

MCCRC RC0783: Randomized Phase II Trial of Pentostatin, Cyclophosphamide, and Rituximab With or Without Concurrent Avastin® for Previously Untreated B-Chronic Lymphocytic Leukemia (CLL)

Fast Facts

Inclusion Criteria

1. Diagnosis of CLL according to the NCI criteria or SLL according to the WHO criteria

This includes previous documentation of:

- Biopsy-proven small lymphocytic lymphoma
- Diagnosis of CLL according to NCI working group criteria as evidenced by all of the following:
- Peripheral blood lymphocyte count of greater than 5,000/mm³ consisting of small to moderate size lymphocytes
- Negative FISH analysis for t(11;14)(IGH/CCND1) on peripheral blood or tissue biopsy
- Immunophenotyping consistent with CLL defined as:
 - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD-5 in the absence of other pan-T-cell markers (CD-3, CD-2, etc.)
 - Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)

NOTE: Splenomegaly, hepatomegaly, or lymphadenopathy are not required for the diagnosis of CLL

2. Has met at least one of the following indications for chemotherapy:

- Evidence of progressive marrow failure as manifested by the development of or worsening anemia (<11 g/dl) and/or thrombocytopenia (<100,000/mm³)
- Symptomatic or progressive lymphadenopathy, splenomegaly or hepatomegaly.
- One or more of the following disease-related symptoms:
 - Weight loss >10% within the previous 6 months
 - Extreme fatigue attributed to CLL
 - Fevers >100.5°F for 2 weeks without evidence of infection
 - Night sweats without evidence of infection
- Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.

Note: Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease are not sufficient for protocol therapy.

3. The following laboratory values obtained \leq 14 days prior to registration

- Creatinine \leq 1.5 x UNL
- Total bilirubin \leq 3.0 x UNL unless due to Gilbert's disease. For those with a total bilirubin >3.0 x UNL, a direct bilirubin should be performed and must be <1.5 mg/dL for Gilbert's to be diagnosed.
- SGOT \leq 3.0 x UNL NOTE: If value is higher due to hepatic involvement by CLL, patient is eligible)

4. \geq 18 years of age.

5. Life expectancy of \geq 12 months.

6. ECOG performance status (PS): 0, 1, 2 or 3.

7. Previous corticosteroids allowed.

8. Willingness to provide mandatory blood and tissue samples as required (see Sections 6.13, 14.2, 17.42 and 17.43).

9. Negative serum or urine pregnancy test done \leq 7 days prior to registration and <10 days prior to first dose of study drug treatment (thus repeat if necessary prior to first dose of study drug if >10 days have elapsed since registration pregnancy test) for women of childbearing potential only.

Exclusion Criteria

1. Any of the following co-morbid conditions:

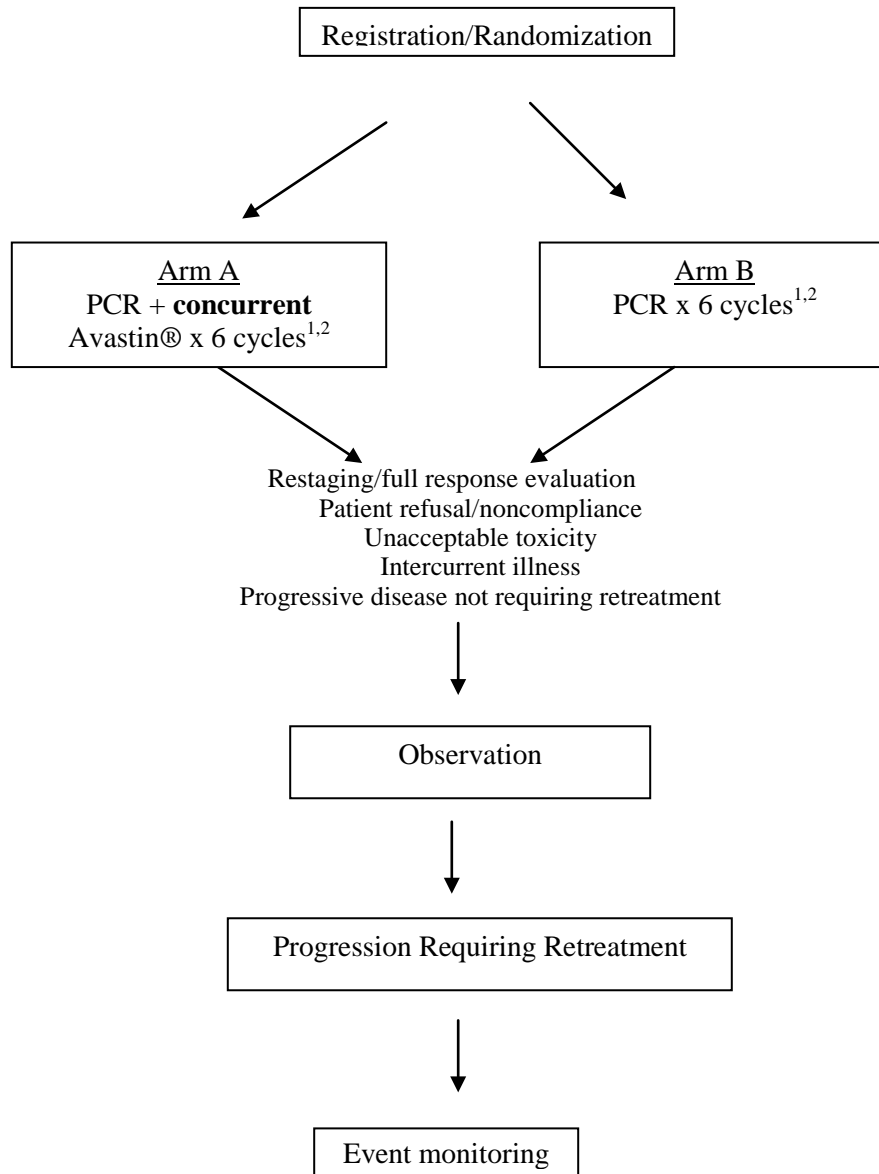
- New York Heart Association Class III or IV heart disease
- Recent myocardial infarction (\leq 6 months prior to registration)
- Unstable angina
- Recent stroke/cerebral vascular accident or transient ischemic attack (TIA) (\leq 6 months prior to registration)

- Recent arterial thromboembolic events (≤ 12 months prior to registration)
 - Clinically significant peripheral vascular disease
 - Evidence of bleeding diathesis or coagulopathy
 - Recent abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess (≤ 6 months prior to registration)
 - Serious, non-healing wound, ulcer, or bone fracture
 - Uncontrolled infection
 - Active peptic ulcer disease
 - Active infection with the human immunodeficiency virus (HIV/AIDS) as further severe immunosuppression with this regimen may occur
 - Uncontrolled hemolytic anemia
2. Any of the following:
 - Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception (condoms, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, abstinence, etc.) during treatment and for 12 months after treatment with rituximab has ended.
 3. Other active primary malignancy (other than non-melanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting survival to ≤ 2 years. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy) for their cancer.
 4. Any radiation therapy ≤ 4 weeks prior to registration.
 5. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days prior to registration, anticipation of need for major surgical procedure during the course of the study. Minor surgical procedures, fine needle aspirations or core biopsies other than bone marrow biopsy ≤ 7 days prior to registration.
 6. Uncontrolled hypertension defined as a systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg. NOTE: Use of anti-hypertensive agents to achieve control of blood pressure is permitted. Patients taking such medications may be registered once they are on a stable anti-hypertensive therapy regimen.
 7. History of deep venous thromboses or pulmonary embolism ≤ 12 months prior to registration.
 8. Required use of therapeutic doses of coumadin-derivative anticoagulants such as warfarin. NOTE: Doses of ≤ 2 mg daily are permitted for prophylaxis of thrombosis. Low molecular weight heparin is permitted at prophylactic doses only.
 9. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude them from meeting the study requirements or comply with study and/or follow-up procedure.
 10. Active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment.
 11. Evidence of ≥ 1.0 gram proteinuria per day as determined by urine protein: urine protein:creatinine (UPC) ratio < 1.0 (calculated in Section 4, footnote 7). NOTE: Patients with a UPC ratio ≥ 1.0 must undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate < 1 gram of protein in order to participate.
 12. Active or recent history of hemoptysis ($\geq 1/2$ teaspoon of bright red blood per episode) ≤ 30 days prior to registration.
 13. History of hypertensive crises or hypertensive encephalopathy.
 14. Receiving any other investigational agent which would be considered as a treatment of the primary neoplasm.
 15. Prior chemotherapy or monoclonal antibody therapy for treatment of chronic lymphocytic leukemia.

Pre-Study Parameters

1. History and physical including height, weight, blood pressure, performance status, tumor measurement by physical exam, AE assessment
2. CBC with differential, CMP, TSH, UPC ratio, Hepatitis B serum antigen testing, pregnancy test for women of child bearing potential (serum or urine)
3. Immunophenotyping by flow cytometry (peripheral blood), serum protein electrophoresis, Beta-2 microglobulin, CLL FISH panel (peripheral blood), serum immunoglobulins, Coombs test
4. CT chest, abdomen, pelvis

Schema



PCR = Pentostatin, Cyclophosphamide, Rituximab

¹ - Cycle length (cycles 1-5) = 21 days

² - Cycle length (cycle 6) = 84 days (+/- 7 days)

Avastin provided.