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A Phase I/II Study of the Combination of Venetoclax, Ponatinib and Corticosteroids in Patients with Relapsed or Refractory Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia and Lymphoid Blast Phase Chronic Myelogenous Leukemia

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1. INTRODUCTION

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL): Ph+ ALL is an aggressive subtype of ALL characterized by the presence of the *BCR-ABL1* gene fusion.[1] Historically, the outcomes of patients with Ph+ ALL were dismal, with a 3-year disease-free survival rate of <15%.[2] However, with the incorporation of tyrosine kinase inhibitors (TKIs) into chemotherapy-based treatment regimens, survival rates of 30-80% have been achieved, with improved long-term survival seen in patients receiving later-generation TKIs.[3-5] These TKIs target the aberrant Bcr-Abl1 protein, which is the primary driver of proliferation and survival of the Ph+ leukemic cells. With the combination of chemotherapy and a TKI, complete remission (CR) rates >90% can be achieved.[4-7] Despite this high CR rate seen with TKI and chemotherapy combination regimens, many patients subsequently relapse; for these patients, outcomes are dismal and there is no clear standard of care. Recent evidence suggests that the bispecific T-cell engaging antibody, blinatumomab, has significant antileukemic efficacy for these patients.[8] However, even with this promising treatment, the overall response rate is only 36% and the median OS is approximately 7 months. Therefore, novel treatment options are needed for patients with Ph+ ALL who are refractory or relapse after initial treatment.

Ponatinib: Ponatinib is a later-generation TKI that is capable of inhibiting the T315I BCR-ABL1 kinase mutation, which commonly arises during treatment with other TKIs such as imatinib or dasatinib. In the phase II PACE trial of single-agent ponatinib in patients with relapsed/refractory Ph+ leukemias, ponatinib resulted in major hematologic response in 41% of patients with Ph+ ALL. However, the vast majority of patients relapsed, and the 1-year progression-free survival was only 7%. These results demonstrate that ponatinib has activity in relapsed and TKI-resistant Ph+ ALL, although as a single agent it does not appear to produce durable responses. In contrast, when combined with hyper-CVAD chemotherapy in patients with newly diagnosed Ph+ ALL, the ponatinib-containing regimen resulted in a CR rate of 100% with 2-year event-free

survival (EFS) and overall survival (OS) rates of 81% and 80%, respectively. Ponatinib can be associated with cardiovascular toxicity, including arterial and thromboembolic events; however, using risk-adapted dosing schedule of ponatinib may reduce this risk. Historical comparisons suggest the results achieved with the combination of hyper-CVAD plus ponatinib may be superior to those achieved with hyper-CVAD plus dasatinib.

Venetoclax: Venetoclax (formerly ABT-199/GDC-0199) is a potent, selective and orally bioavailable small molecule BCL-2 inhibitor that has shown promising anti-leukemia activity in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) as monotherapy and modest single agent activity in select subtypes of acute myeloid leukemia[12-14]; venetoclax is currently FDA approved for the treatment of patients with CLL with del(17)(p13.1) by interphase cytogenetics who have received at least one prior therapy. For patients with AML, combination therapy with venetoclax and other agents appears to be more efficacious that venetoclax monotherapy.[15] BCL-2 is an anti-apoptotic protein that is over-expressed in many hematologic malignancies and is associated with tumor initiation, disease progression and drug resistance.[16] BCL-2 mRNA is highly expressed in multiple subtypes of ALL compared with normal pre-B controls.[17] Recent reports demonstrated that primary B-lineage ALL cells each express high levels of BCL-2 and exhibit significant sensitivity to BCL-2 inhibition by venetoclax, resulting in rapid apoptotic cell death.[18] Specifically, Ph+ ALL appears to be dependent on BCL-2 for survival; consequently, BCL-2 inhibition has been shown to result in apoptosis of Ph+ ALL cell lines.[19]

Rationale for Combination of Ponatinib and Venetoclax: The combination of venetoclax and targeted BCR-ABL1 TKIs has been explored in preclinical studies of Ph+ ALL.[20] In one study, the combination of venetoclax with various TKIs resulted in synergistic *in vitro* inhibition of cell growth and induction of apoptosis. While this synergy was seen across a number of TKIs tested, this effect was most pronounced when venetoclax was combined with either dasatinib or ponatinib. The synergistic inhibition of leukemic growth was likely mediated by the ability of these two TKIs to target the Lck/Yes novel (LYN) tyrosine kinase in addition to ABL. Combination of venetoclax with an inhibitor of LYN resulted in increased expression of the pro-apoptotic BCL-2-like protein 11 (BIM) and lower expression of the anti-apoptotic myeloid cell leukemia 1 (MCL-1). In a patient-derived xenograft ALL mouse model, the combination of a LYN-targeting TKI and ponatinib appeared to prevent the increase in MCL-1 with venetoclax treatment, which is an established mechanism of venetoclax resistance. These findings provide a strong rational for the combination of venetoclax with ponatinib, a potent anti-BCR-ABL1 kinase inhibitor that also targets the LYN tyrosine kinase. This combination approach can also test the hypothesis that inhibition of LYN by ponatinib can alter the balance of apoptotic proteins in favor of a profile that increases leukemia cells' sensitivity to BCL-2-targeted therapies.

Summary: There is an unmet need for novel treatment strategies for patients with relapsed or refractory Ph+ ALL. Ponatinib is a potent anti-BCR-ABL1 TKI capable of inducing deep and long-term remissions when combined with chemotherapy in patients with newly diagnosed Ph+ ALL. Venetoclax also shows promise in the treatment of a number of leukemias and other hematologic malignancies that are dependent on the anti-apoptotic protein BCL-2 for survival. Furthermore, preclinical data suggest that the combination of ponatinib and venetoclax may have synergistic effect in Ph+ ALL, mediated through the targeting of the LYN tyrosine kinase. Taken together, these preclinical and clinical studies provide a strong rationale for a phase I/II trial combining venetoclax with ponatinib in patients with relapsed/refractory Ph+ ALL.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

- *Phase I:* To determine the maximum tolerated dose (MTD) of venetoclax, ponatinib and dexamethasone in patients with relapsed/refractory Ph+ ALL or lymphoid BP-CML
- *Phase II:* To determine the efficacy of the regimen, as defined by the rate of complete remission (CR) or CR with incomplete count recovery (CRi)

2.2 Secondary Objectives

- To determine efficacy outcomes, including rate of minimal residual disease negativity by PCR for BCR-ABL1 transcripts, median relapse-free survival, and median overall survival
- To determine the proportion of patients proceeding to allogeneic stem cell transplant (ASCT)
- To preliminarily determine the safety of the combination regimen

2.3 Exploratory Objectives

- To evaluate the effect of single-agent ponatinib on apoptotic proteins and Bcl-2 dependency
- To correlate apoptotic protein expression and Bcl-2 dependency on response and resistance to the combination regimen
- To assess impact of baseline genomics on outcomes with the combination regimen

3. SELECTION OF PATIENTS

Patients will be selected from those referred to the Leukemia department at M D Anderson Cancer Center through the normal of process of referral. Eligible patients will be registered after the process of consenting on the MD Anderson protocol and data monitoring system.

3.1 Inclusion Criteria

1. Patients ≥ 18 years of age with relapsed/refractory Ph+ ALL or lymphoid blast phase CML [either t(9;22) and/or BCR-ABL1 positive by fluorescent *in situ* hybridization or polymerase chain reaction], including prior therapy with at least one Bcr-Abl tyrosine kinase inhibitor

2. Performance status ≤3 (ECOG Scale)

3. Adequate liver and renal function as defined by the following criteria:
   a) Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome, hemolysis or the underlying leukemia approved by the PI
   b) Alanine aminotransferase (ALT) ≤ 1.5 x ULN, unless due to the underlying leukemia approved by the PI
   c) Aspartate aminotransferase (AST) ≤ 1.5 x ULN unless due to the underlying leukemia approved by the PI
   d) Creatinine clearance ≥30 mL/min

4. Adequate pancreatic function as defined by the following criteria:
   a) Serum lipase and amylase ≤ 1.5 x ULN

5. Ability to swallow

6. Signed informed consent

3.2 Exclusion Criteria

1. Prior history of treatment with venetoclax. Prior ponatinib is allowed.

2. Active serious infection not controlled by oral or intravenous antibiotics (e.g. persistent fever or lack of improvement despite antimicrobial treatment).

3. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis

4. Uncontrolled hypertriglyceridemia (triglycerides > 450mg/dL)

5. Active secondary malignancy that in the investigator's opinion will shorten survival to less than 1 year.

6. Active Grade III-V cardiac failure as defined by the New York Heart Association Criteria.

7. Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
   - History of myocardial infarction (MI), stroke, revascularization, unstable angina or transient ischemic attack within the past 12 months
   - Left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards prior to enrollment
   - Diagnosed or suspected congenital long QT syndrome
   - Any history of clinically significant atrial or ventricular arrhythmias (such as uncontrolled artrial fibrillation, ventricular tachycardia, ventricular fibrillation, or Torsades de pointes) as determined by the treating physician
   - Prolonged QTc interval on pre-entry electrocardiogram (> 480 msec) unless corrected after electrolyte replacement
   - History of venous thromboembolism including deep venous thrombosis or pulmonary embolism within the past 3 months. *Patients with a history of catheter associated upper extremity venous thromboembolism are not excluded.*
   - Uncontrolled hypertension (diastolic blood pressure >100mmHg; systolic >150mmHg).

8. Patients currently taking drugs that are generally accepted to have a high risk of causing Torsades de Pointes (unless these can be changed to acceptable alternatives)

9. Received strong or moderate CYP3A inhibitors or inducers within 3 days of study entry

10. Consumed grapefruit, grapefruit products, Seville oranges, or star fruit within 3 days prior to starting venetoclax

11. Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects has occurred or patient has rapidly progressive disease judged to be life-threatening by the investigator. Prior recent treatment with corticosteroids and hydroxyurea is permitted.

12. Pregnant and lactating women will not be eligible; women of childbearing potential should have a negative pregnancy test prior to entering on the study and be willing to practice methods of contraception throughout the study period. Women do not have childbearing potential if they have had a hysterectomy or are postmenopausal without menses for 12 months. In addition, men enrolled on this study should understand the

risks to any sexual partner of childbearing potential and should practice an effective method of birth control. Appropriate birth control will be determined by the treating physician.

4. TREATMENT OF SUBJECTS

4.1. Variations in doses of the study agents or supportive care medications or dose schedules other than those suggested below are allowed if deemed to be in the best interest of patients. Such changes should be discussed with the principal investigator before they are instituted.

4.2. **Treatment Overview** – The regimen consists of 4 cycles of induction/consolidation followed by up to 2 years of maintenance therapy for responding patients. For patients who have not received ponatinib within 2 weeks of the anticipated start date, the first cycle is 35 days, as single-agent ponatinib will be given for 7 consecutive days, after which venetoclax, ponatinib and corticosteroids will be given in combination. For patients who have received ponatinib within 2 weeks of the anticipated start date, the first cycle is 28 days, as the ponatinib single-agent lead-in will be omitted. For all patients, each consecutive cycle will be 28 days. Patients achieving remission will be referred to ASCT at the discretion of the treating physician, based on donor availability and suitability for ASCT. Patients will be removed from the study and will discontinue venetoclax at the time of ASCT. These patients will still be followed for survival analyses.

4.3 **Cycle 1 (Induction)** – Patients who have not received ponatinib within 2 weeks of the anticipated start date will receive the following agents:

- Ponatinib 45mg orally daily on days 1-35
- Venetoclax orally in a daily dose escalation schema:

	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13-35
Dose level -1 venetoclax	**20 mg**	**50 mg**	**100 mg**	**200 mg**	**200 mg**	**200 mg**
Dose level 1 venetoclax (STARTING DOSE)	**20 mg**	**50 mg**	**100 mg**	**200 mg**	**400 mg**	**400 mg**
Dose level 2 venetoclax	**20 mg**	**50 mg**	**100 mg**	**200 mg**	**400 mg**	**800 mg**

- Dexamethasone 40mg IV/PO on days 8-11
- CNS prophylaxis with methotrexate 12 mg intrathecally (IT) (6 mg via Ommaya reservoir) on day 9 (± 3 days) and cytarabine 100 mg IT on day 14 (± 3 days).
- For patients with CD20 expression (≥20% by flow cytometry), rituximab 375 mg/m^2 may be added at the discretion of the treating physician after the maximum dose of venetoclax has been reached. Rituximab will be given on day 14 (±3 days) and on day 21 (±3 days).

Patients may receive ponatinib monotherapy on days 1-7 as an outpatient. Bone marrow will be performed on day 7 (±1 day) for correlative studies but must be prior to the initiation of venetoclax. Additional hydroxyurea or corticosteroids are allowed during the 7-day ponatinib lead-in after discussion with the PI.

Due to the potential for tumor lysis syndrome (see section 4.6), patients will be hospitalized the day prior to initiation of venetoclax and will remain hospitalized until 24 hours after the completion of the venetoclax dose escalation (day 12-14, depending on the dose level). Patients in both phase I and phase II cohorts will be hospitalized. Hospital stay may be

prolonged in patients with infections or other issues requiring inpatient stay. The remainder of the cycle can be administered as an outpatient. At the end of cycle 1, patients will have bone marrow aspirate/biopsy for response assessment.

For patients who have received ponatinib within 2 weeks of the anticipated start date, both venetoclax, ponatinib, and dexamethasone will be started on day 1 of the first cycle, and the 7-day lead-in of single-agent ponatinib will be omitted. Therefore, all days above will be moved forward 7 days, and the cycle will end on day 28.

4.3 **Cycles 2-4 (Consolidation)** – Patients will receive the following agents:

- Venetoclax orally at the maximum dose used in cycle 1, given daily on days 1-28
- Ponatinib orally daily on days 1-28. The dose of ponatinib will be adjusted according to the remission status as indicated by bone marrow assessment after cycle 1.
    - Patients who have not received CR/CRi: 45mg daily
    - Patients who have achieved CR/CRi but not CMR: 30mg daily
    - Patients who have achieved CR/CRi with CMR: 15mg daily
- Dexamethasone 40mg orally daily on days 1-4
- CNS prophylaxis with methotrexate 12 mg IT (6 mg via Ommaya reservoir) on day 2 (± 3 days) and cytarabine 100 mg IT on day 7 (± 3 days).
- For patients with CD20 expression (≥20% by flow cytometry), rituximab 375 mg/m^2 may be added at the discretion of the treating physician. Up to 2 doses of rituximab may be given during each cycle.

All therapy can be administered in the outpatient setting. A total of 8 doses of IT chemotherapy are planned for cycles 1-4. A total of 8 doses of rituximab may be given for cycles 1-4. Any missed doses of rituximab or IT chemotherapy can be made up in subsequent cycles at the discretion of the treating physician.

4.3 **Cycles 5+ (Maintenance)** – Patients will receive the following agents:

- Venetoclax at the maximum dose used in cycle 1, given daily on days 1-28
- Ponatinib orally daily on days 1-28. The dose of ponatinib will be adjusted according to the remission status as assessed by the last bone marrow assessment performed.
    - Patients who have achieved CR/CRi but not CMR: 30mg daily
    - Patients who have achieved CR/CRi with CMR: 15mg daily
- Dexamethasone 40mg orally daily on days 1-4

All therapy can be administered in the outpatient setting. Up to 24 cycles of maintenance will be administered. The study will end 24 months after the last patient is enrolled.

4.4. General Considerations

- Venetoclax must be administered with food
- Prevention of infection
    - Prophylactic antibiotics may be given with each course until neutrophil recovery to 500/μL or greater
    - Suggestions include: Levaquin 500 mg orally daily (or other appropriate antibacterial agent); caspofungin or other appropriate antifungal agent; valacyclovir 500 mg orally daily or acyclovir 200 mg orally twice daily or other appropriate antiviral agent.
- Prevention and treatment of CNS disease
    - 8 prophylactic IT chemotherapy treatments are recommended. However, if the patient has had prior IT therapy, number of IT chemotherapy can be

reduced if thought by the treating physician to be in the best interest of the patient after discussion with the PI.
    - For patients with active CNS disease, consider methotrexate alternating with cytarabine twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, particularly with cranial nerve root involvement (cranial nerve palsies). Modifications to the regimen thought to be necessary for administration of XRT are allowed after discussion with the PI.
- Venetoclax will provided by the Abbvie through the MDACC pharmacy. Ponatinib is indicated for the disease setting and will be charged to the patient/insurance.

4.5. Suggested Standard Dose Reductions/Modifications:

- Venetoclax
    - Moderate and strong CYP3A inducers and inhibitors are discouraged during venetoclax administraton. If a patient requires use of CYP3A inducers, use with caution. In many instances, such as antifungal prophylaxis with “azole” therapy in neutropenic patients, CYP3A inhibitors are required in ALL patients. Venetoclax should be administered at 50% dose reduction in the setting of moderate CYP3A inhibitors (i.e. isavuconazole, ciprofloxacin, diltiazem), and 75% dose reduction in the setting of strong CYP3A inhibitors (i.e. voriconazole), with the exception of posaconazole in which dose reduction should be approximately 83% (e.g. dose reduction to 70mg if patient would normally be taking 400mg). The venetoclax dose reduction should continue for the duration of co-administration. In the event the co-administered CYP3A inhibitor is discontinued, the assigned venetoclax dose should be resumed 2-3 days after discontinuation. During the venetoclax ramp-up, these agents must be held; however, they may be started or resumed 24 hours after the highest planned dose of venetoclax is given, along with the appropriate dose reduction of venetoclax as above.
    - Non-hematological toxicity - If grade 3 or 4 non-hematologic toxicity is attributable to venetoclax, dose interruption of venetoclax is required. Patients who experience drug-related grade 3 non-hematological toxicity may be given a subsequent course one dose level below the previous course, but the patient must have recovered to grade ≤1 before start of the next course. If a patient has drug-related grade 4 non-hematological toxicity, he/she may receive a subsequent course at one reduced dose level after resolution of toxicity to grade ≤1, only if approved by the PI based on the clinical significance of the toxicity and only if patient has had derived a benefit from the therapy. The dose of venetoclax can be decreased during a cycle, at the discretion of treating physician and PI, for chronic grade 2 non-hematological toxicity. Other dose modifications may be considered as clinically indicated with documentation and approval of the PI. The dose reduction guidelines for venetoclax are in the table below:

Current Venetoclax Dose	**Reduced Dose**
800mg	400mg
400mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg

20mg	Hold venetoclax

- Hematologic toxicity
  - Dose interruptions or modifications will be made for grade 4 hematological toxicities unless it is assessed to be due to the underlying disease. Patients with baseline neutropenia or those who have significant bone marrow involvement may be particularly at high risk.
  - If a subject achieves CRi or has a morphologically leukemia free bone marrow after completion a cycle, venetoclax should be interrupted for up to 14 days after the last day of the cycle or until recovery of ANC >500/μL.
  - If a subject presents with new onset grade 4 during subsequent cycles, unless it is thought to be due to the underlying disease, venetoclax dosing should be interrupted until ANC recovery to >500/μL. Subsequent dosing should be in consultation with the study PI. For the first episode of grade 4 hematologic toxicity the dose of venetoclax may be reduced; however for subsequent episodes of grade 4 hematologic toxicity (not attributed to the underlying disease), the dose of venetoclax should be reduced. The dose reduction guidelines for venetoclax are in the table above (same as for non-hematologic toxicity).

- Ponatinib
  - The following table provides dose reduction guidelines for ponatinib

Current Ponatinib Dose	**Reduced Dose**
45mg	30mg
30mg	15mg
15mg	Hold ponatinib

  - Hematologic toxicity
    - Cytopenias are common in the patient population studied in this trial. Dose modification for ponatinib for hematologic toxicities will be made unless attributed to the underlying leukemia, after appropriate dose reductions of venetoclax have been made, as above.
    - No dose modifications are required for grade 1-2 hematologic toxicity or for grade 3-4 hematologic toxicity attributed to underlying leukemia.
    - For grade 4 hematologic toxicity occurring despite venetoclax dose interruption of ≥1 week, ponatinib should be held until recovery of ANC to ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L, and then resumed at one dose level reduction.
  - Grade II transaminase elevation
    - Hold until grade I or less.
    - After resolution to grade I or less, ponatinib may be resumed but must be reduced by one dose level.
  - Other liver function abnormalities
    - For patients who develop AST or ALT of >=3x ULN and a total bilirubin of >2 x ULN with alkaline phosphatase of <2 x ULN while on treatment, ponatinib should be discontinued. Investigation of other causes of liver abnormalities (e.g. azoles) is recommended.
  - Pancreatitis

        - If asymptomatic grade 1-2 lipase elevation, ponatinib may be held or dose reduced at the discretion of the PI. If held, it should be dose reduced when resumed.
        - If asymptomatic radiologic pancreatitis (grade 2 pancreatitis), asymptomatic grade 3-4 lipase elevation, or symptomatic grade 3 pancreatitis, hold ponatinib until grade 1, then dose reduce by one dose level
        - If grade 4, discontinue ponatinib
    - Arterial or venous thrombosis
        - For patients with arterial thrombosis, ponatinib should be discontinued.
        - For patients with pulmonary embolism or lower extremity deep venous thrombosis, ponatinib should be dose reduced (one dose level) or discontinued.
        - For patients with superficial venous thrombosis or line-associated upper extremity deep venous thrombosis, ponatinib may be continued at the same dose, although holding dose and/or dose reduction (one dose level) can be considered at the discretion of the treating physician according to the assessment of the patient's best interest.
    - Heart failure
        - If grade 1-2, hold ponatinib until resolution then resume at same dose
        - If grade 3, hold ponatinib until grade 1 or resolved, then reduce dose by one dose level
        - If grade 4, discontinue ponatinib
    - Hemorrhage or fluid retention (edema)
        - If grade 3-4, hold ponatinib until grade I or less, then reduce dose by one dose level.
    - Grade III-IV non-hematological toxicity (excluding specific toxicities listed above) attributed to ponatinib:
        - Hold until grade I or less.
        - Ponatinib may be resumed at one dose level reduction after resolution to grade I or less, if resolves within 4 weeks of discontinuation. If the same grade III-IV toxicity recurs, ponatinib should be discontinued.
    - Major surgery
        - Ponatinib should be held for at least 1 week prior to any planned major surgery, as determined by the PI.

- Dexamethasone
    - Dose should remain at 40mg unless grade 3 or 4 steroid myopathy or other significant toxicity occurs.
    - For grade 3 or higher pancreatitis, dexamethasone should be held until resolved to grade 1 or less, after which it may be resumed at the same dose.
    - For other grade 3 or 4 toxicities attributed to dexamethasone, dexamethasone should be held until resolved to grade 1 or less, after which it may be resumed at the same dose or dose reduced (at the discretion of the PI).
    - Dexamethasone is not required to be dose-adjusted for hyperglycemia.
    - If dose reductions of dexamethasone are performed, guidelines are in the table below:

Current Dexamethasone Dose	**Reduced Dose**
40mg	20mg
20mg	10mg
10mg	Hold dexamethasone

- Further reductions beyond what is shown in the table above may be allowed if recommended by the treating physician and after discussion with the PI.

4.6 Prophylaxis and Management of TLS

- There is a potential for TLS, especially in those with elevated pretreatment LDH levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk for TLS, subjects will receive tumor lysis prophylaxis, including hydration (e.g., oral, intravenous) and treatment with an agent to reduce the uric acid level (e.g., allopurinol, rasburicase) prior to and during the inpatient portion of cycle 1. For subjects who had dose delay or interruptions, TLS prophylactic measures may need to be implemented based on the disease status prior to resuming treatment. TLS prophylaxis must be initiated in all such subjects prior to the first venetoclax dose or first new escalated dose.
- Cycle 1
    - Hospitalization (required) starting the night before the initial dose of venetoclax for cycle 1 and for up until 24 hours after reaching the target dose (day 12-14 for patients without recent ponatinib exposure or day 5-7 for patients with recent ponatinib exposure, depending on the dose level)
    - An oral agent to reduce the uric acid level (e.g., allopurinol or substitute) must be initiated prior to first venetoclax dose. Subjects allergic to or otherwise unable to receive allopurinol must use another uric acid reducer or rasburicase prior to venetoclax dosing.
    - Intravenous hydration must be started upon admission (i.e. the day prior to initiation of venetoclax) at a rate as clinically appropriate and will continue throughout the hospitalization. Urine output must be monitored. Diuretics may be used per investigator discretion.
    - TLS chemistry tests (calcium, phosphorus, potassium, uric acid, and creatinine) on the first day of venetoclax and each day of a new dose within 6 hours (+/-2 hours prior to venetoclax dosing. TLS chemistries should also be checked 6 hours after (+/-2 hours) after the first dose or new dose level.
    - TLS chemistry test results (calcium, inorganic phosphorus, potassium, uric acid, and creatinine) must be reviewed by the investigator in real time and prior to the subject's next dose to ensure appropriate subject management.
    - If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution.
- Cycles 2+
    - If any laboratory changes are noted in cycle 1, and deemed clinically significant for TLS by the investigator, no additional venetoclax doses should be administered until resolution. TLS prophylaxis may need to be continued with subsequent cycles based on the ongoing risk of development of TLS.
    - Drug interruption for up to 48 hours following transient chemical changes and laboratory TLS may be allowed and will not require a dose reduction. If the TLS has not resolved within 48 hours, then the dose should be reduced.

- **4.7 Completion of Phase I** – The phase I portion will define the DLTs , MTD and RP2D of the combination treatment. Dose escalation will proceed in standard '3+3' design (see Statistical Methods section). Once the MTD is established (or if the MTD is not reached with 800 mg of venetoclax), the phase II portion of the study will commence.

- **4.8 Definition of DLT** –

  A DLT will be defined as any of the following adverse events that cannot be considered primarily related to the underlying malignancy, or a comorbid condition, occurring:

- For patients without recent ponatinib exposure, between day 8 and day 35 of cycle 1 (with the exception of hematologic toxicity which may be assessed up to day 49 of cycle 1)
- For patients with recent ponatinib exposure, between day 1 and day 28 of cycle 1 (with the exception of hematologic toxicity which may be assessed up to day 42 of cycle 1)

Any ≥ grade 3 non-hematologic toxicity with the following exceptions:

- Grade 3 alopecia
- Grade 3 nausea, vomiting, diarrhea with electrolyte abnormalities lasting less than 48 hours that are not clinically significant and that does not require total parenteral nutrition (TPN), tube-feeding, or hospitalization
- Infection, unless the infection resulted from unexpectedly complicated by the degree or duration of myelosuppression in the absence of persistent leukemia.

Patients who receive at least a full course of therapy will be considered to be evaluable for toxicity/DLT and will not be replaced unless the PI determines that further additional patients at that dose level are required for safety purposes.

Hematologic toxicity will be defined as:

- For patients without recent ponatinib exposure, failure to recover ANC > 500/μL or platelet count > 25,000/μL by day 49.
- For patients with recent ponatinib exposure, failure to recover ANC > 500/μL or platelet count > 25,000/μL by day 42.

This will be considered DLT. For patients with $\geq$ 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil or platelet count may not be considered DLT as this could be the result of persistent disease.

5. CONCOMITANT MEDICATIONS

Short-acting antacid agents may be taken, but it is recommended that these not be taken from 2 hours before to 2 hours after dosing of ponatinib. Proton pump inhibitors may be administered concomitantly with ponatinib if felt to be in the patient's best interest.

Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (including: quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, erythromycins, clarithromycin, chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide, cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine) should change these to acceptable alternatives, if possible.

General guidelines regarding excluded and cautionary medications are summarized in Table 1 below.

Table 1. Excluded and Cautionary Medications

Excluded
Anticancer therapies including chemotherapy or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration
Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent: Excluded 30 days or 5 half-lives (whichever is shorter) prior to first dose and throughout venetoclax administration. Rituximab given as part of this treatment protocol is an exception.
Grapefruit and grapefruit products
Seville Oranges (including marmalade containing Seville oranges)
Starfruit
Cautionary
Warfarin and coumarin derivatives
P-gp substrates
BCRP substrates
OATP1B1/1B3 substrates
P-gp inhibitors
BCRP inhibitors
Strong and Moderate CYP3A inhibitors
Strong and Moderate CYP3A inducers

Localized radiation is allowed if deemed in the best interest of the patient and after approval by the PI.

Drugs involving these enzymes and transporters can be found in the following webpage:
http://medicine.iupui.edu/clinpharm/ddis/main-table/

6. STUDY PROCEDURES

6.1. Pre-Treatment Evaluation

1. History and physical examination, including height and weight, vital signs (blood pressure, respiratory rate, pulse and temperature) and ECOG performance status
2. Concomitant medication and medical history assessment within 24 hours of first dose
3. CBC with differential, electrolytes (potassium, calcium, magnesium, phosphorus), LDH, uric acid, creatinine, liver function tests (AST, ALT, total bilirubin), lipase, amylase, triglycerides, hepatitis B antibodies
4. Bone marrow aspirate, cytogenetics and PCR for *BCR-ABL1*. Quick Philadelphia screen (FISH) is acceptable.
5. EKG
6. Pregnancy test in female patients of appropriate age and menopausal state within 1 week of first dose
7. Echocardiogram or MUGA scan to assess cardiac function
8. Biomarker studies including CyTOF, BH3 profiling, and next-generation targeted sequencing and SNP array (performed on bone marrow and peripheral blood)

All pretreatment evaluation must be performed within 2 weeks of first dose of the study drug, unless otherwise specified as above.

6.2 Evaluation During Study

1. History and physical examination, including vital signs (blood pressure, respiratory rate, pulse and temperature) and ECOG performance status prior to each cycle
2. Evaluation for toxicity assessment prior to each cycle
3. Assessment of concomitant medications prior to each cycle.
4. CBC with differential 1-2 times weekly for cycle 1, then prior to each subsequent cycle
5. In addition to TLS monitoring during the venetoclax ramp-up period (section 4.6), electrolytes (potassium, calcium, magnesium, phosphorus), LDH, uric acid, creatinine, liver function tests (AST, ALT, total bilirubin) at least weekly for cycle 1, then prior to each subsequent cycle
6. Amylase and lipase as clinically indicated (e.g. for patients with abdominal pain)
7. Bone marrow aspiration to be performed cycle 1 on day 7 (± 2 days) in patients without recent ponatinib exposure only but must be prior to the initiation of venetoclax, and again at day 28 (± 5 days) for patients with recent ponatinib exposure or day 35 (± 5 days) for patients without recent ponatinib exposure but must be prior to the beginning of cycle 2. Additional bone marrow assessment every 2-3 cycles or as clinically indicated. Cytogenetics (unless previously diploid) and PCR for *BCR-ABL1* should be sent with each bone marrow evaluation.
8. EKG at baseline, during cycle 3, then every 3 months
9. Echocardiogram or MUGA during cycle 4 and then every 3 months, and as clinically indicated
10. Biomarker studies including CyTOF (on day 7 ± 2 days of cycle 1 for patients without recent ponatinib exposure only, at the end of cycle 1 and at the time of relapse), BH3 profiling (on day 7 ± 2 days of cycle 1 for patients without recent ponatinib exposure only, at the time of relapse). Relapse samples will be collected from bone marrow and peripheral blood.

Failure to collect biomarker studies at any time point due to logistical reasons will not be considered a protocol deviation or violation.

A study visit is a visit to MD Anderson Cancer Center every course.

	Pre	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycles 5+**	**Follow-Up**
Informed consent	X						
History + physical	X	X	X	X	X	X Every cycle	
Vital signs	X	X	X	X	X	X Every cycle	
Performance Status	X						
Concomitant medication assessment[5]	X	X	X	X	X	X Every cycle	X
Toxicity (AE) assessment		X	X	X	X	X Every cycle	X
CBC with diff	X	X	X	X	X	X Every cycle	
Electrolytes (potassium, calcium, magnesium, phosphorus), LDH, uric acid, creatinine, liver function tests (AST, ALT, total bilirubin), lipase and amylase[4]	X	X	X	X	X	X Every cycle	
Triglycerides	X						

Hepatitis B antibodies	X						
Bone marrow aspirate	X	X[1]	X			X[2]	
Pregnancy test (If indicated)	X						
EKG	X			X		X Every 3 months	
Echocardiogram or MUGA	X				X	X Every 3 months	
CyTOF[6]	X	X[3]					
BH3 profiling[6]	X	X[3]					
Next-generation sequencing and SNP array[6]	X						
Survival status and subsequent treatment							X

[1]Bone marrow aspiration on day 7 (±1 days) for patients without recent ponatinib exposure only and at end of cycle 1 (day 28 [±5 days] for patients with recent ponatinib exposure and day 35 [±5 days] for patients without recent ponatinib exposure).
[2]After achieving CR/CRi, bone marrow should be performed every 2-3 cycles or as clinically indicated.
[3]In patients without recent ponatinib exposure, BH3 profiling will be assessed on days 1 and 7 of cycle 1, CyTOF will be assessed on days 1, 7 and 35 of cycle 1. In patients with recent ponatinib exposure, BH3 profiling will be assessed on day 1 of cycle 1, CyTOF will be assessed on days 1 and 28 of cycle 1. CyTOF and BH3 profiling will also be performed at the time of relapse.
[4]Amylase and lipase will be checked in all patients at screening. Subsequent amylase and lipase only need to be checked as clinically indicated (e.g. for patients with abdominal pain)
[5] Concomitant medication data will not be entered into the case report form (Prometheus); however, concomitant medications will be documented in the subject's electronic medical record.
[6] Biomarker studies will not be captured in the case report form.

6.3 Follow-up

Thirty days after last dose of the study drugs concomitant medication and AE assessment will be recorded. This may be done over the phone with a member of the study staff.

Patients discontinued from study treatment for any reason other than withdrawal of consent for treatment will continue to be assessed for survival. Survival information (i.e. the date and cause of death) and subsequent treatment will be collected via telephone calls and/or clinical visits every 6 months (+/- 2 months) until death or withdrawal of consent.

7. EFFICACY AND SAFETY ASSESSMENTS

7.1. CRITERIA FOR RESPONSE

1. Complete Remission (CR): Normalization of the peripheral blood and bone marrow with 5% or less blasts in normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above, and platelet count of 100 x 10^9/L. Complete resolution of all sites of extramedullary disease is required for CR.
2. Complete remission without recovery of counts (CRi): Peripheral blood and marrow results as for CR, but with incomplete recover of counts (platelets < 100 x 10^9/L; neutrophils < 1 x 10^9/L).
3. Complete cytogenetic response (CCyR): Same as for CR with cytogenetics showing diploid karyotype (valid only for patients with abnormal cytogenetics at enrollment)

4. Complete molecular response (CMR): Same as for CR with RT-PCR for BCR-ABL <0.01%.[21]
5. Major molecular response (MMR): Same as for CR with RT-PCR for BCR-ABL with 3 log reduction from baseline (for p190 transcripts) and/or ≤0.1% by the International Scale (for p210 transcripts)
6. Partial Response (PR): As above for CR except for the presence of 6-25% marrow blasts.
7. Progressive Disease (PD): increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
8. Relapse Disease: reappearance of blasts in the blood or bone marrow >5% or development of extramedullary disease after initial response.

7.2. EVALUATION OF TOXICITY

1. Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Event Reporting Version 4.0. The toxicity of the regimen will be monitored continuously during the course of the study.
2. AEs will be recorded in the subject's source documents from the first dose through 30 days after the last dose. Serious Adverse Events (SAEs) will be captured from the time of the first protocol-specific intervention. The Principal Investigator will sign and date the Adverse Event Record (AE logs) per patient after the completion of each course. Following signature, the AE logs will be used as source documentation for the adverse events for attribution.

7.3. CRITERIA TO STOP TREATMENT

1. Failure to achieve CR/CRi after 2 cycles of treatment, unless the patient is deemed to be deriving clinical benefit (e.g. blast reduction not meeting criteria for CR/CRi) as assessed by the treating physician and PI
2. Unacceptable toxicity judged to be related to therapy by the investigator, as defined by the NCI Common Toxicity Criteria (irreversible or prolonged (> 42 days) grade 4 hematological toxicity or grade 4 non-hematological toxicity thought to be related to ponatinib or venetoclax), unless it has been been judged by the treating physician and PI that the patient is achieving clinical benefit.
3. Non-compliance by the patient with protocol requirements or patient's request to be removed from the study.
4. Relapse, defined as >5% bone marrow blasts not attributed to hematopoietic recovery, occurring after initial response to therapy

Patients coming off treatment due to the above issues will continue to be followed for survival outcomes.

7.4 DEFINITION OF STUDY END-POINTS

1. **Relapse-free survival** is the time from documented CR/CRi until relapse or death.

2. **Event-free survival** is the time from the first day of treatment until any treatment failure (lack of response, relapse, or death).

3. **Overall response rate** is defined as the percentage of patients achieving CR or CRi

4. **Overall survival** is defined as the time from the first day of treatment to time of death from any cause.

In the primary analysis, survival will not be censored for stem cell transplant.

8. REPORTING REQUIREMENTS

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines (Appendix C).

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

These adverse events will be recorded in the Case Report Form (CRF):

- Any grade adverse event that is possibly, probably, or definitely related to the study drug(s)
- All serious adverse events regardless of attribution to the study drug(s)
- Any grade adverse event regardless of attribution to the study drugs(s) that results in any dose modification

Patients will be registered in CORe. Prometheus will be used for data entry and AE capture.

Baseline events will be recorded in the medical history section of the case report form (Prometheus) and will include the terminology event name, grade, and start date of the event. Abnormal laboratory values or test results will not be recorded or reported as adverse events unless it leads to therapeutic intervention, results in dose modification or interruption, or meets the protocol definition of a DLT or SAE.

AEs will be shared with AbbVie on an annual basis.

Serious Adverse Event Reporting (SAE) for M. D. Anderson-sponsored IND Protocols

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 (with the exception of planned hospitalization period for cycle 1) 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).

- 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.

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines, located in protocol appendix A.

- An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.
- The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

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.

Reporting to Abbvie:

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

In addition to compliance with all FDA reporting requirements pursuant to 21 C.F.R. § 312, the PI shall:

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

- copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and

- notify AbbVie upon any subject receiving an AbbVie Product who becomes pregnant

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

9. OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT

9.1 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.

9.2 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

9.3 Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

9.4 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.

9.5 A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician. A copy of the REMS (**R**isk **E**valuation and **M**itigation **S**trategy) documentation on ponatinib will also be provided to the local physician.

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

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

10. STATISTICAL METHODOLOGY

This is a single arm, open label, phase I/II study to assess the MTD and the efficacy of the combination regimen of venetoclax, ponatinib and corticosteroids in patients with relapsed/refractory Ph+ ALL.

Phase I: The primary objective is to determine the optimal dosing and schedule of the combination regimen. This aim will consist of a phase I trial to determine the maximum tolerated dose (MTD) of venetoclax when given in combination with ponatinib and dexamethasone. A standard 3+3 dose escalation design will be employed: Two dose levels of venetoclax will be explored. Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable. A dose-limiting toxicity (DLT) is defined in "Definition of DLT" in section 4.8.

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

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

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

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

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

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

Table 1 below gives the probabilities of dose escalation based on true DLT risk in the 3+3 design.

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

A minimum of 6 patients and a maximum of 12 patients will be enrolled to the phase I portion of the trial.

Phase II: The primary objective is to determine the overall response rate, defined as the rate or CR + CRi occurring at the end of 2 cycles of treatment. A total of up to 26 patients will be in the phase II part including patients who received the MTD dose level in the phase I portion and those enrolled in the phase II portion of the study. The target overall response (OR) rate is 60%. This regimen of the combination treatment will be considered worthy of further investigation if it elicits an increase in OR to 60% with

acceptable toxicity. A >15% drug-related grade 4-5 toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions below, were constructed that meet the following two conditions,

1) Stop if Prob[p(OR, E) < 0.60 | data] > 0.975, or

2) Stop if Prob[p(TOX, E) > 0.15 | data] > 0.8,

where p(OR, E) and p(TOX, E) are the true OR and toxicity rates for the combination treatment. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability < 2.5%) that OR rate of the combination treatment is greater than 0.6. The second condition will stop the study early if excessive therapy-related grade 4-5 toxicity (>15%) is highly probable (i.e., probability >80%) for the combination treatment. Monitoring for toxicity and futility will not begin until 6 patients have been evaluated, and cohort size for future evaluations is 2.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in Table 2. For example, accrual will cease if 2 or more patients experience toxicities among the first 6 patients. Toxicities will be continually monitored and will count towards this stopping rule if they occur while the patient is still on study.

Table 2. Stop accrual if there are this many drug-related grade 4-5 toxicities among the number of patients evaluated

# patients evaluated	# patients with toxicities
6	2-6
8-10	3-10
12-16	4-16
18-20	5-20
22-24	6-24
26	Stop due to maximum sample size

Monitoring the OR rate, based on the above assumptions and monitoring conditions is found in Table 3. For example, accrual will cease if no patients experience an overall response in the first 6 patients treated.

Table 3. Stop accrual if there are this many response (i.e., # patients with overall response) among the number of patients evaluated

# patients evaluated	# patients with overall response
6	0
8	0-1
10	0-2
12	0-3
14	0-4
16	0-5
18	0-6
20	0-7
22	0-8
24	0-9
26	Stop due to maximum sample size

Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the operating characteristics table (Table 3). In order to utilize the software for the design, a 60% constant rate and beta (1.2, 0.8) priors were assumed for the standard treatment response rate and experimental treatment response prior distribution, respectively. In addition, a 15% constant rate and beta (0.3, 1.7) priors were assumed for the standard treatment toxicity rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true OR of the combination treatment was 60% and the true toxicity rate was 15% was 39.24%. Probabilities of stopping early for high true toxicity rates (i.e., 40%) were 98.27% when the true OR was 60% and 99.79% when true OR rate was 30%.

Table 4. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment

True Toxicity Rate	True OR	Prob(stop the trial early)
0.10	0.30	0.9028
	0.40	0.6445
	0.50	0.3561
	0.60	0.2064
	0.70	0.1688
0.15	0.30	0.9256
	0.40	0.7278
	0.50	0.5070
	0.60	**0.3924**
	0.70	0.3636
0.2	0.30	0.9506
	0.40	0.8193
	0.50	0.6727
	0.60	0.5966
	0.70	0.5775
0.3	0.30	0.9861
	0.40	0.9490
	0.50	0.9076
	0.60	0.8861
	0.70	0.8808
0.4	0.30	0.9979
	0.40	0.9922
	0.50	0.9860
	0.60	0.9827
	0.70	0.9819

Secondary objectives include: the rate of minimal residual disease negativity by PCR for BCR-ABL1 transcripts, proportion of patients proceeding to ASCT, relapse-free survival, overall survival, and the safety of the combination regimen.

The investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

- Phase I: A toxicity summary must be submitted after the first 3 evaluable patients, complete 1 cycle of study treatment, and every 3 evaluable patients thereafter, IND office approval must be obtained prior to advancing/changing dose levels.
- Phase II: A efficacy/toxicity summary must be submitted after the first 6 evaluable patients complete the second cycle of study treatment, and every 2 patients thereafter.

  A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Analysis Plan: Demographic/clinical characteristics and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range.

For the primary efficacy analysis, we will estimate the OR for the combination treatment (defined as the proportion of patients achieving CR or CRi after 2 cycles of treatment), along with the 95% credible interval. This regimen will be considered worthy of further investigation if an OR rate of at least 60% is achieved. Patients who drop out of the study before completing 2 cycles will be treated as "failures" for the primary analysis. The association between response and patient's clinical characteristics such as apoptotic protein expression, will be examined by Wilcoxon's rank sum test or Fisher's exact test, as appropriate.

The proportion of patient achieving CMR (as assessed by PCR for BCR-ABL transcripts) after 2 cycles of therapy will be estimated. The proportion of patients proceeding to ASCT and median time to ASCT will also be reported.

Kaplan-Meier curves will be used to estimate unadjusted OS and RFS distributions. Overall survival defined as the time from treatment initiation to death or last follow-up. RFS is defined as the time from the date of remission to relapse from CR or death from any cause whichever occurs first. Median OS and RFS as well as 1-year OS and RFS rates will be reported. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests.

Patients who enrolled in the phase I part of the trial who receive the MTD of venetoclax will be included in all efficacy analyses.

Toxicity type, severity and attribution will be summarized for each patient using frequency tables.

Sample Size: We will treat up to 26 patients at the recommended phase II dose (including patients who received the MTD dose level in the phase I portion and those enrolled in the phase II portion of the study). For the efficacy endpoint, with a sample size of 26 patients, If the study is not stopped early and 26 patients have been treated and evaluated in the study, assuming 16 of the 26 patients achieve OR, then the 95% credible interval for OR rate will be (0.43,0.79).

Approximately 10 patients per year are expected to be enrolled. The total study duration is expected to be 5 years (3 years of new patient enrollment, plus an additional 2 years of follow-up).

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