Cancer Research Consortium of West Michigan
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FAST FACTS

A051301: A RANDOMIZED DOUBLE-BLIND PHASE III STUDY OF IBRUTINIB DURING AND FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA OF THE ACTIVATED B-CELL SUBTYPE

NCI-supplied agent: Ibrutinib

Eligibility Criteria

On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

NOTE that these guidelines are phrased in the negative; i.e., these are potential participants who should not be enrolled to the study.

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of ibrutinib.
- Significant non-hematologic toxicity from salvage therapy except for alopecia and fatigue.

Pre-Registration Eligibility Criteria (Step 0)

Central pathology review submission

Patients must have paraffin tissue from the diagnostic or relapse biopsy available to be submitted for central pathology review and integral molecular subtyping. This review is mandatory prior to registration to confirm eligibility and should be initiated as soon as possible. Determination of cell-of-origin subtype will be performed using the Lymphoma Subtyping Test (LST) assay. See section 6.2 for details on specimen collection and submission.

Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28. A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

1. **Documentation of Disease:**
    - Diagnosis of WHO diffuse large B-cell lymphoma, high grade B-cell lymphoma not otherwise specified, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma.
    - Determination of ABC subtype by pre-registration central review.

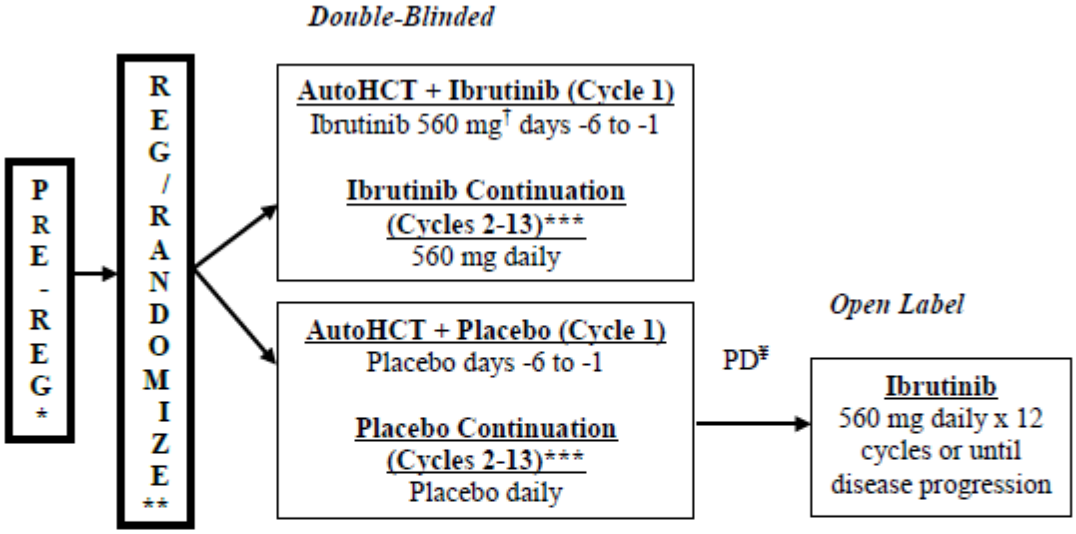
2. **Eligible for high-dose therapy and AutoHCT**
    - Patient must be deemed eligible to proceed with high-dose chemotherapy and autologous stem cell transplantation by local transplant center.
3. **Adequate organ function to proceed to transplant**
   Patient must have adequate organ function to proceed to transplant as defined below:
    - **Cardiac:** New York Heart Association Class I or less. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or angina pain. Patients 60 years or older must have a left ventricular ejection fraction (LVEF) at rest ≥ 40% measured by echocardiogram or MUGA.
    - **Pulmonary:** DLCO (corrected or uncorrected for hemoglobin per institutional standards), FEV1, FVC ≥ 40% of predicted
    - **Hepatic:** Total Bilirubin ≤ 1.5 x upper limit of normal (ULN) unless isolated hyperbilirubinemia attributed to Gilbert's syndrome. AST and ALT ≤ 3 x upper limit of normal (ULN).
    - **Renal:** Creatinine ≤ 2.0 mg/dL OR creatinine clearance (calculated clearance permitted) ≥ 40 mL/min by Cockcroft-Gault formula.
    - PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN
4. **Prior Treatment**
    - Patient must have progressed or be refractory to prior anthracycline-containing chemotherapy (e.g. R-CHOP, DA-EPOCH-R, etc).
    - No more than 3 prior regimens for large cell component (e.g. one induction and two salvage therapies). Monoclonal antibody alone or involved field/involved site radiotherapy do not count as lines of therapy.
    - Prior use of ibrutinib is allowed unless patient has had disease progression while receiving ibrutinib.
    - Patient must have chemosensitive disease as defined by at least a partial response to salvage therapy at their latest assessment.
    - No major surgery ≤ 7 days prior to registration and no minor surgery ≤ 3 days prior to registration (with the exception of intravenous access placement, e.g. Hickman or PICC).
5. **Not pregnant and not nursing,** No major surgery ≤ 7 days prior to registration and no minor surgery ≤ 3 days prior to registration (with the exception of intravenous access placement, e.g. Hickman or PICC).
6. Women of childbearing potential must use adequate contraception from study start to one month after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence. Men must practice complete abstinence or agree to use an adequate contraception method from study start to one month after the last dose of protocol therapy.**Age ≥ 18 years**
7. **Concomitant medications**
    - Patients should not require chronic use of strong CYP3A inhibitors or strong CYP3A inducers (see Appendix II).
    - Patients should not require concurrent therapeutic doses of steroids (> 20 mg of prednisone/day or equivalent) unless they need them for the indications listed in Appendix II. Steroids should be discontinued for 14 days before starting protocol treatment.
8. **Intercurrent or Recent Illness**
   HIV infected patients are eligible provided they meet all other eligibility criteria, and:
    - There is no prior history of AIDS defining conditions other than historically low CD4+ T-cell count or B-cell lymphoma
    - In the opinion of an expert in HIV disease, prospects for long-term survival are excellent were it not for the diagnosis of lymphoma
    - Use of HIV protease inhibitors as part of the anti-HIV regimen OR as a pharmacologic booster is not allowed
    - Zidovudine is not allowed
    - Once daily combination pills for HIV containing a pharmacologic booster such as cobicistat are not allowed
    - Patients with multi-drug resistant HIV are not eligible

   Patients cannot have:

- Active central nervous system or meningeal involvement by lymphoma. Patients with a history of CNS or meningeal involvement must be in a documented remission by CSF evaluation and contrast-enhanced MRI imaging for at least 91 days prior to registration.
- Evidence of myelodysplasia or cytogenetic abnormality indicative of myelodysplasia on any bone marrow biopsy prior to initiation of therapy.
- A known bleeding diathesis.
- Requirement for warfarin or similar vitamin K antagonists. These drugs are prohibited 28 days prior to the first treatment and throughout the trial.
- History of stroke or intracranial hemorrhage ≤ 6 months before treatment.
- Currently active, clinically significant hepatic impairment (Child-Pugh class B or C according to the Child Pugh classification [see Appendix V]).
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib or other agents used in study.
- Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment. (PCR positive patients will be excluded.)

9. ECOG Performance Status must be ≤ 2

RANDOMIZED STUDY SCHEMA



* Determination of ABC subtype will be performed by central review using the paraffin tissue from the diagnostic biopsy (initial diagnosis or relapse).

** Patients will be stratified by prior use of ibrutinib, type of planned transplant (CBV or BEAM), and time to relapse (≤ or > 12 months from diagnosis).

*** 1 cycle = 28 days for cycles 2-13.

† In Cycle 1, ibrutinib/placebo should be dose reduced to 140 mg daily IF administered concurrently with aprepitant. Dose reduction is NOT necessary with fosaprepitant.

¥ Progression is defined as PD by the CT-based response criteria. If a patient experiences disease progression and is found to be receiving placebo, they may elect to crossover to treatment with ibrutinib. Patients who opt to cross over to active drug must be re-registered to the study.

Registration Parameters following Pre-Registration Central Pathology Review and PET

1. H&P, weight, height, PS and AE/con med assessment
2. Blood pressure and pulse
3. ECG
4. CBC with diff
5. CMP
6. Serum HCG
7. PFTs
8. PT/INR,PTT
9. Serum immunoglobulins, absolute B-cells, T-cell subsets
10. CT chest/abd/pelvis
11. Bone marrow biopsy