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A Phase II Study of Venetoclax and Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL)

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1.0 OBJECTIVES

Primary Objective:

1. Estimate therapeutic activity (best response (CR/CRi)) of combined ibrutinib and venetoclax in patients with CLL/SLL.

Secondary Objectives:

1. To determine the safety of this combination strategy.
2. To estimate the time to best response with this combination.
3. To determine the progression-free (PFS) and overall survival (OS).
4. To test pharmacodynamic endpoints and molecular interactions between these two drugs.
5. To assess the therapeutic activity (best response (CR/CRi)) in subgroups of patients defined by *IGHV* mutation or FISH subtype.

Exploratory Objectives:

1. To study immunological and molecular changes in the peripheral blood and the bone marrow in response to ibrutinib and venetoclax.

2.0 BACKGROUND AND RATIONALE

2.1 Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): CLL/SLL is the most common leukemia in the United States and Western hemisphere.[1] There is remarkable clinical diversity in patients with CLL. Following diagnosis, some patients have smoldering, asymptomatic disease that may not progress for many years; others are diagnosed with advanced stage, and still others are diagnosed with early stage disease that rapidly progresses, causing symptoms and/or bone marrow failure and requiring treatment. Various genetic/molecular prognostic markers have been established and validated and are routinely used in clinical practice.[1] These include β2-microglobulin, cytogenetics, immunoglobulin variable heavy chain gene (*IGHV*) mutational status, zeta chain-associated protein 70 (ZAP-70) expression, and CD38 expression. The presence of del17p (and/or mutated *TP53*), which result in loss of p53 function is associated with the worst clinical outcomes.[2-4] Patients with CLL whose disease has relapsed or is refractory to treatment has poor outcomes. These subgroups of patients with CLL – relapsed/refractory patients, and untreated patients with high-risk molecular markers (unmutated IGHV or TP53 alternations) are the focus of this study.

2.2 Venetoclax, a selective Bcl-2 inhibitor: Bcl-2 overexpression is seen in majority of lymphoid malignancies, including CLL. Venetoclax is a new BH3 mimetic that was developed to specifically target Bcl-2 with reduced affinity for Bcl-XL, hence avoiding thrombocytopenia intrinsic to 1st generation BH3 mimetics like ABT-263.[5] Preclinical and emerging clinical evidence showed significant monotherapy activity in patients with relapsed/refractory CLL. In an update (Seymour et al. ASCO 2014), data was presented for 105 patients with R/R CLL/SLL treated with venetoclax monotherapy. The median number of prior therapies was 4 (1-11). A total of 75% of patients had unmutated *IGHV* and 28% had del(17p). ORR was noted to be 77% (23% CR, 54% PR) and was independent of *IGHV* mutation status, cytogenetics, and fludarabine-refractory status. All patients (except 1) had >50% decrease in absolute lymphocyte count with a median time to 50% reduction of 14 days (range, 1-49). Of the evaluable patients, 84% had ≥ 50% reduction in nodal mass at a median time of 1.4 months (range, 0.6-13.7). Of the evaluable patients, 90% had ≥ 50% reduction in bone marrow infiltrate at a median time of 5.5 months (range, 1.9-17.4). Thus, anti-tumor activity of venetoclax was seen in all tumor compartments. Of the 105 patients, 37 discontinued treatment – 22 for progressive disease (including 15 due to Richter's transformation), 12 due to adverse events, and 3 other reasons. Adverse events (G3/4) occurring in ≥5% of patients included neutropenia (33%), anemia (10%), febrile neutropenia (7%), thrombocytopenia (7%), hyperglycemia (7%), tumor lysis syndrome (TLS) (7%), and hypokalemia (5%). The estimated 2-year PFS at 400mg or greater dose level was 59%.

2.3 Ibrutinib: There is strong rationale to target BTK in CLL. B-cell receptor (BCR) activation-signaling plays a crucial role in the pathogenesis in CLL.[6-9] BTK activates downstream molecules such as nuclear-factor-kappa B and MEK/ERK, which are involved in many cellular processes including proliferation, survival, differentiation, apoptosis, and metabolism. Gene expression profiling has shown that BCR signaling is the most expressed signaling pathway in patients with CLL.[8] Ibrutinib, a BTK inhibitor, has impressive monotherapy activity in patients with relapsed CLL. Byrd et al. reported an overall response rate (ORR) of 71% with ibrutinib in the relapsed setting. Most of the responses were partial responses. In the first-line setting, O'Brien et al. reported an ORR of 71% (CR 13%) in elderly patients with ibrutinib monotherapy. The 2-year PFS was very promising at 96%. Ibrutinib is well tolerated with diarrhea being the most common adverse event (mostly grade 1-2).[10] Based on these data, Ibrutinib was approved by the FDA for patients with CLL who received at least one prior therapy and for first-line treatment of patients with del(17p).

2.4 Rationale for the Combination: There is a strong scientific rationale for targeting Bcl-2 in CLL because of the consistently high expression of Bcl-2 protein in CLL. High Bcl-2 expression can block the initiation of the intrinsic apoptosis pathway, rendering CLL cells resistant to the effects of chemotherapy or other pro-apoptotic stimuli. Inhibition of the anti-apoptotic Bcl-2 protein removes the blockage of the apoptosis pathway and, hence, lowers the threshold for cell death. Similarly, there is strong rationale to target BTK in CLL. Several lines of argument support the combination of venetoclax and ibrutinib for patients with CLL.

(A) Both drugs have shown impressive monotherapy activity in patients with CLL. Ibrutinib is very effective in controlling lymph node disease; however, most patients continue to have marrow disease and consequently, there are only few complete responses with single-agent ibrutinib. Venetoclax tends to have a better control of disease in the marrow with 90% of patients experiencing >50%

decrease in marrow infiltrate with single-agent venetoclax. Therefore, the two drugs can complement each other in clinical activity.

(B) Venetoclax and ibrutinib have different mechanisms of action – Venetoclax inhibits anti-apoptotic protein Bcl-2 allowing caspase-mediated apoptosis, while ibrutinib targets the BTK which impacts the downstream B-cell receptor pathway.

(C) There is emerging preclinical evidence that the combination of venetoclax and ibrutinib is synergistic. We (MDACC) analyzed primary CLL cells obtained from CLL patients at the time of lymphocytosis while receiving ibrutinib therapy (Cervantes-Gomez et al. AACR 2014). These cells were incubated ex-vivo with several drugs, including ABT-737, venetoclax, additional ibrutinib (IB) PI3K inhibitors (IPI-145, and GS-1101 (idelalisib)), and chemotherapy (bendamustine). Among these targeted drugs, venetoclax showed maximum cellular death in this setting (Figure 1). This was recapitulated in several patient samples after ibrutinib therapy (Figure 2). Just to emphasize, all drugs were used at physiologically achievable concentrations. Venetoclax was at 5 and 10 nM. Synergy between venetoclax and ibrutinib was also observed during in vitro incubations (data not shown) and has also been reported in CLL and mantle cell lymphoma cell lines (Zhao 2013; Brett 2013). Reverse-phase protein array analysis (RPPA) identified Mcl-1 as one of the proteins that was consistently decreased in circulating CLL cells during ibrutinib therapy (Figure 3). This was validated using immunoblot assay in 6 CLL patient samples (Figure 4). Quantitation of these data demonstrated statistically significant dissipation of Mcl-1 protein (Figure 4; p = 0.0004); Cervantes-Gomez et al. AACR 2014; Cinar et al. Leuk Res 2013). It is also known that high Mcl-1 leads to resistance to venetoclax. Therefore, this observation provides a strong molecular rationale to combine venetoclax with ibrutinib. Importantly, these data also suggested that in contrast to Mcl-1, Bcl-2 protein was either unchanged or increased after ibrutinib therapy (Figure 4 and

Figure 1. Pharmacological profiling of CLL cells treated with ibrutinib in a single patient

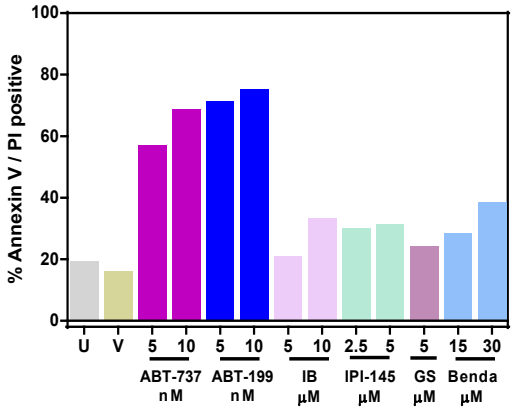


Figure 2. Pharmacological profiling of CLL cells from 10 patients treated with ibrutinib

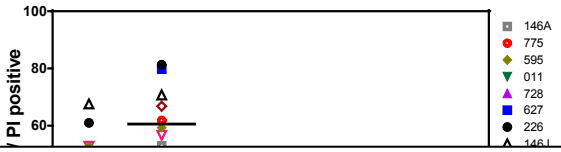
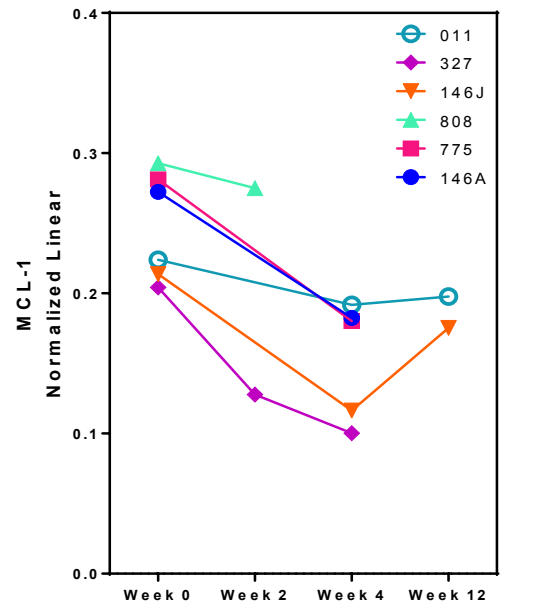


Figure 3. Reverse-phase protein array (RPPA) analysis for Mcl-1 protein in CLL cells after start of ibrutinib



6). Because Bcl-2 is targeted by venetoclax, these data further support the combination of ibrutinib and venetoclax.

2.5 Toxicity of the Proposed Regimen: Ibrutinib is well tolerated with grade 1-2 diarrhea being the most common toxicity encountered. Neutropenia has been observed with single-agent ibrutinib (grade 3-4 neutropenia: 3% in the first-line setting in the elderly patients,[10] 15% in the relapsed/refractory setting).[11] Venetoclax is well tolerated with neutropenia being the most common adverse event (Grade 3/4 - 33%; febrile neutropenia - 7%). We do not anticipate excess toxicity in combining ibrutinib with venetoclax though we will closely monitor for excess neutropenia and febrile neutropenia.

One of the major concerns with venetoclax treatment has been the risk of TLS. It is known that the risk of tumor lysis is related to CLL tumor burden (lymphocytosis and lymphadenopathy). In this study, patients will receive ibrutinib monotherapy for the first 3 cycles (months) as a debulking strategy. We expect that this would lower the risk of TLS when venetoclax is added at the start of cycle 4.

Figure 4. Ibrutinib therapy impacts Bcl-2 family survival proteins in circulating leukemia CLL cells

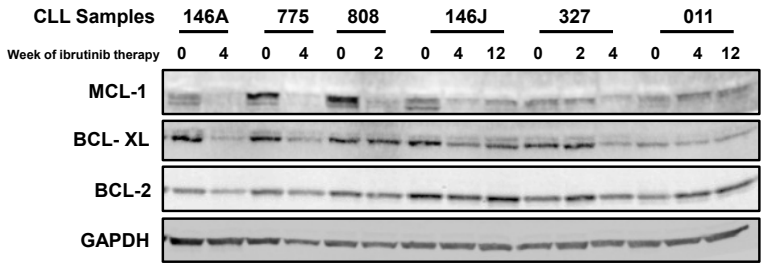


Figure5. Ibrutinib therapy results in a decline in Mcl-1 protein levels in circulating CLL cells

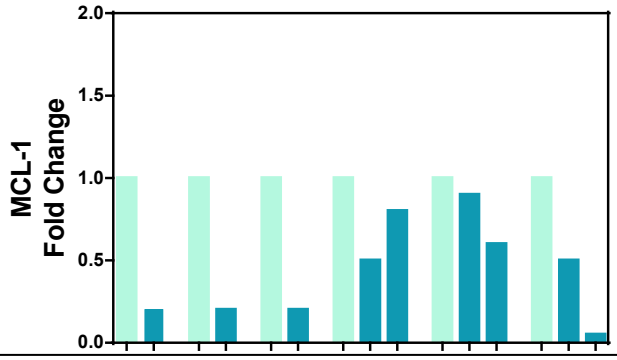
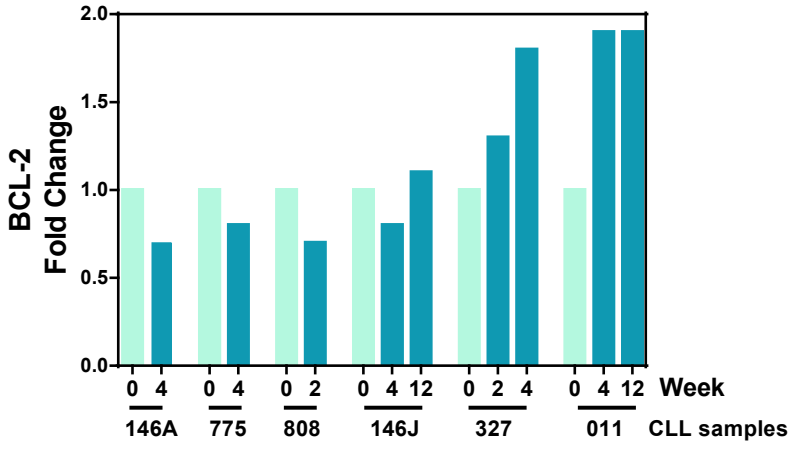


Figure 6. Ibrutinib therapy results in either an increase or unchanged Bcl-2 protein levels in circulating CLL cells



2.6 Patient Selection:

High-risk first-line patients: FCR chemoimmunotherapy has been the standard therapy for patients with CLL who are deemed fit

for myelosuppressive therapy.[12-14] In the MDACC dataset, the following pretreatment characteristics have been associated with poor progression-free survival after the first-line FCR therapy – presence of del(17p) (HR 14.9, p <0.0001) and unmutated *IGHV* (HR 3.6, p=0.04). These two factors have also been identified by the German CLL study group as associated with poor PFS.[14] In the MD Anderson dataset, only 10% of the with unmutated *IGHV* who received first-line FCR had maintained progression-free remission beyond 9 years follow up (compared to 60% for patients with mutated *IGHV*) (MDACC, unpublished data). In addition, patients with del(17p) or *TP53* gene mutation have poor outcomes with conventional chemoimmunotherapy regimens such as FCR, in part due to lack of wild-type p53 function, an important pathway for mediating cytotoxicity of purine analogs.[12,14] In the randomized first-line FC *vs.* FCR German CLL Study Group (GCLLSG) trial, CLL8, only 1 of the 22 (5%) patients treated on the FCR arm achieved CR with a median PFS of only 11.3 months.[14] Similarly, in the phase II firstline BR (bendamustine-rituximab) trial of the GCLLSG, none of the 8 patients with del(17p) achieved CR and the median PFS was only 7.9 months.[15] In a retrospective analysis of patients (n=63) with del(17p) receiving firstline therapy (majority FCR) at MDACC, 30% achieved CR, 3% nPR, and 30% PR.[16] Median PFS was 14 months. Based on these observations, it is clear that chemoimmunotherapy (CIT) is not an optimal first-line strategy for patients with unmutated *IGHV* and in those with del(17p)/*TP53* mutation. These patient are in need for novel therapy options and will be included this in trial.

Relapsed/refractory patients – Patients with relapsed/refractory CLL have very poor outcomes with the currently available chemotherapy regimens and therefore, will be included in the proposed study.

Combined venetoclax and ibrutinib offers a non-chemotherapy treatment option for these very high-risk patients who have no standard therapeutic option, and for whom standard regimens offer poor response rates with very poor durability.

Trial Update (June 7, 2017)

Cohort 1 (Relapsed/refractory). A total of 32 patients enrolled. Median age 58.5 (range, 32-76).
Prognostic markers: *IGHV* status [unmutated (n=22), mutated (n=4), no PCR (n=6)]; FISH status [del17p (n=9), del11q (n=12), T12 (n=5), neg (n=2), del13q (n=4)]
Responses: A total of 12 patients have reached 3 months of the combination therapy. Of these 12 pts, 4 have achieved CR, and 8 are in PR. All patients are MRD + (0.06-6.3%). A total of 6 patients have reached 6 months of the combination therapy. 4 are in CR (1 MRD negative); 1 PR, and one patient developed Hodgkin's transformation.

Cohort 2 (High-risk Frontline). A total of 39 patients enrolled. Median age 65 (range, 35-82).
Prognostic markers: *IGHV* status [unmutated (n=27), mutated (n=7), no PCR (n=4), not done (n=1)]; FISH status [del17p (n=7), del11q (n=10), T12 (n=5), neg (n=4), del13q (n=13)]
MRD responses: A total of 11 patients have reached 3 months of the combination therapy. Of these 11 pts, 4 are MRD negative in the bone marrow, and remaining patients have low level MRD (0.02-2.1%).
A total of 3 patients have reached 6 months of the combination therapy – all 3 are in CR and MRD negative.

Given encouraging clinical activity, the protocol was discussed in the Leukemia meeting, and in discussion with the trial sponsor, we propose to increase the sample size of the current cohorts to better assess the toxicity and efficacy of the regimen.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Patients with a diagnosis of CLL/SLL:
   Cohort 1: Refractory to and/or relapsed after at least one prior therapy will be eligible
   Cohort 2: Untreated patients with high-risk features (del(17p), or mutated *TP53*, or del(11q), or unmutated *IGHV*, or ≥65 years of age) provided they have active disease requiring treatment as defined by the International Working Group for CLL (IWCLL).
2. Age 18 years or older
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
4. Patients must have adequate renal and hepatic function
   - Total bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for patients with Gilbert's disease (In pts with elevated total bilirubin due to increased indirect bilirubin, pts with direct bilirubin ≤1.5 x ULN are eligible)
   - Creatinine clearance >50 mL/min (calculated according to institutional standards or using Cockcroft-Gault, MDRD, or CKD-EPI formula)
   - ALT and AST ≤3.0 x ULN, unless clearly due to disease involvement
5. Platelet count of greater than 20,000/µl, with no platelet transfusion in 2 weeks prior to registration. This criteria is waived if the thrombocytopenia is due to bone marrow involvement with the disease
6. Women of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of study drugs and must agree to use an effective contraception method during the study and for 30 days following the last dose of study drug. Women of non- childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Men who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug
7. Free of prior malignancies for 2 years with exception of patients diagnosed with basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast, who are eligible even if they are currently treated or have been treated and/or diagnosed in the past 2 years prior to study enrolment. If patients have another malignancy that was treated within the last 2 years, such patients may be enrolled, if the likelihood of requiring systemic therapy for this other malignancy within 2 years is less than 10%, as determined by an expert in that particular malignancy at MD Anderson Cancer Center, and after consultation with the Principal Investigator.
8. Patients or their legally authorized representative must provide written informed consent

3.2 Exclusion Criteria

1. Major surgery, radiotherapy, chemotherapy, biologic therapy, immunotherapy, investigational therapy within 3 weeks prior to the first dose of the study drugs

2. Uncontrolled active systemic infection (viral, bacterial, and fungal)
3. Known positive serology for human immunodeficiency virus (HIV), due to potential drug-drug interactions between anti-retroviral medications and the study drugs
4. Active hepatitis B infection (defined as the presence of detectable HBV DNA, HBe antigen or HBs antigen). Subjects with serologic evidence of prior vaccination (HBsAg negative, anti-HBs antibody positive, anti-HBc antibody negative) are eligible. Patients who are HBsAg negative/HBsAb positive but HBcAb positive are eligible, provided HBV DNA is negative.
5. Active hepatitis C, defined by the detectable hepatitis C RNA in plasma by PCR
6. Active, uncontrolled autoimmune phenomenon (autoimmune hemolytic anemia or immune thrombocytopenia) requiring steroid therapy with >20mg daily of prednisone dose or equivalent
7. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 2 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
8. Patient is pregnant or breast-feeding
9. Concurrent use of warfarin
10. Received strong CYP3A inhibitors or strong CYP3A inducers within 7 days of starting study drugs
11. Consumed grapefruit, grapefruit products, Seville oranges, or star fruit within 7 days of starting study drugs.
12. Prior treatment with venetoclax or ibrutinib
13. Malabsorption syndrome or other condition that precludes enteral route of administration
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.

4.0 TREATMENT PLAN

This is an open-label Phase II study. Patients will receive treatment according to the table (TABLE 1) below. Each cycle is 4 weeks.

TABLE 1

	C1D1-28	C2D1-28	C3D1-28	C4D1 ---> C27D28
Ibrutinib	**420mg once daily**	**420mg once daily**	**420mg once daily**	**420mg once daily**
Venetoclax	**-**	**-**	**-**	**20mg daily x1 week then; 50mg daily x1 week then; 100mg daily x1 week then; 200mg daily x1 week then; 400mg daily continuous**

Patients will receive ibrutinib monotherapy for 3 cycles. Each cycle is 4 weeks. At the start of cycle 4, venetoclax will be added as per the schema above (weekly dose escalation). The combination of venetoclax and ibrutinib will continue for an additional 24 cycles for a total of 27 cycles of treatment. Disease assessment with bone marrow and imaging (CT scan or PET) will be scheduled at the

following time points: Baseline and at the completion of cycle 3, 6, 9, 15, and 27. Patients who are BM MRD negative at cycle 27 can stop ibrutinib (other patients may continue ibrutinib). Venetoclax will stop at cycle 27 for all BM MRD negative patients. For patients who are BM MRD positive at end of cycle 27, can continue the combination of ibrutinib and venetoclax for 12 additional cycles. (Note: For patients who have already completed C27 and were MRD+ and are currently on ibrutinib monotherapy – venetoclax can be added for a total of 12 cycles. Venetoclax will be added at the same dose that they were on at the time of stopping venetoclax. A bone marrow assessment is required at the end of this additional 12 cycle s of the combination of ibrutinib and venetoclax)

Subsequent cycles can be initiated +/- 7 days to accommodate for patient travel, logistics, and holidays. Longer delays (>7 days) are allowed (such as patients undergoing surgery, other medical conditions) – These should be discussed with the study PI, and the reason for such delays should be documented in the medical record. NOTE: for venetoclax dose ramp-up period, the weekly dose-escalation can be delayed by up to 14 days to accommodate for travel, logistics, intercurrent illness, and holidays.

The following are recommended prophylactic medications. For individuals who are allergic, an equivalent replacement may be identified.

- Allopurinol 300 mg PO daily (or another uric acid lowering agent) for the first 7 days of cycle 1 (at the start of ibrutinib monotherapy) is recommended for tumor lysis prophylaxis.
- Valacyclovir 500 mg PO daily (or acyclovir) for all treatment cycles and for at least 3 months after completion of treatment is recommended for herpes virus prophylaxis.
- PCP prophylaxis may be given at the discretion of the treating physician but is recommended for recent or concurrent corticosteroid use.
- Hematopoietic growth factors may be used at the discretion of the treating physician.

5.0 Tumor Lysis Syndrome (TLS) Management

The main toxicity in the Phase I study of venetoclax was first-dose-related TLS, which has been effectively managed with the current dosing schedule and the use of TLS prophylaxis. Experience from the Phase I study provided a dosing schedule designed to mitigate the risk of TLS by decreasing peripheral lymphocyte counts gradually during a step-up dosing period. Initiation of ibrutinib prior to venetoclax may also mitigate the risk of TLS. The Cairo-Bishop definition and grading of TLS is provided in Appendix 1.

The following three risk categories for developing TLS are identified (the risk category will be assigned based on the blood counts and imaging studies, done prior to initiation of venetoclax):

1. Low-risk category:
   The presence of all measurable lymph nodes with the largest diameter < 5 cm by radiographic assessment AND absolute lymphocyte counts < 25×10^9/L.
2. Medium-risk category: patients who meet ONLY ONE of the following criteria at screening will be classified as medium risk:
   An absolute lymphocyte count ≥ 25×10^9/L
   OR

The presence of lymph nodes with the largest diameter ≥ 5 cm and < 10 cm by radiologic assessment

3. High-risk category: Patients who meet the following criteria will be classified as high risk for developing TLS:

   The presence of BOTH an absolute lymphocyte count ≥ 25 × 10^9/L AND a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment

   OR

   The presence of any lymph node with the largest diameter ≥ 10 cm by radiologic assessment

All patients, irrespective of their TLS risk category, must receive the following TLS prophylaxis prior to the initiation of the first dose and subsequent dose escalations of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 48-72 hours prior to dose
- Oral hydration will be done as standard of care (per package insert)
- Serum chemistry and hematology laboratory samples must be drawn any time within 72 hours prior to first dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax in the dose escalation period. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, the first dose of venetoclax must be delayed until resolution. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for subjects with CrCl <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6 to 8, and 24 hours

ALC = absolute lymphocyte count; LN = lymph node.

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

Note: 24 hour labs can be done +/- 6 hours; 4, 8, 12 hours labs can be done +/-3 hours.

For hospitalized patients, the morning labs (typically obtained early am) will serve as pre-dose labs for that day

– The 6-8 hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

– Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

– Additional laboratory assessments may be performed per investigator discretion.

– For High-Risk pts for dose escalation beyond 50mg dose level: hospitalization may be considered, especially if decreased renal function, or prior evidence of TLS during ramp up.

- Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax and ibrutinib dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per Appendix 2. Please note Appendix 2 provides suggested management guidelines. Individual management variations are allowed in the best interest of the patient as per the judgement of the treating physician and/or PI. For patients with lab marker(s) indicative of TLS, the lab(s) could be repeated before TLS management is initiated. Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if the dose is held more than 7 days, with the exception of initial dose level of 20 mg (400 mg $\rightarrow$ 200 mg, 200 mg $\rightarrow$ 100 mg, 100 mg $\rightarrow$ 50 mg, 50 mg $\rightarrow$ 20 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose. Patients who are unable to dose-escalate to the next dose level due to either intercurrent illness, toxicity, logistics, etc. may continue the current venetoclax dose level and resume dose escalation at a later time point.

Downgrading Tumor Lysis Syndrome Risk Category

Patients classified as TLS high risk due to an ALC $\geq 25 \times 10^9$/L and a measurable lymph node with the largest diameter ≥ 5 cm but less than 10 cm by radiologic assessment may have a re-evaluation of their TLS risk category based on their most recent ALC for dose increases above 50 mg. Based on those results, one of the following two options may be implemented:

- If the patient's ALC decreases to $< 25 \times 10^9$/L, the patient may be categorized as TLS medium risk and follow the management guidelines for the TLS medium-risk category for subsequent dose increases (to 100, 200, and 400 mg) of venetoclax during the ramp-up period.
- If the patient's ALC remains $\geq 25 \times 10^9$/L, the patient will remain in the TLS high-risk category and continue to follow management guidelines for TLS high-risk patients for subsequent dose increases of venetoclax during the ramp-up period. Re-assessment of the patient's TLS risk category can occur prior to each subsequent dose increase.

NOTE: TLS medium risk patients who are admitted for close monitoring (such as those with low kidney function, or very high WBC counts, or other reason as determined by the treating physician in the best interest of the patient) can have subsequent dose escalation done as outpatient (and follow TLS medium risk guidelines) if they tolerated the previous dose-escalation without any major issues.

6.0 Background Drug Information

6.1 Venetoclax

6.1.1 Formulation

The venetoclax tablets will be packaged in plastic bottles or blister cards and labeled per local regulatory requirements. The tablets must be stored at 15°C to 25°C (59°F to 77°F). For further details, see the venetoclax Investigator's Brochure.

6.1.2 Dosage, Administration, and Storage
Venetoclax will be supplied by Abbvie. Study patients will self-administer venetoclax tablets by mouth once daily. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast.

If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the study log. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken. Unused portions of the study drug will be discarded as per the institutional policies.

6.2 Ibrutinib
The insurance provider and/or the patient will be responsible for the cost of ibrutinib. Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Ibrutinib 420 mg will be administered orally once daily. Ibrutinib should be administered with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Ibrutinib should be taken at approximately the same time each day. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose. Unused portions of the study drug will be discarded as per the institutional policies.

6.2.1 How Supplied
Supplied as 140mg capsules

6.2.2 Stability
Store bottles at room temperature 20°C to 25°C

6.2.3 Pharmacokinetics
Absorption: Ibrutinib is absorbed after oral administration with a median Tmax of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC (mean ± standard deviation) in patients at 420 mg is 680 ± 517 ng·h/mL. Administration with food increased ibrutinib AUC by approximately 2-fold.
Distribution: Reversible binding of ibrutinib to human plasma protein in vitro was 97.3%.
Metabolism: Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib.
Elimination: The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces.
Renal Impairment: Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is <

10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to ibrutinib. There are no data in patients with severe renal impairment (creatinine clearance < 25 mL/min) or in patients on dialysis.
Hepatic Impairment: Ibrutinib is metabolized in the liver. No clinical trials have been completed in patients with impaired hepatic function.

7.0 Dose Delays and Modifications

Patients who experience Grade 3 or 4 toxicity that can be clearly attributed to either venetoclax or ibrutinib may continue treatment with the other agent while the causative agent is delayed until resolution of toxicity to grade ≤1 or baseline. In cases where Grade 3 or 4 toxicity cannot be attributed to a specific study drug, both study drugs should be stopped regardless of attribution of toxicity until the toxicity is resolved to grade ≤1 or baseline. Note: In selected cases, consideration may be made for dose reductions/modifications of the study drugs for less than G3 toxicities (for e.g. persistent grade 2 diarrhea, grade 2 skin rash etc).

Dose modifications for hematologic toxicity must be made with consideration of the increased frequency of hematologic compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2 –4 hematologic toxicity at presentation. As a consequence, dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the National Cancer Institute-Working Group (NCI-WG) CLL grading scale (see Appendix 3). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE, v4.03, will be used. In some patients with hyperleukocytosis with lymphocytosis, it may be difficult to evaluate for neutropenia – these patients with ANC <1.0 will be discussed with the study PI to assess the grade of neutropenia.

Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider withholding ibrutinib treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, consider decreasing ibrutinib to 140mg once daily, and monitor subject for toxicity.

Note: Specific guidelines for use of azole therapy and ibrutinib dosing. With the use of voriconazole, fluconazole, posaconazole (posaconazole dose ≤200 mg BID): decrease ibrutinib to 140mg once daily. For posaconazole dose >200mg BID: interrupt ibrutinib.

Venetoclax should not be administered with moderate CYP3A inhibitors or P-gp inhibitors unless absolutely necessary. If a moderate CYP3A inhibitor or P-gp inhibitor absolutely must be used, venetoclax should be dose reduced by at least 50% and these patients should be monitored closely for toxicities. If a strong CYP3A inhibitor absolutely must be used, venetoclax should be dose reduced by at least 75% and these patients should be monitored closely for toxicities. Note: Concomitant use of venetoclax with strong CYP3A inhibitors at the start of venetoclax and during ramp-up phase is contraindicated.

Note: Specific guidelines for use of azole therapy and venetoclax dosing. Fluconazole: at least 50% dose reduction. Voriconazole and posaconazole: at least 75% dose reduction. Concomitant use of

venetoclax with voriconazole/posaconazole at the start of venetoclax and during ramp-up phase is contraindicated. See Table 2 below for recommended Venetoclax Dose reductions for concomitant

Assigned Venetoclax Dose	**Dose if Co-Administered with Moderate CYP3A or P-gp Inhibitor or Fluconazole**	**Dose if Co-Administered with a Strong CYP3A Inhibitor or Voriconazole or Posaconazole**
400 mg daily	200mg daily	100mg daily
200 mg daily	100mg daily	50mg daily
100 mg daily	50mg daily	20mg daily
50 mg daily	20mg daily	10mg daily

medications.

Concomitant use of Strong CYP3A inhibitors, voriconazole, and posaconazole during ramp-up phase is prohibited.

Table 3. Dose Modifications for Hematologic Toxicity: Venetoclax and Ibrutinib

Hematologic Toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 neutropenia, without infection or fever, first episode*; Grade 3 thrombocytopenia, first episode	• Hold venetoclax and ibrutinib. • When counts recover to ≤ Grade 2, resume previous doses of venetoclax and ibrutinib. • Consider G-CSF or growth factors for neutropenia as indicated.
Grade 3 or 4 neutropenia with infection and/or fever, first episode	• Hold venetoclax and ibrutinib until fever and/or infection resolves. • Consider G-CSF or growth factors for neutropenia as indicated. • When counts recover to ≤ Grade 2 and infection has been fully treated, resume previous doses of venetoclax and ibrutinib.
Recurrent Grade 3* or 4 neutropenia with/without fever and infection despite G-CSF; recurrent Grade 3 thrombocytopenia	• Hold venetoclax and ibrutinib • Consider G-CSF or growth factors for neutropenia as indicated. • When counts recover to ≤ Grade 2 and/or platelets are ≥ 75×10^9/L, resume venetoclax and ibrutinib at one dose level reduction (For patients with second or subsequent episodes of G3 neutropenia without infection/fever: the doses of ibrutinib/venetoclax may be resumed without dose reduction, after counts recover to ≤ Grade 2)
Grade 4 thrombocytopenia and/or symptomatic bleeding	• Hold venetoclax and ibrutinib for at least 7 days and until resolution of bleeding. • Platelets may be transfused at the discretion of the investigator. • When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax and ibrutinib at one dose level reduction.

G-CSF = granulocyte colony-stimulating factor.

* in patients with Grade 3 neutropenia (without infection/fever), the study drugs may continue without interruption.

Table 4. Dose Modifications for Non-Hematologic Toxicity: Venetoclax and Ibrutinib

Non-hematologic Toxicity	
Event(s)	**Dose Delay or Modification**
Blood chemistry changes or symptoms suggestive of TLS	• Withhold the next day's dose of both venetoclax and ibrutinib. If resolved within 24 to 48 hours of last dose, resume at the same dose. • For any blood chemistry changes requiring more than 48 hours to resolve, resume venetoclax at a reduced dose • For any events of clinical TLS, resume venetoclax at a reduced dose following resolution
Grade 3 or 4 non-hematologic toxicity not specifically described above	• Delay venetoclax and ibrutinib for a maximum of 28 days. • First episode: If improvement to Grade $\leq$ 1 or baseline, resume previous doses of venetoclax and ibrutinib. • For subsequent episodes: If improvement to Grade $\leq$ 1 or baseline, restart venetoclax and ibrutinib at one dose level reduction.

Table 5. Venetoclax Dose Reduction

Venetoclax Current Dose Level	Venetoclax Dose Reduction
400 mg daily	300 mg daily
300 mg daily	200 mg daily
200 mg daily	100 mg daily
100 mg daily	50 mg daily
50 mg daily	Discontinue venetoclax, or consider 20 mg daily
20 mg daily	Discontinue venetoclax

Table 6. Ibrutinib Dose Reduction

Ibrutinib Current Dose Level	Ibrutinib Dose Reduction
420 mg daily	280 mg daily
280 mg daily	140 mg daily
140 mg daily	Discontinue ibrutinib, or consider a schedule of 70mg daily (or 140mg every other day*)

* this would be done rarely, on a case by case basis, and the reason would be documented in the medical record

Note: : For toxicities that could be attributable to either drug, venetoclax or ibrutinib or both could be held/modified, based on the perceived contribution (as per treating physician, in discussion with PI) of respective drug to the toxicity.

Note: Patients who discontinue one of the study drugs completely, may continue with the other drug and stay on the study.

Gradual dose increase following resolution of toxicity leading to a dose reduction may be considered on a case-by-case basis in discussion with the study PI.

Dose modifications other than as stated above are permitted in the best interest of the patient, after discussion with the study PI, and will be documented in the medical record.

Occasional missed doses of venetoclax and/or Ibrutinib for any reason will not be considered a protocol deviation. A protocol deviation will result when patients miss >2 consecutive weeks of venetoclax and/or Ibrutinib for any reason (excluding patients who are holding therapy under Section 7.0)

8.0 Concomitant Therapy

8.1 Allowed concomitant therapy

All concomitant medications will be noted in the medical record. Patients should receive full supportive care during study participation, including transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Anti-infective prophylaxis for viral, fungal, bacterial or *Pneumocystis* infections is permitted. Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects; therefore, trimethoprim sulfamethoxazole can be considered for *Pneumocystis* prophylaxis with close clinical monitoring. However, this prophylaxis is not required per protocol and would only be given in specific patient circumstances. Patients may receive hematopoietic neutrophil, erythrocyte, and platelet growth factor support according to ASCO guidelines. Patients may receive IVIG support for hypogammaglobulinemia as recommended by NCCN guidelines.

8.2 Excluded concomitant therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Immunotherapy
- Any therapies intended for the treatment of CLL/SLL whether FDA-approved or experimental (outside of this study)
- The use of warfarin is not allowed during this study.
- Receipt of live viral vaccines within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment

Please note: Concurrent localized radiation including I-131 treatment is allowed'

The following concomitant medications are not allowed from 7 days prior to the first dose of study drugs and during the study drug administration:

- Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids (Chronic use of steroids at prednisone dose less

than 20mg is permitted such as for patients with immune cytopenias, rheumatological disorders is permitted; Brief use of higher dose steroids is permitted such as for arthritis, gout, skin rash, asthma exacerbation and other medical conditions). Patients who are taking chronic steroids for non-cancer related medical reasons are allowed to continue steroids during the study.

- Strong CYP3A inducers such as rifampin, rifabutin, phenytoin, carbamazepine, and St. John's Wort.
- Grapefruit, Seville oranges, Star fruit

9.0 Pretreatment Evaluations

1. Pretreatment evaluation will include a complete history and physical examination including vital signs, ECOG performance status, height and weight and recording of concurrent medications (within 7 days of the first dose) (For height: any prior measurement at MDACC is allowed; it does not have to be within 7 days of the first dose)
2. Complete blood count (hemoglobin, white blood cell count, platelet count, white blood count differential) (within 7 days of the first dose)
3. Clinical laboratory evaluation will include serum sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH, β-2 microglobulin, immunoglobulins (within 7 days of the first dose)
4. PT, aPTT (within 14 days of the first dose)
5. Urinalysis (within 14 days of the first dose)
6. HIV Ab, Hepatitis C ab, HBsAg, anti-HBcAb (within 90 days of the first dose)
7. Women of childbearing potential must have a negative serum or urine β-hCG pregnancy test result within 7 days of the first dose.
8. 12-lead EKG (within 30 days of the first dose)
9. MUGA or Echocardiogram (within 30 days of the first dose)
10. Bone marrow aspiration and biopsy (within 90 days of the first dose if no intervening treatment for CLL given)
11. CT scan of the neck (if indicated), chest, abdomen, and pelvis with contrast, within 60 days of the first dose with no intervening treatment for CLL given. Patients with palpable cervical lymphadenopathy noted at screening physical examinations should have imaging of the neck included in their screening imaging studies and at subsequent time points for response assessment. Note: PET scan may be used instead of the CT scan imaging.
    Note: Contrast administration may be withheld for patients with contrast allergy, poor renal function, or other reasons, in the best interest of the patient (This applies to pretreatment evaluation, and evaluations during the study)
12. B, T cell counts and subset analyses on the peripheral blood (within 14 days of the first dose)

Note: In this protocol, the patient receives ibrutinib via prescription through their health insurance. Patients are generally able to receive ibrutinib within 1 week of their pretreatment evaluation at MDACC. In an occasional patient, the ibrutinib supply is delayed. If such patient is from out of town, the patient may be able to start ibrutinib, provided it is still within 14 days of their pretreatment evaluation at MDACC, and they had a physical examination and CBC with differential, and basic chemistries done via a local physician within 7 days of starting ibrutinib.

10.0 Evaluations During The Study

Note: all evaluations could be performed +/-7 days to account for holidays, patient travel schedule etc.

Cycles 1-3 (Ibrutinib monotherapy)

1. Patients will have CBC, platelet count and differential at least weekly during cycle 1 and at least every 2 weeks during cycles 2-3.
2. Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH will be performed at least weekly during cycle 1 and at least every 2 weeks during cycles 2-3.
3. Complete history and physical examination including vital signs at least every 2 weeks during cycle 1, and monthly during cycles 2-3.
4. Serum immunoglobulins, serum β-2 microglobulin (end of cycle 3)
5. B, T cell counts and subset analyses on the peripheral blood (end of cycle 3)
6. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation (end of cycle 3).
7. CT scan of the neck (if indicated), chest, abdomen, and pelvis with contrast (end of cycle 3). PET scan may be used instead of the CT scan imaging.

Cycles 4-6 (Venetoclax + Ibrutinib)

1. TLS monitoring will be required at the time of initiation of venetoclax (per section 5.0).
2. Patients will have CBC, platelet count and differential at least weekly during cycle 4, and at least every 2 weeks during cycles 5 and 6.
2. Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH will be performed at least weekly during cycle 4, and at least every 2 weeks during cycles 5 and 6.
3. Complete history and physical examination including vital signs at least weekly during cycles 4, and monthly during cycles 5 and 6.
4. Serum immunoglobulins, serum β-2 microglobulin (end of cycle 6)
5. B, T cell counts and subset analyses on the peripheral blood (end of cycle 6)
6. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation (end of cycle 6).
7. CT scan of the neck (if indicated), chest, abdomen, and pelvis with contrast (end of cycle 6). PET scan may be used instead of the CT scan imaging.

Cycle 7 onwards (Venetoclax + Ibrutinib)

1. Patients will have CBC, platelet count and differential at least monthly (+/- 7 days) for the first year of the trial, then every 3 months (+/- 7 days).
2. Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH will be performed at least monthly (+/- 7 days) for the first year of the trial, then every 3 months (+/_ 7 days).
3. Complete history and physical examination including vital signs at least every 3 months (+/- 7 days).

4. Serum immunoglobulins, serum β-2 microglobulin (approximately every 3 months for the first year, then every 3-6 months)
5. B, T cell counts and subset analyses on the peripheral blood (approximately every 3 months for the first year, then every 3-6 months)
6. Bone marrow aspiration and biopsy with multi-color flow cytometry for MRD evaluation (end of cycle 9, 15, and 27). After cycle 27, for patients who are MRD+ in bone marrow: bone marrow will be done approximately once yearly. Serial bone marrow will stop once MRD negative. (Note: if the patient has a bone marrow flow performed, peripheral blood flow could be skipped for that time-point, and vice versa)
7. After completion of cycle 27, peripheral blood flow-cytometry approximately every 6 months.
8. CT scan of the neck (if indicated), chest, abdomen, and pelvis with contrast (end of cycle 9, 15, and 27). After cycle 27, for patients who have residual disease on imaging studies: CT scan (or PET scan) will be done once yearly (+/- 1 month). Serial imaging studies will stop once no active disease noted.

NOTE: Assessments during extended cycle 3.
For some patients, venetoclax addition (i.e. start of cycle 4) will be delayed. These patients will enter an extended cycle 3 phase of ibrutinib monotherapy. During this time, patients will have labs at least monthly, history and physical examination at least monthly, and return to MDACC at least every 3 months. The end of cycle 3 evaluations (such as bone marrow and imaging studies) can be delayed to be closer to the venetoclax addition.

NOTE: All treatment decisions will be made by the physicians at the MDACC. Patients will be seen at MDACC at least monthly for the first 6 cycles, and at least every 3 months thereafter. After cycle 27, patients will return to MDACC at least every 6 months (+/- 6 weeks).
For patients continuing ibrutinib after cycle 27, CBC will be obtained every approximately 3 months.
Patients may have laboratory work and physical examination done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at a local clinic will be forwarded to the patient's attending physician at MDACC, or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Due to COVID-19 pandemic, many patients in follow-up (those without any active therapy) are unable to return to MDACC due to concerns for travel and COVID-19 infection. At this time, we will allow some flexibility in return to MDACC as long as the patients are able to see their doctor for labs and physical examination. These records will be sent to the study and signed by the study PI.
The following guidelines will apply due to the COVID-19 pandemic.

For patient beyond cycle 27 who have completed all protocol specified therapy and have stopped both ibrutinib and venetoclax, patient's follow-up will be as follows:

- MDACC visits every approximately 12 months (+/- 3 months). In rare situations, a longer time-interval between MDACC may be allowed due to travel issues. These will be granted on a case by case basis in discussion with PI and the reason recorded in the medical record.
- Labs (CBC with diff, basic chemistries) and physical examination every approximately 6 months

- Peripheral blood flow-cytometry for CLL MRD assessment every 6-12 months (preference will be for them to be done every 6 months at MDACC). Note: An outside lab assay with a sensitivity of 10^{-4} is acceptable.

For patients beyond cycle 27 who are still taking either ibrutinib or venetoclax or both, patient's follow-up will be as follows:

- MDACC visits every approximately 6 months (+/- 3 months). In rare situations, a longer time-interval between MDACC may be allowed due to travel issues. These will be granted on a case by case basis in discussion with PI and the reason recorded in the medical record.
- Labs (CBC with diff, basic chemistries) and physical examination every approximately 3 months
- Peripheral blood flow-cytometry for CLL MRD assessment every 6-12 months (preference will be for them to be done every 6 months at MDACC). Note: An outside lab assay with a sensitivity of 10^{-4} is acceptable.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix 4)

3. Protocol required evaluations outside MDACC will be documented by fax. Faxed evaluations will be dated and signed by the MDACC physician/investigator indicating that they have reviewed it.

4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

6. The home physician will be requested to report to the MDACC physician/investigator all life threatening events within 24 hours of documented occurrence.

7. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

11.0 Criteria for Response

Response will be assessed by the investigator, based on physical examinations, CT scans, laboratory results, and bone marrow examinations, using modified response criteria for CLL. OR is defined as a CR or PR (or CR with incomplete marrow recovery) as determined by investigator assessment using CLL

response criteria.[17] Patients with missing or no response assessments will be classified as non-responders.

12.0 Adverse Event Reporting

12.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines
These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.
The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all patients enrolled on the trial.

12.1.1 PDMS/CORe will be used as the electronic case report form for this protocol. Adverse events will be documented in the medical record and entered into PDMS/CORe.
12.1.2 These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

a. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event.
    i. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
        a. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        b. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
b. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
c. These adverse events will be recorded in the case report form:
    i. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    ii. All serious adverse events regardless of attribution to the study drug(s).
    iii. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.

d. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    i. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
e. Serious adverse events will be reported according to institutional policy.
f. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

12.1.3 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32). Pregnancy, drug overdose, and secondary malignancy (except squamous cell cancer of skin, basal cell cancer of skin) will be handled as SAE.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

- Any individual expedited SAE reports required by the FDA will be reported to Abbvie.
- **All Serious Adverse Events must be reported to Abbvie within 7 days.**

- All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:
    - **AbbVie :** Email: PPDINDPharmacovigilance@abbvie.com
    - Fax: (847) 938-0660

13.0 Discontinuation of Study treatment

A patient's treatment with study drugs may be discontinued for any of the following reasons:

- Clinically significant progressive disease
- Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient.
- Investigator decision
- Patient decision (e.g., withdrawal of consent)
- Study termination by Sponsor

14.0 Optional Correlative Studies

Peripheral blood samples will be obtained from patients who agree for correlative studies. Missed time points will not be considered a protocol deviation.

Approximately 40ml of peripheral blood will be collected at the following time-points (pretreatment, C1D1, C1D15, C2D1, C3D1, C4D1, C5D1, end of C6, end of C9, end of C12, end of C15, end of C21, end of C27, and then approximately yearly) and stored in the Leukemia Research Bank. Approximately 5cc of bone marrow aspirate will be collected at the following time-points (pretreatment, end of C3, end of C6, end of C9, end of C15, and end of C27) and stored in the Leukemia Research Bank. Approximately 5cc of bone marrow aspirate will be collected for patients having a bone marrow after C27 (such as those who are MRD+) and stored in the Leukemia Research Bank.

Please see Appendix 5 for description of additional blood/aspirate samples. These samples will be processed to save plasma samples and isolate CLL cells and isolated leukemia cells and plasma will be used for several different assays. These include levels of cytokines such as CCL3 and CCL4, percent of CD19 and CD5 positive cells, ex vivo testing with venetoclax after C2 or C3 of ibrutinib, pre and post samples for pseudoemperipolesis and migration assays with stroma, transcript levels of BCR pathway and Bcl-2 family survival and proapoptotic family members. All pre and post samples will be analyzed for 260 total and/or phospho proteins by RPPA assay. These include Bcl-2 anti-and pro-apoptotic proteins, BCR receptor axis proteins such as total and phospho Akt, ERK, GSK3beta etc. These results will be validated and compared with decline in phospho-BTK protein levels.

Bone marrow aspirate (4 ml) samples will be used for RPPA assay and will be compared with the data obtained in peripheral blood. The aim of these laboratory studies is to determine changes in cell surface markers, gene expression, responsiveness of the leukemia cells to Bcl-2 and BTK inhibition, and plasma cytokine and biomarker levels. These studies will also identify if ex vivo combination testing compares with the in vivo combinations.

A sputum sample will be collected at screening which will be stored in the Leukemia Research Bank for genetic testing.

In addition, the samples collected above will be examined by the MD Anderson MoonShot CLL group for DNA/RNA sequencing, metabolic changes, anti-apoptotic protein expression, and drug synergism in a series of correlative studies developed under the MoonShot program and conducted by the members of the CLL MoonShot group.

Isolated CLL cells from blood and marrow will be sent to Dr. Chiorazzi (Karches Center for Oncology Research, The Feinstein Institute for Medical Research Professor of Medicine and of Molecular Medicine Hofstra Northwell School of Medicine, 350 Community Drive, Manhasset, NY 11030). Proliferative and resting clones of cells will be separated by his lab and these cells will be analyzed for omics to determine if there are specific signatures in cells that predict for achievement of MRD negativity.

Isolated CLL cells from blood and marrow will be sent to Drs. Cathy Wu and Matthew Davids (Dana Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215) for BH3 profiling, and DNA/RNA sequencing with the goal to identify markers of response/resistance.

As standard-of-care, we will perform targeted gene sequencing to assess for known CLL-associated genetic mutations at baseline and relapse (such as p53, ATM, NOTCH1, SF3B1, MYD88, BIRC3, others) and correlate these with clinical response, disease-progression, and Bcl-2 family pro- and anti-apoptotic protein levels.

15.0 Statistical Considerations

This is a phase II open-label parallel study to assess the efficacy and safety of the combination therapy with venetoclax and Ibrutinib in high risk CLL patients. The primary endpoint is the best response (CR/CRi) achieved at any time during the study period for up to 2 months after completion of the combination therapy. The study would involve two parallel cohorts:
Cohort 1 – Relapsed/refractory patients (N=80 patients)
Cohort 2 – High-risk CLL patients with no prior therapy (N=120 patients)

To better assess the toxicity and efficacy of the combination Therapy and to allow for adequate power in the subgroup analyses, we will enroll an additional 41 patients for cohort 1 to reach a total sample size of 80. Also, we will enroll an additional 81 patients for cohort 2 to reach an overall sample size of 120. For Cohorts 1 and 2 an optimal three-stage design will be used (Chen, T.T. 1997. Statistics in Medicine, pages 2701-2711). For cohort 1, the design assumes a sample size of 15 and 39 respectively, for the first and second stage, and a maximum sample size of 80. For cohort 2, the design assumes a sample size of 19 and 39 respectively, for the first and second stage, and a maximum sample size of 120.

For Cohort 1, a historical response rate of 20% and a target response rate of 40% are assumed under the null and the alternative hypotheses, respectively. In the first stage, we will enroll 15 patients; if 3 or fewer achieve best response of CR/CRi, we will stop enrolling patients in this cohort. Otherwise, we will continue to enroll additional 24 patients in the second stage. If 11 or fewer achieve best response of CR/CRi among the total 39 patients from Stages I and II, we will stop enrolling patients in this cohort. Otherwise, we will continue enrollment until a total of 80 patients have been reached. The combination therapy is deemed as promising if there are 20 or more responders out of these 80 patients. The design

has a type I error rate of 0.043, an 85.6% power and a probability of early termination of 64.8% and 93.8% respectively at first stage and second stage, under the null hypothesis.

For Cohort 2, a historical response rate of 25% and a target response rate of 50% are assumed under the null and the alternative hypotheses, respectively. In the first stage, we will enroll 19 patients; if 5 or fewer achieve best response of CR/CRi, we will stop enrolling patients in this cohort. Otherwise, we will continue to enroll additional 20 patients in the second stage. If 13 or fewer achieve best response of CR/CRi among the total 39 patients from Stages I and II, we will stop enrolling patients in this cohort. Otherwise, we will continue enrollment until a total of 120 patients have been reached. The combination therapy is deemed as promising if there are 38 or more responders out of these 120 patients. The design has a type I error rate of 0.021, a 95.2% power and a probability of early termination of 66.8% and 92.6% respectively at first stage and second stage, under the null hypothesis.

For each cohort, patient enrollment will be temporarily suspended when the enrollment for the first stage or second stage patients has been completed yet not enough responders have been observed to trigger the start of the next stage.

In order not to delay patient enrollment, patients will be allowed to enroll on the protocol and start ibrutinib monotherapy while previously enrolled patients are undergoing toxicity and response assessment of the combination therapy. Venetoclax will not be added unless the toxicity stopping rules and response criteria (per the three-stage design) have not been met. In this situation, ibrutinib monotherapy cycle 3 may be extended for up to 6 months.

As a secondary objective, we will also assess if the combination therapy results in improvement in the rate of CR/CRi in subgroups of patients defined by IGHV mutation status or FISH subtypes. For example, we expect that ~80% of enrolled patients will have IGHV unmutated. For cohort 1, we assume that the CR/CRi rate is 15% and 30% under the null and alternative hypotheses, respectively. Thus with a total of 64 patients in this subgroup (i.e., IGHV unmutated), we will have 84% power to detect such as 15% difference using exact binomial best and with a type I error rate of 0.034. For cohort 2, we assume that the CR/CRi rate is 20% and 40% under the null and alternative hypotheses, respectively. Thus with a total of 96 patients in this subgroup, we will have 99% power to detect such as 20% difference using exact binomial test and with a type I error rate of 0.040.

Similarly, we anticipate ~40 to 60% (n=32 to 48) of patients will have del17p or del11q. For cohort 1, we assume that the CR/CRi rate is 10% and 25% under the null and alternative hypotheses, respectively. Thus with a total of 32 (48) patients in this subgroup (i.e., del17p or del11q), we will have 57% (80%) power to detect such as 15% difference using exact binomial best and with a type I error rate of 0.046 (0.025). For cohort 2, we assume that the CR/CRi rate is 15% and 35% under the null and alternative hypotheses, respectively. Thus with a total of 48 (72) patients in this subgroup (i.e., del17p or del11q), we will have 91% (97%) power to detect such as 20% difference using exact binomial best and with a type I error rate of 0.04 (0.03).

Additionally, toxicities (defined as prolonged grade ≥3 neutropenia or thrombocytopenia lasting >42 days; febrile neutropenia; hospitalization due to infection; early death; major bleeding due to thrombocytopenia)

will be monitored in each disease cohort separately using the Bayesian method of Thall, Simon and Estey.[18] Toxicity monitoring window will be from the start of combination therapy to up to 6 weeks of the combination therapy.

In the event that excess toxicities are noted, the trial enrollment will cease. The decision to enroll patients at a lower starting dose level will be made by the PI in discussion with the pharmaceutical sponsor after reviewing all the toxicity and efficacy data. A protocol amendment will then be submitted explaining the rationale for the lower dose level.

We will enroll both cohorts concurrently and for each cohort, we will apply the toxicity monitoring rule separately in cohort size of 3, starting from the 6th patient. The toxicity stopping rule to be applied to each cohort separately is as follows: a disease cohort will be stopped early if Prob(p>0.30 |data) > .92, where p denotes the probability of toxicity. This decision criterion will be applied for each disease cohort separately, after 6 patients have been enrolled and evaluated. Assuming a beta(.6, 1,4) priori for p, the above decision criterion implies that we will stop a cohort according to the tables 7a (for cohort 1) and 7b (for cohort 2) below. For example, we will stop the enrollment to a cohort if 5 or more patients experienced toxicities among the first 9 patients enrolled in that cohort.

Table 7a. Toxicity stopping boundaries for each cohort 1 (N=80).

Number of evaluable patients in a cohort	Number of patients with toxicities in a cohort is **at least**
6	4
9	5
12	7
15	8
18	9
21	10
24	11
27	12
30	13
33	14
36	15
39	17
42	18
45	19
48	20
51	21
54	22
57	23
60	24
63	25
66	26
69	27

72	28
75	29
78	30

Table 7b. Toxicity stopping boundaries for each cohort 2 (N=120).

Number of evaluable patients in a cohort	Number of patients with toxicities in a cohort is **at least**
6	4
9	5
12	7
15	8
18	9
21	10
24	11
27	12
30	13
33	14
36	15
39	17
42	18
45	19
48	20
51	21
54	22
57	23
60	24
63	25
66	26
69	27
72	28
75	29
78	30
81	31
84	32
87	33
90	34
93	35
96	36
99	37
102	38
105	39

108	40
111	41
114	42
117	43

The operating characteristics of this study design based on 5,000 simulations are illustrated in Table 8a (for cohort 1) and Table 8b (for cohort 2) respectively. The stopping boundary and the operating characteristics were generated using Shiny applications for toxicity monitoring (https://biostatistics.mdanderson.org/softwareOnline/) (developed by the Department of Biostatistics, M. D. Anderson Cancer Center.

Table 8a. Operating Characteristics for Toxicity Monitoring Rule in cohort 1.

True toxicity rate	Prob (stop early)	Average Sample Size
0.10	0.002	79.9
0.20	0.034	77.6
0.30	0.254	65.4
0.40	0.795	36.9
0.50	0.992	16.8

Table 8b. Operating Characteristics for Toxicity Monitoring Rule in cohort 2.

True toxicity rate	Prob (stop early)	Average Sample Size
0.10	0.002	119.8
0.20	0.034	116.3
0.30	0.291	93.9
0.40	0.899	42.0
0.50	0.999	16.8

For each cohort, the best response (CR/CRi) rate will be estimated along with the exact 95% confidence interval. Patients who drop out of the study prior to the assessment of response will be counted as non-responders for the primary analysis. Similar analyses will be performed to assess the CR/CRi rate in each subgroups of patients defined by IGHV mutation or FISH subtype. Safety data will be summarized using descriptive statistics. Time-to-event outcomes, including time to response, overall survival, progression-free survival will be estimated using the Kaplan-Meier method in each cohort. The immunological and molecular biomarker changes will be summarized over time and will be assessed using linear or non-linear mixed effect models as appropriate.

16.0 References

1. Gribben JG, O'Brien S. Update on therapy of chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(5):544-550.
2. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic

lymphocytic leukemia. *The New England journal of medicine.* 2000;343(26):1910-1916.
3. Gonzalez D, Martinez P, Wade R, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(16):2223-2229.
4. Jain N, O'Brien S. Chronic lymphocytic leukemia with deletion 17p: emerging treatment options. *Oncology.* 2012;26(11):1067, 1070.
5. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nature medicine.* 2013;19(2):202-208.
6. Chiorazzi N, Ferrarini M. B cell chronic lymphocytic leukemia: lessons learned from studies of the B cell antigen receptor. *Annual review of immunology.* 2003;21:841-894.
7. Stevenson FK, Caligaris-Cappio F. Chronic lymphocytic leukemia: revelations from the B-cell receptor. *Blood.* 2004;103(12):4389-4395.
8. Herishanu Y, Perez-Galan P, Liu D, et al. The lymph node microenvironment promotes B-cell receptor signaling, NF-kappaB activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood.* 2011;117(2):563-574.
9. Burger JA. Nurture versus nature: the microenvironment in chronic lymphocytic leukemia. *Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program.* 2011;2011:96-103.
10. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *The lancet oncology.* 2014;15(1):48-58.
11. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *The New England journal of medicine.* 2013;369(1):32-42.
12. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood.* 2008;112(4):975-980.
13. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(18):4079-4088.
14. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet.* 2010;376(9747):1164-1174.
15. Fischer K, Cramer P, Busch R, et al. Bendamustine in Combination With Rituximab for Previously Untreated Patients With Chronic Lymphocytic Leukemia: A Multicenter Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(26):3209-3216.
16. Strati P, Keating MJ, SM OB, et al. Outcomes of first-line treatment for chronic lymphocytic leukemia with 17p deletion. *Haematologica.* 2014.
17. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008;111(12):5446-5456.

18. Thall PF, Simon RM, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1996;14(1):296-303.

APPENDIX 1
Cairo-Bishop Definition and Grading of Tumor Lysis Syndrome

From: Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3-11.

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

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

Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:

1. Creatinine: ≥ 1.5 upper limit of normal
2. Cardiac arrhythmia / sudden death
3. Seizure

APPENDIX 1 (cont'd)
Cairo-Bishop Definition of Tumor Lysis Syndrome

Cairo-Bishop Grading System for Tumor Lysis Syndrome

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

LTLS = laboratory tumor lysis syndrome; ULN = upper limit of normal; ADL = activities of daily living.
*Probably or definitely attributable to clinical TLS.

APPENDIX 2
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

1. FIRST DOSE OF Venetoclax OR DOSE INCREASE

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

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

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

APPENDIX 2 (cont'd)
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
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 assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/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.

APPENDIX 2 (cont'd)

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μmol/L)	• Consider rasburicase (dose per institutional guidelines). – 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 predose level	• Administer rasburicase (dose per institutional guidelines). – If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • 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.
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) OR Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• 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.
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 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.

IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.

APPENDIX 2 (cont'd)

2. ONGOING DOSING OF Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as below. Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

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

Appendix 3
National Cancer Institute-Sponsored Working Group Hematologic Adverse Event Grading Scale for Chronic Lymphocytic Leukemia for Patients with Baseline Abnormal Hematologic Laboratory Values

Decrease in Platelets [a] or Hgb [b] from Pretreatment Value	Grade	ANC/μL [c] (nadir) ($\times 10^9$ cells/L)
No change–10%	0	≥2000 (≥2.00)
11%–24%	1	≥1500 and <2000 (≥1.5 and <2.0)
25%–49%	2	≥1000 and <1500 (≥1.0 and <1.5)
50%–74%	3	≥500 and <1000 (≥0.5 and <1.0)
≥75%	4	<500 (<0.5)

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood 2008;111:5446–56.

ANC = absolute neutrophil count; Hgb = hemoglobin; Grades: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening.

[a] If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20,000/μL), this will be considered a Grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20×10^9/L [20,000/μL]), was present before treatment, in which case the patient is not evaluable for toxicity with regard to platelets.

[b] Baseline and subsequent Hgb determinations must be performed before any given infusion.

[c] If ANC was $< 1 \times 10^9$/L prior to therapy, the patient is not evaluable for toxicity in ANC.

Appendix 4

Outside Physician Letter

[DATE]

Dear Doctor [_____],

_____ **(name)** is a mutual patient of ours with _____. We have placed him/her on a protocol: "A Phase II Study of Venetoclax and Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL)" that is being conducted at M.D. Anderson. A copy of the abstract, treatment schedule and consent form will be sent to you for your reference. **(Name)** started treatment on **[Date].** Ibrutinib and venetoclax is given weekly on day 1 of specified courses (there are 27 courses). Ibrutinib is given weekly during cycle 1-3 and then on day 1 of courses 4-27 venetoclax is taken along with ibrutinib. The principal investigator on this study is Dr. Nitin Jain, and (**Name**)'s treating physician is Dr. **[NAME]**.

In order to allow the patient to spend as much time as possible at home, we request your cooperation in the following.

While at home the patient will need the following:

During Courses 1-3 (while taking ibrutinib only)

- CBC, platelet count and differential at least weekly during course 1 and at least every 2 weeks.
- Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH will be performed at least weekly during course 1 and at least every 2 weeks during courses 2-3.
- Complete history and physical examination including vital signs at least every 2 weeks during course 1, and monthly during courses 2-3 until he/she returns to M.D. Anderson.

During Courses 4-6 (while taking venetoclax + ibrutinib)

- CBC, platelet count and differential at least weekly during course 4 and at least every 2 weeks during courses 5-6.
- Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH will be performed at least weekly during course 4 and at least every 2 weeks during courses 5-6.
- Complete history and physical examination including vital signs at least every 2 weeks during course 4, and monthly during course 5-6.

Courses 7-27 (Venetoclax + Ibrutinib)

- CBC, platelet count and differential at least monthly.
- Clinical laboratory evaluation will include sodium, potassium, calcium, BUN, creatinine, glucose, phosphorous, magnesium, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, LDH will be performed at least monthly.

- Complete history and physical examination including vital signs at least monthly.

Please fax all clinic notes, progress notes, labs, imaging and pathology studies to the attention of **[RESEARCH NURSE]** at **[PHONE]** as soon as they become available.

Please notify [**RESEARCH NURSE**] of hospitalizations for any reason, or any other serious adverse events at telephone number [_____] or pager number [_____].

Please contact Dr. [**NAME**] or myself before adding any new medications as concurrent medications are strictly regulated and must be documented on this protocol.

By signing below, you indicate:
1) Confirmation of your willingness to perform the physical exam, vital signs, hematologic and biochemical profiles, and toxicity notation on the dates indicated below;

2) Fax a copy of all patient's visit note as required by the protocol and you deem necessary, (receipt of this documentation will enable us to meet NCI requirements related to the submission of specific paperwork) and allow us to adjust the dose per protocol;

3) Fax a copy of your lab's certification.

4) All protocol-specific decisions must be made by the MD Anderson investigator/physician.

If you agree with these requests, please sign and return this letter as confirmation that we will receive by fax a copy of all labs, and a copy of the dictated or handwritten clinic visit notes regarding assessments.

Signature: _____, Date _____ Tel: _____, Email _____

A follow up visit at MDACC, for evaluation of response and additional testing is scheduled for: _____ [date] _____

For any questions please do not hesitate to contact the research nurse or the Principal Investigator for this study – contact details below.

Sincerely,

Nitin Jain, MD
Principal Investigator
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APPENDIX 5
Blood/Aspirate Samples
A Phase II Study of Venetoclax and Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL)

Pharmacodynamic Investigations
The objectives of the pharmacodynamic investigations during this clinical trial are as follows:

To investigate the effects of venetoclax combination to ibrutinib on protein and RNA homeostasis.

All patients will be investigated as this clinical trial is designed with pharmacodynamics as the primary investigation. Patients will sign consent forms to enter these investigations. Once a patient has consented to participate in the investigation, please contact (1) Dr Betty Lamothe (713 792 5961) and (2) Ms Yuling Chen (713 404 2550) or (3) Dr. Gandhi's office (713 792 2989) in the Department of Experimental Therapeutics/Leukemia. Please collect blood samples (total 5 time points and relapse) as indicated below and bone marrow samples (total 2 and relapse) at the following times.

(A) Blood samples
Pre-Dose (Pretreatment sample) - (four green top tubes) and (two yellow top tubes)
Cycle 2, Day 1 - 0 hr - (four green top tubes)
Cycle 4, Day 1 - 0 hr (just before starting venetoclax) - (four green top tubes)
Cycle 4, Day 8 - 0 hr (after 1 week of venetoclax) - (four green top tubes)
Cycle 5, Day 1 - 0 hr (after 4 weeks of venetoclax) - (four green top tubes)
Any relapse – whenever relapse was identified - (four green top tubes)

(B) Bone marrow aspirate samples (4 ml in a yellow-top tube)
Pre-Dose (Pretreatment sample)
Cycle 4, Day 1 - 0 hr (just before starting venetoclax)
Any relapse – whenever relapse was identified and BM collected

Each sample (blood or marrow aspirate) will be mixed and immediately put on ice-bath. Tubes will be picked up by Dr. Gandhi's laboratory personnel and further processed to isolate CLL lymphocytes. Plasma will be used for ibrutinib and venetoclax pharmacology and for cytokine/chemokine assays; while fresh cells will be cryopreserved to evaluate changes in protein and mRNA homeostasis.

Plasma pharmacokinetics: Plasma will be separated from peripheral blood samples and stored at -80^{0}C. As needed, the samples will be analyzed in a reference laboratory to determine plasma concentration of ibrutinib and venetoclax.

Chemokine profiling: Plasma will be separated from peripheral blood samples and stored at -80^{0}C. Plasma will be used to quantitate changes in the levels of CCL3, CCL4, and other chemokines or cytokines if applicable.

Protein and RNA homeostasis profiling: The lymphocytes obtained in real-time during pre- and post-therapy will be cryopreserved and later appropriately processed to be sent to a reference core facility to identify molecular changes that occur during therapy.

Ex vivo evaluation of venetoclax combination: Pretreatment sample and Cycle2 Day1 (Day 28) samples will also be tested for combination efficacy by ex vivo treatment with venetoclax. The results will be correlated to the efficacy observed during clinical trial after combination of venetoclax.