed and it is less than 4 hours from usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing for the next planned dose. If you miss a dose record "0" for Number Taken on the next page.
- If you accidentally take an extra dose during a day, hold the next planned dose and resume normal dosing for the following dose.
- Please bring any unused duvelisib tablets, all empty duvelisib containers and diary to your next visit.

Venetoclax:

- Venetoclax should be taken by mouth once per day, preferably in the morning. Venetoclax should be taken with food, preferably within 30 minutes of a meal and with a full glass of water (approximately 8 oz).
- Do not consume grapefruit, grapefruit juice or Seville oranges while taking venetoclax. Do not take fish oil or vitamin E supplements. Consult your doctor before making any changes to medications or supplements.
- If a dose is missed and it is less than 8 hours from the usual time of dosing, then you may take that dose. Otherwise that dose should be skipped and NOT taken. You should resume regular dosing the following day. If you miss a dose record "0" for Number Taken on the next page.
- If you vomit drug, please record this in diary as a missed dose and do not take another dose of drug that day.

FOR CLINIC USE ONLY

Give patient all 2 pages of Drug Diary stapled together. Provide one diary per cycle (28 days).

- Complete patient identifiers and medical team contact information on page 2.
- Complete correct dose levels for venetoclax on page 2.
- When patient returns pill bottles and diary perform a duvelisib and venetoclax pill count and record adherence information in the box to the right

DFCI Trial 18-089 Duvelisib + Venetoclax for CLL or Richter's Syndrome
SELF-ADMINISTERED DIARY

Participant Identifier: _____ Cycle #: _____

Your MD:_____ Phone: _____

Your RN:_____ Phone: _____

		Duvelisib AM		Duvelisib PM		Venetoclax		Comments
	Date	Number Taken	Time Taken	Number Taken	Time Taken	Number Taken	Time Taken	
Example	9/12/17	1	8:00 AM	1	8:00 PM	1	8:00 AM	With breakfast
Day 1								
Day 2								
Day 3								
Day 4								
Day 5								
Day 6								
Day 7								
Day 8								
Day 9								
Day 10								
Day 11								
Day12								
Day 13								
Day 14								
Day 15								
Day 16								
Day 17								
Day 18								
Day 19								
Day 20								
Day 21								
Day 22								
Day 23								
Day 24								
Day 25								
Day 26								
Day 27								
Day 28								

DFCI Trial 18-089 Duvelisib + Venetoclax for CLL or Richter's Syndrome

SELF-ADMINISTERED DIARY – CYCLE 1 ONLY

Participant Identifier:_____

Cycle #: ___1_____

Your MD:_____

Phone: _____

Your RN: _____

Phone: _____

		Duvelisib AM		Duvelisib PM		Venetoclax		Comments
	Date	Number Taken	Time Taken	Number Taken	Time Taken	Number Taken	Time Taken	
Example	9/12/17	1	8:00 AM	1	8:00 PM	1	8:00 AM	With breakfast
Day 29								
Day 30								
Day 31								
Day 32								
Day 33								
Day 34								
Day 35								
Day 36								
Day 37								
Day 38								
Day 39								
Day 40								
Day 41								
Day 42								
Day 43								
Day 44								
Day 45								
Day 46								
Day 47								
Day 48								
Day 49								

APPENDIX G: QUALITY OF LIFE QUESTIONNAIRE

Participant Identifier: _____

Visit: C1D1____
C1D8____

Please answer the following questions about your lymph nodes. If you answer "Yes" to any question, please **circle** the number on the scale that best describes the severity (1=none at all, 10=severe).

1. Do your lymph nodes cause pain? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

2. Do your lymph nodes cause you embarrassment? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

3. Do your lymph nodes affect how your clothes fit? Y__ N __

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

4. Do your lymph nodes cause discomfort when you swallow? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

5. Do your lymph nodes cause you to feel "full" early when eating? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

6. Do your lymph nodes prevent you from doing activities that you normally enjoy? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

7. Do your lymph nodes affect your sleep? Y__ N__

   0 (none)_1_2_3_4_5_6_7_8_9_10 (severe)

Signature: _____ Date: _____

APPENDIX H: GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

Table 5. Grading scale for hematologic toxicity in CLL studies

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

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

†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20 000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20×10^9/L [20 000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

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

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

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APPENDIX I: DF/HCC MULTICENTER DATA SAFETY AND MONITORING PLAN

DFCI IRB Protocol #:18-089

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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15. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

15.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

15.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC

Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

16. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

16.1 DF/HCC Sponsor

The DF/HCC Sponsor, Matthew Davids, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.

- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

16.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting pPolicy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

16.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

17. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

17.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

17.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

17.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

17.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

17.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

17.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

17.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

17.7 DF/HCC Multi-Center Protocol Registration Policy

17.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center lead project manager

- Copy of required laboratory tests and documents that support all aspects of the eligibility checklist
- Signed informed consent document

- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

17.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

17.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

17.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

17.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures

from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

17.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

17.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

17.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

17.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor/Coordinating Center following the DFCI IRB Adverse Event Reporting Policy of the IRB of record.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

17.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

17.10 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

18. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol under investigational agent ordering.

19. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

19.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring on a periodic basis. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center. A study specific monitoring plan will be shared with your site during the site initiation visit.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in occasional (usually monthly) Coordinating Center initiated teleconferences. Minutes of these meetings should be kept and referenced when needed. At least one member of the study team should be able to join the teleconference each time one is held, and at minimum provide updates about the site's patients if they are unable to join.

Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification under special circumstances.

On-Site Monitoring will occur according to the study specific monitoring plan. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. A letter outlining what will be reviewed will be sent prior to each visit.

19.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

19.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The following **minimum** accrual requirements are recommended:

1) Phase I: 2 per site/annually
2) Note: Diseases that are extremely rare may have accrual expectations of 0-1 accruals/year.

20. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

20.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

20.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

20.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

20.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.