Patient Population

- Diagnosis of CLL (NCI/IWCLL criteria) or SLL (WHO criteria) per protocol
- No prior chemotherapy or monoclonal anti-body therapy for treatment of CLL or SLL
- Has met at least one of the following: 1) evidence of progressive marrow failure as manifested by the development of worsening anemia and/or thrombocytopenia, 2) symptomatic/progressive lymphadenopathy/splenomegaly/hepatomegaly, 3) 1 or more of the following symptoms: weight loss ≥ 10% within < 6 months, grade 2 or 3 fatigue attributed to CLL, fevers > 100.5°F for 2 weeks without evidence of infection, clinically significant night sweats without evidence of infection, 4) progressive lymphocytosis (not due to corticosteroids) with an increase of > 50% over a 2 month period or an anticipated doubling time of < 6 months
- Age ≥ 18 years and ≤ 70, ECOG PS 0-2, life expectancy of ≥ 12 months, and adequate lab values
- Ability to tolerate FCR based therapy
- 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 exception), and no previous use of corticosteroids for autoimmune complications that have developed since the initial diagnosis of CLL
- No major surgery within ≤ 28 days prior to registration or minor surgery within the last 5 days; No RT ≤ 4 weeks prior to registration
- No NYHA class III/IV heart disease, MI within ≤ 3 months, uncontrolled/HepC infection, CVA/intracranial bleed within ≤ 6 months, or positive serology for HepB
- No chronic use of strong or moderate CYP3A4/5 inhibitors/inducers at the time of registration
- Must not have received warfarin/vitamin K antagonist within the past 30 days

Treatment Plan

One Cycle = 28 days

**Arm A - Ibrutinib w/Rituximab:**
- For the 1st month, patients will receive Ibrutinib alone (420 mg orally once per day for 28 days +/- 4 days of cycles 1-7)
- Beginning the 2nd cycle, patients will receive Ibrutinib plus rituximab (50 mg/m² IV on day 1 of cycle 2, and 325 mg/m² IV on day 2 of cycle 2, then 500 mg/m² IV on day 1 of cycles 3-7)
- After cycle 7, patients will continue on daily oral Ibrutinib (420 mg) until disease progression. During this phase, patients will be seen every 90 days (+/- 7 days)

**Arm B - FCR for 6 cycles:**
- Rituximab (50 mg/m² IV on day 1 and 325 mg/m² on day 2 of cycle 1 and 500 mg/m² on day 1 of cycles 2-6)
- Fludarabine 25 mg/m² IV on days 1, 2, 3
- Cyclophosphamide 250 mg/m² IV on days 1, 2, 3
- Repeat cycles every 28 days (+/- 4 days) for 6 cycles

Patients with progressive disease are considered to have failed treatment. Many patients with progressive disease are asymptomatic and can be observed until they experience the criteria per protocol. Patients fulfilling the criteria for progressive disease an in need of salvage therapy may be treated with the salvage therapy deemed most appropriate by their treating physician

Notes:
- Doses should be according to actual body weight, and can be rounded per protocol
- See protocol for pre-medications, antibiotic prophylaxis, and criteria for platelet transfusion

Please Enroll Your Eligible Patients!
E1912 Available Through ECOG-ACRIN

A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)

Schema

Arm A
- Cycles 1-7
  - Ibrutinib 420 mg PO, each day, days 1-28, cycles 1-7
  - Rituximab 50 mg/m² IV, day 1, cycle 2, then 325 mg/m² IV, day 2, cycle 2
  - Rituximab 500 mg/m² IV, day 1, cycles 3-7
  - Subsequent cycles (8, 9, 10...) Ibrutinib 420 mg PO daily, days 1-28 until disease progression

Stratification:
- Age < 60 yrs. vs ≥ 60 yrs.
- PS 0-1 vs 2
- Stage 3/4 vs 1/2
- Del 11q22.3(ATM) vs other

Arm B
- Cycles 1-6
  - Rituximab 50 mg/m² IV, day 1, cycle 1
  - 325 mg/m² IV, day 2, cycle 1
  - 500 mg/m² IV, day 1, cycles 2-6
  - Fludarabine 25 mg/m² IV, days 1, 2, and 3, x 6 cycles
  - Cyclophosphamide 250 mg/m² IV, days 1, 2, and 3

Accrual: 519
Cycle length = 28 days

1. Arm B – Sequence of drug administration is rituximab, then fludarabine, then cyclophosphamide. See Section 5.1.3.