FAST FACTS

A041702 - A RANDOMIZED PHASE III STUDY OF IBRUTINIB PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX AND OBINUTUZUMAB IN UNTREATED OLDER PATIENTS (≥ 70 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Pre-registration eligibility criteria (Step 0)

1. CLL or SLL diagnosis
   - Patients must have been diagnosed with CLL (> 5000 B-cells per uL of peripheral blood at any point during the course of their disease) or Small lymphocytic lymphoma (SLL) with <5000 B-cells per µL of blood but with disease-associated lymphadenopathy.
2. Central FISH blood submission
   - This blood submission is mandatory prior to registration/randomization to perform FISH
     centrally that will be used for stratification. It should be obtained as soon after preregistration
     as possible. See Sections 4.4 and 6.2 for more information.

Registration eligibility criteria (Step 1)

1. Documentation of disease
   Patients must be diagnosed with CLL or SLL in accordance with 2018 IWCLL criteria that includes all of the following:
   - ≥5x10^9 B lymphocytes (5000/µL) in the peripheral blood measured by flow cytometry at any point in the course of the disease or less peripheral blood involvement but disease-associated lymphadenopathy.
   - On local morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes.
   - Neoplastic cells on immunophenotype (performed locally) must reveal a clonal B-cell population, which express the B cell surface markers of CD19 and CD20, as well as the T-cell antigen CD5. Patients with bright surface immunoglobulin expression or lack of CD23 expression in >10% of cells must lack t(11;14) translocation by interphase cytogenetics.
2. Staging and indication for therapy
   Patients must be intermediate or high-risk Rai stage CLL or SLL.

Intermediate Risk (Formerly Stage I/II)	Lymphadenopathy and/or hepatomegaly or splenomegaly without anemia or thrombocytopenia

High Risk (Formerly Stage III/IV)	Splenomegaly and/or Anemia (hemoglobin <11g/dL) not attributable to autoimmune hemolytic anemia and/or Thrombocytopenia (plt <100 x109/L) not attributable to autoimmune thrombocytopenia

- Patients must meet criteria for treatment as defined by 2018 IWCLL guidelines which includes at least one of the following criteria:
  - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
  - Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
  - Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
  - Progressive lymphocytosis with a lymphocyte doubling time < 6 months or an increase of ≥ 50% over a 2 month period
  - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
  - Symptomatic or functional extranodal involvement (e.g. skin, kidney, lung, spine)
  - Constitutional symptoms, which include any of the following:
    - Unintentional weight loss of 10% or more within 6 months
    - Significant fatigue
    - Fevers >100.5 degrees F for 2 weeks or more without evidence of infection
    - Night sweats ≥1 month without evidence of infection

3. Prior treatment
   - Patients must not have had prior therapy for CLL/SLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids).
   - Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL/SLL must be complete at least 4 weeks prior to enrollment. Palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration.
4. Age ≥ 70 years or ≥ 65 years with the presence of del(17p) on FISH
5. ECOG performance status 0-2
6. Required initial laboratory values
   - Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3 except if due to bone marrow involvementPlatelet Count (untransfused) ≥ 30,000/mm^3 except if due to bone marrow involvement
   - Calc. Creatinine Clearance ≥ 40 mL/min (by Cockcroft-Gault)
   - Bilirubin ≤ 1.5 x upper limit of normal (ULN) except if due to liver involvement, hemolysis, or Gilbert's disease
   - AST / ALT ≤ 2.5 x upper limit of normal (ULN) except if due to liver involvement
7. Comorbid conditions or other active diseases
   - Patients must not have any history of Richter's transformation or prolymphocytic leukemia (prolymphocytes in blood > 55%).

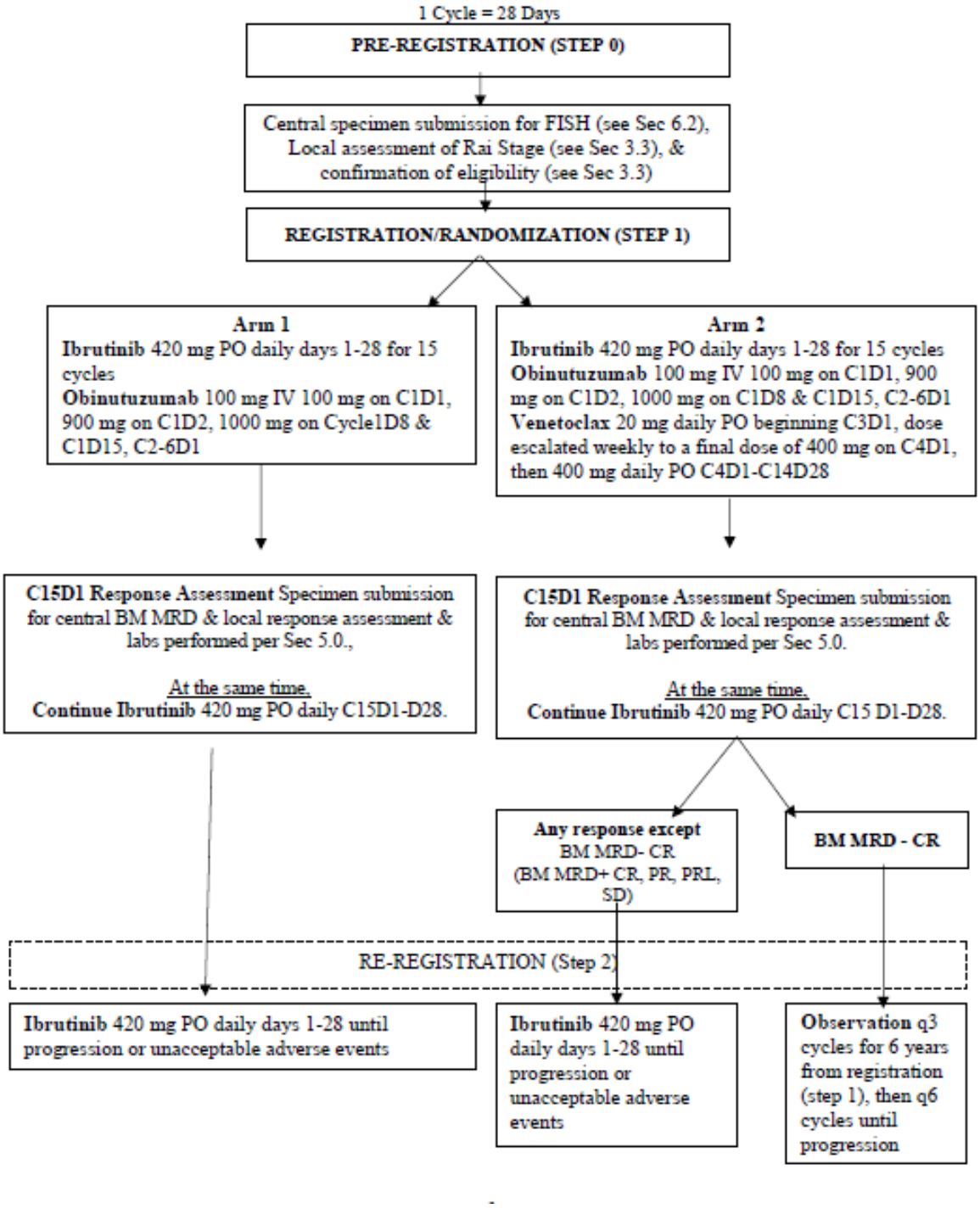
- If evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy if indicated.
- Please note: IVIG can cause a false positive hepatitis B serology. If patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B DNA) they may still participate in the study, must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.
- If history of hepatitis C virus (HCV) infection, must be treated with undetectable HCV viral load
- Patients with Class III or Class IV heart failure by New York Heart Association, those with unstable angina, and those with uncontrolled arrhythmia are not eligible.
- Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months are not eligible.
- Human immunodeficiency virus (HIV)-infected patients on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial

8. Concomitant medications
    - Patients must not be receiving active systemic anticoagulation with heparin or warfarin. Patients on warfarin must discontinue the drug for at least 10 days prior to registration on the study.
    - Chronic concomitant treatment with strong inhibitors of CYP3A4/5 is not allowed on this study. Patients on strong CYP3A inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 8.1.9 for more information.
    - Chronic concomitant treatment with strong CYP3A4/5 inducers is not allowed. Patients must discontinue the drug 14 days prior to registration on the study. See Section 8.1.10 for more information.
    - Patients must not require more than 20 mg prednisone or equivalent corticosteroid daily.
    - Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics.
9. Other
    - Patients must be able to swallow capsules and not have the following conditions: disease significantly affecting gastrointestinal absorption, resection of the stomach or small bowel, partial or complete bowel obstruction.
    - Patients must not have a known allergy to mannitol.
    - Patients must not have prior significant hypersensitivity to rituximab (not including infusion reactions).
    - Patients may not have had major surgery within 10 days prior to registration, or minor surgery within 7 days prior to registration. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration for a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.
    - Patients must be able to receive either a xanthine oxidase inhibitor or rasburicase for prophylaxis/treatment of TLS.

Eligibility criteria for re-registration (Step 2)

1. Completion of treatment through Cycle 14 Day 28, and remain on ibrutinib therapy.
2. Receipt of central BM MRD results
3. Response assessment completed per Section 5.0.

Schema


1 Cycle = 28 Days
PRE-REGISTRATION (STEP 0)
Central specimen submission for FISH (see Sec 6.2), Local assessment of Rai Stage (see Sec 3.3), & confirmation of eligibility (see Sec 3.3)
REGISTRATION/RANDOMIZATION (STEP 1)
Arm 1
Ibrutinib 420 mg PO daily days 1-28 for 15 cycles
Obinutuzumab 100 mg IV 100 mg on C1D1, 900 mg on C1D2, 1000 mg on Cycle1D8 & C1D15, C2-6D1
Arm 2
Ibrutinib 420 mg PO daily days 1-28 for 15 cycles
Obinutuzumab 100 mg IV 100 mg on C1D1, 900 mg on C1D2, 1000 mg on C1D8 & C1D15, C2-6D1
Venetoclax 20 mg daily PO beginning C3D1, dose escalated weekly to a final dose of 400 mg on C4D1, then 400 mg daily PO C4D1-C14D28
C15D1 Response Assessment Specimen submission for central BM MRD & local response assessment & labs performed per Sec 5.0.,
At the same time,
Continue Ibrutinib 420 mg PO daily C15D1-D28.
C15D1 Response Assessment Specimen submission for central BM MRD & local response assessment & labs performed per Sec 5.0.
At the same time,
Continue Ibrutinib 420 mg PO daily C15 D1-D28.
Any response except BM MRD- CR (BM MRD+ CR, PR, PRL, SD)
BM MRD - CR
RE-REGISTRATION (Step 2)
Ibrutinib 420 mg PO daily days 1-28 until progression or unacceptable adverse events
Ibrutinib 420 mg PO daily days 1-28 until progression or unacceptable adverse events
Observation q3 cycles for 6 years from registration (step 1), then q6 cycles until progression