Alliance A041702: A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib Plus Venetoclax and Obinutuzumab in Untreated Older Patients (>/= 70 Years of Age) with Chronic Lymphocytic Leukemia (CLL)

Jennifer Woyach

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Rationale

The recently completed Alliance trial A041202 established ibrutinib as a frontline treatment for CLL [1]. While ibrutinib is highly effective in previously untreated patients with CLL, there do remain disadvantage to this therapy. Specifically, the low rate of complete response (CR) and need for continuous administration. Currently, a number of studies have been designed with the goal of discontinuing ibrutinib therapy by administering combinations with either chemotherapy or additional targeted therapies. However, no studies have been completed which use a response-adapted strategy to discontinuation. Alliance A041702 has the potential to diminish toxicity of the drug as well as drug costs significantly for patients who attain bone marrow (BM) minimal residue disease (MRD) status and can go off therapy.

Venetoclax has demonstrated considerable efficacy in CLL, both alone and in combination with ibrutinib or monoclonal antibody therapy. It has been well tolerated across studies, and is a rational drug to combine with ibrutinib given preclinical data suggesting synergy, as well as extraordinary clinical results as a single agent including impressive CR rates even in the relapsed population [2-3]. The combination of ibrutinib with venetoclax and obinutuzumab is currently under investigation in the phase I/II setting in both treatment-naïve and relapsed/refractory CLL. Based on previous trials showing a survival advantage for initial therapy even in the setting of active agents for second line therapy, Alliance investigators find that investigation of a combination of these most active agents in the up-front setting is justified [4-5]. As a secondary endpoint, this trial will collect overall survival (OS) data.

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Objective

Primary

- To compare the progression-free survival (PFS) between control treatment and experimental treatment strategies: ibrutinib/obinutuzumab (IO) with ibrutinib maintenance (IM) versus ibrutinib/venetoclax/obinutuzumab (IVO) regardless of IM or observation.

Secondary

- To compare BM MRD complete response (CR) rates and depth of response at cycle 15 day 1 between patients treated with IO versus IVO.
- To compare OS between the control and experimental treatment strategies: IO with IM versus IVO regardless of IM or observation.
- To compare the 5-year PFS and OS for the control and experimental treatment strategies: IO with IM versus IVO regardless of IM or observation.
- To describe the toxicity profile for each of the treatment strategies and by each treatment course.

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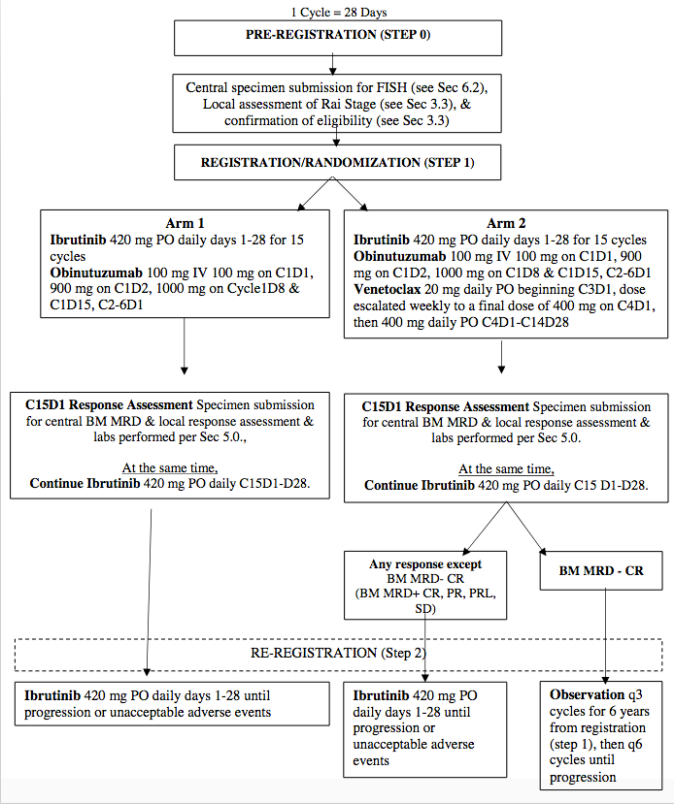
Study Schema



Patients will be followed for 10 years from study registration (Step 1) or until death, whichever comes first.

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network
a National Cancer Institute program

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Treatment Plan

- Patients will be randomized into one of two groups.
- Those in Group 1 will receive ibrutinib orally once daily continuously in 28-day cycles. They will also receive obinutuzumab intravenously for six cycles. Treatment continues indefinitely in the absence of disease progression or unacceptable toxicity. Beginning with course 16, patients receive ibrutinib orally once daily every 28 days in the absence of disease progression or unacceptable toxicity.
- Those patients in Group 2 will receive ibrutinib orally once daily continuously in 28-day cycles. They also receive obinutuzumab intravenously days for six cycles. Beginning with cycle 3, patients also receive venetoclax orally once daily continuously in 28-day cycles. Treatment continues every 28 days for up to 15 total cycles from the start of therapy. Beginning with cycle 16, patients who do not achieve a BM MRD negative CR, receive ibrutinib orally once daily continuously until disease progression or unacceptable toxicity. Patients who achieve a BM MRD negative CR discontinue therapy and undergo observation every three cycles for six years, then every six cycles thereafter.
- After completion of study treatment, patients will be followed every six months for 10 years from registration.

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Eligibility Criteria

Inclusion Criteria:

Pre-Registration Eligibility Criteria (Step 0)

- Patients must have been diagnosed with CLL and have > 5000 B-cells per uL of peripheral blood at any point during the course of their disease
- Blood submission is mandatory prior to registration/randomization to perform fluorescence in situ hybridization (FISH) centrally that will be used for stratification. It should be obtained as soon after pre-registration as possible

Registration Eligibility Criteria (Step 1)

- Patients must be diagnosed with CLL in accordance with 2018 IWCLL criteria
- Patients must be intermediate or high-risk Rai stage CLL
- Patients must meet criteria for treatment as defined by 2018 IWCLL guidelines
- 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 four 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
- Age ≥ 70 years
- ECOG Performance Status 0-2

Re-Registration Eligibility Criteria (Step 2)

- Completion of treatment through cycle 14 day 28, and remain on ibrutinib therapy
- Receipt of central BM MRD results
- Response assessment completed with CR determination

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