

FAST FACTS

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

Pre-registration eligibility criteria (Step 0)

1. CLL diagnosis
 - Patients must have been diagnosed with CLL and have > 5000 B-cells per μL of peripheral blood at any point during the course of their disease.
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 in accordance with 2018 IWCLL criteria that includes all of the following:

 - $\geq 5 \times 10^9$ B lymphocytes ($5000/\mu\text{L}$) in the peripheral blood measured by flow cytometry at any point in the course of the disease.
 - On local morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes.
 - CLL 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.

 - Intermediate risk (formerly Rai stage I/II) is defined by lymphocytosis plus any of the following: enlarged lymph nodes, hepatomegaly, or splenomegaly.
 - High risk (formerly Rai stage III/IV) is defined by lymphocytosis with or without enlarged nodes and spleen plus disease-related anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count $<100 \times 10^9/\text{L}$) that is not attributable to autoimmune hemolytic anemia or 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 $\geq 50\%$ 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 (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 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
5. ECOG performance status 0-2
6. Required initial laboratory values
- Absolute Neutrophil Count (ANC) $\geq 1,000/\text{mm}^3$ except if due to bone marrow involvement
 - Platelet Count (untransfused) $\geq 30,000/\text{mm}^3$
 - 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 with CR determination.

Schema

