Patient Population
See Section 3.0 for Complete Eligibility Details

- Diagnosis of CLL (NCI/IWCLL criteria) or SLL (WHO criteria); see protocol for details
- No prior chemotherapy, BTK inhibitor therapy, venetoclax, small molecule signaling inhibitor, or monoclonal anti-body therapy for treatment of CLL/SLL
- Has met AT LEAST ONE of the following:
  ◦ Evidence of progressive marrow failure as manifested by the development of worsening anemia/thrombocytopenia (see protocol)
  ◦ Symptomatic/progressive lymphadenopathy, splenomegaly, or hepatomegaly
  ◦ One or more of: weight loss ≥10% within the previous 6 months, grade 2/3 fatigue attributed to CLL, fevers > 100.5°F for 2 weeks without evidence of infection, clinically significant night sweats without evidence of infection
  ◦ Progressive lymphocytosis (not due to corticosteroids) with an increase of > 50% over a 2 month period or anticipated doubling time of < 6 months
- Age ≥ 18 and < 70, ECOG PS 0-2, adequate lab values
- Life expectancy ≥ 12 months
- No deletion of 17p13 on cytogenetic analysis by FISH
- No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment; no current use of corticosteroids (see protocol for exceptions)
- No major surgery within 4 weeks, or minor surgery within 3 days, of first dose of study drug
- No radiation therapy ≤ 4 weeks prior to registration
- See protocol for excluded conditions (i.e., relating to heart, infections, GI, etc.)
- No patients requiring treatment with a strong cytochrome P450(CYP)3A inhibitor
- No bleeding disorders/hemophilia; no currently active, clinically significant hepatic impairment
- Must be able to receive xanthine oxidase inhibitor/rasburicase for TLS prophylaxis

Treatment Plan
See Section 5.0 for Complete Treatment Details

Arm A (Ibrutinib, obinutuzumab, venetoclax):
- For the 1st cycle, patients will receive ibrutinib in combination with the dose escalation of obinutuzumab
- For the 2nd cycle, patients will receive ibrutinib in combination with one dose of obinutuzumab
- Beginning with the 3rd cycle, patients will begin the dose escalation schedule of venetoclax
- After cycle 6, patients will continue on daily oral ibrutinib and venetoclax only until the completion of cycle 14, then patients will continue on daily oral ibrutinib only until the completion of cycle 19
- Patients will be assessed prior to cycle 1-7 as per Section 7.1; beginning day 1 of cycle 8, patients will be seen every 90 days (+/- 7 days)

Arm B (Ibrutinib and obinutuzumab):
- For the 1st cycle, patients will receive ibrutinib in combination with the dose escalation of obinutuzumab
- After completion of cycle 6, patients will continue on daily oral ibrutinib until progression
- Patients will be assessed prior to cycle 1-7 as per Section 7.1; beginning day 1 of cycle 7, patients will be seen every 90 days (+/- 7 days)

Notes:
- Restaging/follow-up testing to occur post cycle 19; Arm A will complete active treatment, Arm B will continue on ibrutinib monotherapy until disease progression
- See protocol for specific details regarding each cycle, and required pre-medications
- IV medications can be administered via peripheral IV, Port-a-cath, central line, PICC or Hickman
- Patients should take oral medications at the same time each day; ibrutinib taken whole with 8oz of water
- Patients require antibiotic prophylaxis for PCP/PJP and zoster
EA9161

Available Through ECOG-ACRIN Cancer Research Group

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)

Schema

Step 0

PRE-REGISTRATION

Step 1

RANDOMIZE

Arm A

Ibrutinib:
Cycle 1-19: d1-d28 420mg PO daily
Obinutuzumab:
Cycle 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
Cycle 2-6: d1 1000mg IV
Venetoclax:
Cycle 3: d1-d7 20mg PO daily
d8-d14 50mg PO daily
d15-d21 100mg PO daily
d22-d28 200mg PO daily
Cycle 4-14: d1-d28 400mg PO daily

Arm B

Ibrutinib:
Cycle 1-19: d1-d28 420mg PO daily
Obinutuzumab:
Cycle 1: d1 100mg IV
d2 900mg IV
d8 1000mg IV
d15 1000mg IV
Cycle 2-6: d1 1000mg IV

Stratification

- Age: <65 yrs vs 65 yrs and <70 yrs
- PS: 0, 1, vs. 2
- Stage: 0, 1, or 2 vs. 3, 4
- del11q22.3 (ATM) vs. other

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
2. Submission of pre-study specimens per patient consent.