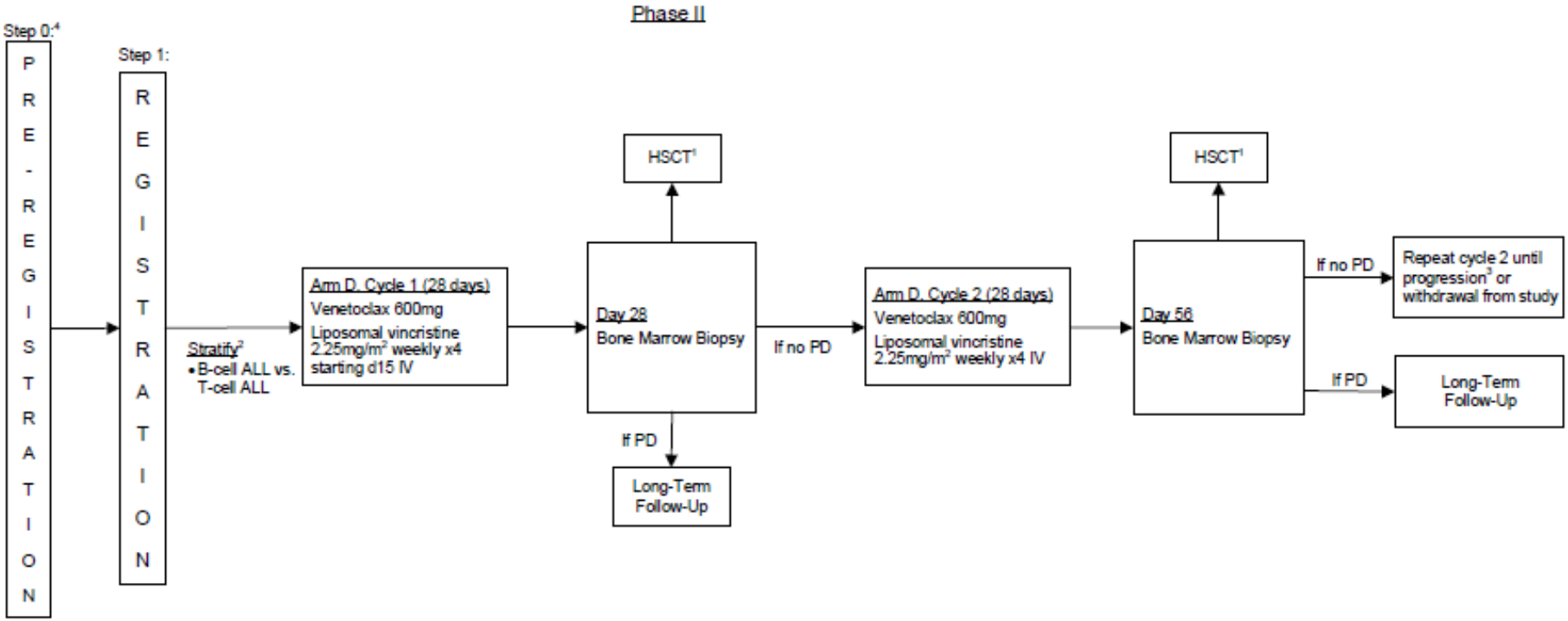
Schema



Phase II Accrual Goal: 56 patients (including the patients from the Phase I arm with the MTD dose)

1. If patient demonstrates CR or Cri at day 28 or day 56 bone marrow biopsies, they may continue on combination therapy or proceed to HSCT if deemed fit for transplant and advised by treating physician. Patient may proceed to HSCT at any point at treating physician's discretion (if not day 28 or 56).
2. Patients will be stratified by immunophenotype: "B-cell ALL" vs. "T-cell ALL".
3. If patient does not demonstrate any signs of progression, they may continue on combination therapy as long as they are receiving benefit per treating physician. Patients, if in CR/Cri by the end of cycle 2 may continue on combination or single agent venetoclax at the discretion of the treating physician.
4. Bone marrow and peripheral blood specimens must be submitted for mandatory central review.

3.3 Eligibility Criteria – Phase II (Arm D) – Step 0

_____3.3.1 Patient must be considered a potential candidate for the trial.

NOTE: Enrollment to Step 0 may occur prior to or following completion of the assessments to verify patient eligibility for Step 1 registration. Bone marrow and/or peripheral blood specimens collected during Step 0 or prior to treatment on Step 1 must be submitted for central review in order for the patient to be considered evaluable. Results will not be reported to the site and will not impact patient participation in the trial.

3.4 Eligibility Criteria – Phase II (Arm D) – Step 1

_____3.4.1 Relapsed or refractory B-cell or T-cell ALL, including lymphoblastic lymphoma, after multi-agent chemotherapy.

_____3.4.2 Age ≥ 18 years.

_____3.4.3 ECOG performance status 0-2.

_____3.4.4 Adequate liver function with AST/ALT less than 3X upper limit of normal and total bilirubin less than 2 mg/dL within 10 days prior to first dose of study agent.

_____3.4.5 Circulating WBC count must not be above 25 $x10^9$/L at the time of registration to step 1.

3.4.5.1 Patients with WBC count above 25 $x10^9$/L are eligible if they have started steroids or hydroxyurea per institutional guidelines. Please see Section 5.6.2 for additional details.

_____3.4.6 GFR of at least 40 mL/min within 7 days prior to first dose of study agent.

_____ 3.4.7 Women must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

_____3.4.8 All females of childbearing potential must have a blood test or urine study with a minimum sensitivity 25 IU/L or equivalent units of HCG within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential?_____(Yes or No)

Date of blood or urine test: _____

_____3.4.9 Women of childbearing potential and sexually active males must use an accepted and highly effective method of contraception or to abstain

from sexual intercourse for the duration of their participation in the study and for 30 days after the last dose of venetoclax.

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

3.4.10 No evidence of prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical carcinoma, or any surgically- or radiation-cured malignancy continuously disease free for ≥ 2 years.

3.4.11 Patients with isolated testicular or CNS relapsed disease are not eligible.

3.4.12 Patients must not have Burkitt's lymphoma/leukemia based on the WHO criteria.

3.4.13 Patients must not have active central nervous system (CNS) leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF) or the use of CNS-directed local treatment for active disease within the prior 28 days. Prophylactic intrathecal chemotherapy is allowed. Previously treated CNS disease with documented clearance of the CSF will be allowed and once cleared, prophylactic intrathecal chemotherapy can be continued.

3.4.14 Patients will not be enrolled if they received prior chemotherapy within 2 weeks before enrollment with the following exceptions: to reduce the circulating lymphoblast count or palliation (i.e., steroids or hydroxyurea), for ALL maintenance (mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors).

3.4.15 Patients may be enrolled with a prior allogeneic hematopoietic stem cell transplant (HSCT) but the transplant date must be at least 90 days before date of enrollment. Patient must be off immunosuppression and without active GVHD prior to enrollment if previous HSCT.

3.4.16 Patients cannot have poorly controlled chronic viral infections including Hepatitis B, C, or HIV. HIV positive patients are allowed on this study if they have a CD4 count ≥ 400, and are on a stable antiviral regimen.

3.4.17 Patients with NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia may not be enrolled.

3.4.18 Patients with serious medical or psychiatric illness that in the opinion of the primary investigator is likely to interfere with study participation may not be enrolled.

3.4.19 Patients must not be participating in any other clinical trial or taking any other experimental medications within 21 days prior to registration.

3.4.20 Patients should not have received the following **within 7 days** prior to the first dose of study drug:

- Strong and Moderate CYP3A inhibitors (see Appendix V for details);
- Strong and Moderate CYP3A inducers (see Appendix V for details)

See Section 5.6.3 for discussion of the use of azole anti-fungals.

3.4.21 Patients must not have grade 3 or higher peripheral neuropathy or history of grade 3 peripheral neuropathy. Patients with familial demyelinating diseases like Charcot-Marie-Tooth disease also excluded.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.