Overall EA9161 Study Objective
To compare the progression-free survival of time-limited treatment with the combination of venetoclax, ibrutinib, and obinutuzumab to ibrutinib (administered indefinitely) and obinutuzumab in untreated CLL patients younger than 70 years of age.

Accrual goal = 720 patients.
Patients in both arms will be assessed with a physical exam, complete blood count, and chemistries prior to cycles 1-7.
Beginning day 1 of cycle 8, patients will be seen every 90 days (± 7 d).
*Submission of prestudy specimens per patient consent.
†The following prestudy tests are to be completed ≤ 2 weeks before registration: history and physical; imaging; CBC with differential; and renal, hepatic, and hematologic function. Bone marrow biopsy (required) and CLL FISH panel must be done ≤ 3 months prior to registration.
‡For patients on arm B who complete 19 cycles of study treatment, ibrutinib should continue at a rate of 420 mg PO qd under observation until disease progression.

A Randomized Phase III Study of the Addition of Venetoclax to Ibrutinib and Obinutuzumab Versus Ibrutinib and Obinutuzumab in Untreated Younger Patients With Chronic Lymphocytic Leukemia (CLL)

Study Schema
Arm A
Ibrutinib
Cycles 1-19: d 1-28 420 mg PO qd
Obinutuzumab
Cycle 1: d 1 100 mg IV
d 2 900 mg IV
d 8 and 15 1000 mg IV
Cycles 2-6: d 1 1000 mg IV
Venetoclax
Cycle 3: d 1-7 20 mg PO qd
d 8-14 50 mg PO qd
d 15-21 100 mg PO qd
d 22-28 200 mg PO qd
Cycles 4-14: d 1-28 400 mg PO qd

Arm B
Ibrutinib‡
Cycles 1-19+: d 1-28 420 mg PO qd
Obinutuzumab
Cycle 1: d 1 100 mg IV
d 2 900 mg IV
d 8 and 15 1000 mg IV
Cycles 2-6: d 1 1000 mg IV

Stratification
• Age: < 65 years vs ≥ 65 years and < 70 years
• ECOG performance score: 0, 1 vs 2
• Stage: 0, 1, or 2 vs 3, 4
• del11q22.3 (ATM) vs other

Step 0
PRE-REGISTRATION
Stratification
• Age: < 65 years vs ≥ 65 years and < 70 years
• ECOG performance score: 0, 1 vs 2
• Stage: 0, 1, or 2 vs 3, 4
• del11q22.3 (ATM) vs other

Step 1
RANDOMIZATION
Study Objectives

**Primary Objective**
- Compare progression-free survival (PFS) of the 2 treatments

**Secondary Objectives**
- Evaluate overall survival (OS)
- Monitor and assess toxicity
- Compare minimal residual disease (MRD) status assessed by flow cytometry at baseline and during treatment
- Collect baseline and response evaluation (after cycle 19) bone marrow and paired blood specimens for evaluation of MRD

**Quality of Life (QOL) Objectives**
- Compare QOL during the first 19 cycles of treatment
- Compare QOL over the long term in patients receiving continuous ibrutinib versus time-limited treatment
- Evaluate adherence and explore how adherence relates to PFS

Eligibility Criteria*

**Main Inclusion Criteria**
- ≥ 18 and < 70 years of age with a life expectancy of ≥ 12 months
- Diagnosis of CLL according to the NCI/IWCLL criteria or small lymphocytic lymphoma (SLL) according to WHO criteria
- Met at least one of the following indications for treatment: evidence of progressive marrow failure manifested by worsening anemia (Hg < 11 g/dL) and/or thrombocytopenia (platelets < 100 × 10^9/L); symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly; one or more disease-related symptoms; or progressive lymphocytosis with an increase of > 50% over a 2-month period or anticipated doubling time of < 6 months
- ECOG performance status 0-2
- Adequate renal, hepatic, and hematologic function ≤ 14 days prior to registration
- Able to swallow capsules

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
• Able to receive xanthine oxidase inhibitor or rasburicase for tumor lysis syndrome prophylaxis
• Complete assessment with Timed Up and Go (TUG) test and comorbidity index
• Use of effective contraception or abstinence

Main Exclusion Criteria
• Prior chemotherapy, Bruton’s tyrosine kinase inhibitor therapy, venetoclax, small molecule signaling inhibitor, or monoclonal antibody therapy for CLL or SLL
• Deletion of 17p13 on cytogenetic analysis by FISH
• Active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment, with exceptions
• Current use of corticosteroids, with exceptions
• Previous autoimmune complications that have developed since the initial diagnosis of CLL and have required treatment with high-dose corticosteroids, monoclonal antibody–based therapy, or chemotherapy
• Other active primary malignancy (except nonmelanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting expected survival to ≤ 2 years
• Major surgery within 4 weeks (28 d) of first dose of study drug or minor surgery within 3 days of the first dose of study drug
• Radiation therapy ≤ 4 weeks prior to registration
• Known congestive heart failure or NYHA 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; cerebral vascular accident or intracranial bleed within the last 6 months; infection with known chronic, active hepatitis C; or positive serology for hepatitis B defined as positive for HBsAg, with exceptions
• Require treatment with a strong cytochrome P450 (CYP) 3A inhibitor

(Continued)
Main Exclusion Criteria (cont)

- Received steroid therapy for antineoplastic intent, or strong and moderate CYP3A inhibitors or inducers within 7 days prior to the first dose of study drug
- Receiving other investigational agents
- Received warfarin or another vitamin K antagonist in the preceding 30 days
- Gastrointestinal (GI) conditions such as disease significantly affecting GI function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, ulcerative colitis, or partial or complete bowel obstruction
- Currently on any systemic immunosuppressant therapy other than corticosteroids within 28 days of the first dose of study drug
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug
- Known bleeding disorders or hemophilia
- Currently active, clinically significant hepatic impairment
- Pregnancy or breastfeeding