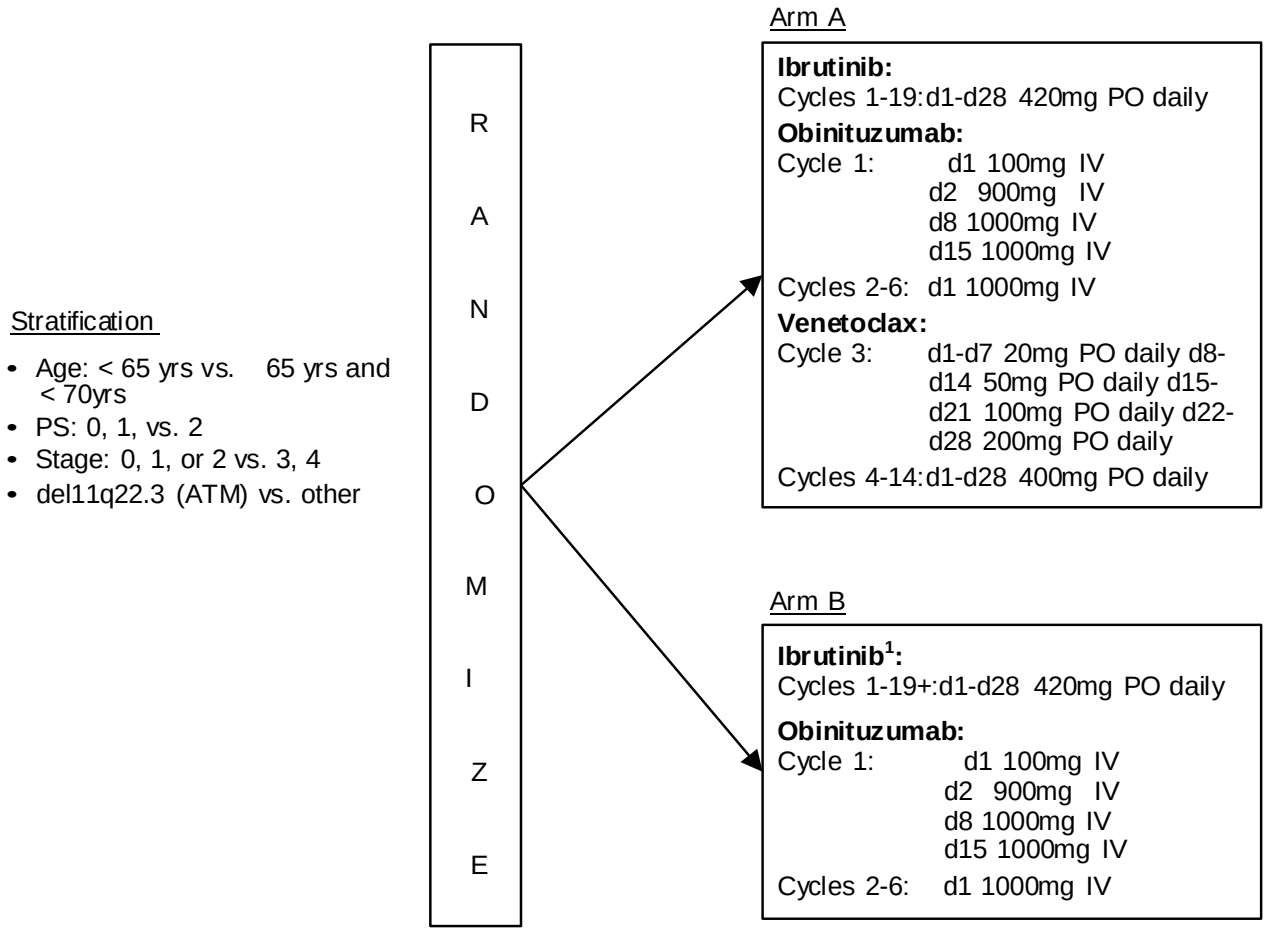
Schema



Accrual = 720
Cycle length = 28 days

1. For patients on Arm B who complete 19 cycles of study treatment, ibrutinib should be continued at a rate of 420mg PO once daily under observation until disease progression

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Diagnosis of CLL according to the NCI/IWCLL criteria or SLL according to the WHO criteria.

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma

  OR

- Diagnosis of CLL according to the NCI/IWCLL criteria as evidenced by all of the following:
  - Peripheral blood lymphocyte count of greater than 5 $x10^9$/L
  - Immunophenotype consistent with CLL defined as:
    - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).
    - Clonality as evidenced by **κ** or **λ** light chain restriction (typically dim immunoglobulin expression)
- Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) or negative

immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy.

_____ 3.1.2 No prior chemotherapy, BTK inhibitor therapy, venetoclax, small molecule signaling inhibitor, or monoclonal anti-body therapy for treatment of CLL or SLL

_____ 3.1.3 Has met **at least one** of the following indications for treatment:

- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10^9/L)
- Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
- One or more of the following disease-related symptoms:
  - Weight loss ≥ 10% within the previous 6 months
  - Grade 2 or 3 fatigue attributed to CLL
  - Fevers >100.5^{o}F for 2 weeks without evidence of infection
  - Clinically significant night sweats without evidence of infection
- Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.

_____ 3.1.4 Age ≥ 18 years and < 70.

_____ 3.1.5 ECOG performance status between 0-2.

_____ 3.1.6 Life expectancy of ≥ 12 months.

_____ 3.1.7 No deletion of 17p13 on cytogenetic analysis by FISH

_____ 3.1.8 The following laboratory values obtained ≤ 14 days prior to registration:

_____ Glomerular filtration rate (GFR) > 40 mL/minute as calculated by the Cockcroft-Gault Formula:

$$\text{CrCl}\left(\frac{\text{ml}}{\text{min}}\right)=\frac{(140-\text{age in years})*(\text{actual weight (in kg)})}{72*\text{serum creatinine}\left(\frac{\text{mg}}{\text{dl}}\right)}*0.85\ \text{(for female pts)}$$

_____ Total bilirubin ≤ 1.5 x ULN unless due to Gilbert's disease. For those with a total bilirubin > 1.5 x ULN, a direct bilirubin should be performed and must be < 1.5 mg/dL for Gilbert's to be diagnosed.

_____ SGOT (AST)/SGPT (ALT) ≤ 3.0 x the institutional ULN

_____ PT/INR < 1.5 ULN and PTT (aPTT) < 1.5 X ULN

NOTE: If value is higher due to hepatic involvement by CLL, patient is eligible.

_____ 3.1.9 No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation.

_____ 3.1.10 No current use of corticosteroids. EXCEPTION: Low doses of steroids (< 10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical condition (e.g. chronic adrenal insufficiency) is permitted.

_____ 3.1.11 No previous autoimmune complications (e.g. autoimmune hemolytic anemia or immune thrombocytopenia) that have developed since the initial diagnosis of CLL and have required treatment with high dose corticosteroids (e.g. equivalent of >20 mg/day of prednisone), monoclonal antibody based therapy, or chemotherapy. Prior use of corticosteroids for reasons other than treatment of autoimmune complications is allowed.

_____ 3.1.12 No other active primary malignancy (other than non-melanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting expected survival to ≤ 2 years.

NOTE: If there is a history of prior malignancy, the patient must not currently be receiving other specific treatment (other than hormonal therapy for their cancer).

_____ 3.1.13 Able to adhere to the study visit schedule and other protocol requirements.

_____ 3.1.14 No major surgery within 4 weeks (28 days) of first dose of study drug or minor surgery within 3 days of first dose of study drug.

_____ 3.1.15 No radiation therapy ≤ 4 weeks prior to registration

_____ 3.1.16 Patients who are HIV+ with undetectable HIV viral load are eligible provided they meet all other protocol criteria for participation and are not being treated with protease inhibitors or any NNRTI that are CYP3A4 inducers; if being treated for HIV, patients should be receiving an alternative ART that is not a CYP3A inhibitor.

_____ 3.1.17 Patients must not have any of the following conditions:

- Congestive heart failure or New York Heart Association Functional Classification III or IV congestive heart failure
- History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration.
- Recent infections requiring systemic treatment; need to have completed anti-biotic therapy >14 days before the first dose of study drug.
- Cerebral vascular accident or intracranial bleed within the last 6 months
- Infection with known chronic, active hepatitis C.
- Serologic status reflecting active hepatitis B or C infection. Patients with hepatitis B or C infection may be eligible if viral loads are undetectable. Patients may be on suppressive therapy.

_____ 3.1.18 Patients are not eligible if they require treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix X). For additional information regarding use of moderate CYP3A4/5 inhibitors see Section 8.1.11

_____ 3.1.19 Patients may not have received the following **within 7 days** prior to the first dose of study drug:

- Steroid therapy for anti-neoplastic intent;
- Strong and Moderate CYP3A inhibitors (see Appendix X for details)
- Strong and Moderate CYP3A inducers (see Appendix X for details)

_____ 3.1.20 Patients may not be on any other investigational agents

_____ 3.1.21 Patients may not have received warfarin or another vitamin K antagonist in the preceding 30 days.

_____ 3.1.22 Women must not be pregnant or breast-feeding since this study involves investigational agents whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown.

All females of childbearing potential must have a blood test within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) 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? _____(Yes or No)

Date of blood test: _____

_____ 3.1.23 Women of childbearing potential and sexually active males must be strongly advised to use accepted and highly effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for:

- 18 months after the last dose of obinutuzumab
- 90 days after the last dose of ibrutinib, and
- 30 days after the last dose of venetoclax

Male subjects must also agree to refrain from sperm donation until 90 days after the last dose of protocol treatment.

_____ 3.1.24 Patient must be able to swallow capsules and not have the following conditions:

- disease significantly affecting gastrointestinal function
- resection of the stomach or small bowel
- symptomatic inflammatory bowel disease
- ulcerative colitis
- partial or complete bowel obstruction

_____ 3.1.25 Patient must not be on any other systemic immunosuppressant therapy other than corticosteroids within 28 days of the first dose of study drug.

_____ 3.1.26 Patient must not be vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.

_____ 3.1.27 Patient must not have any known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.

_____ 3.1.28 Patient must not have currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child Pugh classification [Appendix XIII]

_____ 3.1.29 Patient must undergo assessment with Timed Up and Go (TUG) test (see Appendix XI) and comorbidity index.

_____ 3.1.30 Patient must be able to receive xanthine oxidase inhibitor or rasburicase for TLS prophylaxis.

_____ _____

Physician Signature Date

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