Summary B1931022/Ino-Vate

Title

An Open-label, Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigator's Choice in Adult Patients with Relapsed or Refractory CD22-Positive Acute Lymphoblastic Leukemia (ALL)

Background

Inotuzumab ozogamicin is an antibody directed against the CD22 antigen, conjugated with a cytotoxic antitumor antibiotic (calicheamicin) in development for the treatment of B cell malignancies such as non-Hodgkin's lymphoma (NHL) and ALL. CD22 is expressed on the malignant cells of the majority of B-lymphocyte malignancies, including on the surface of B cell ALL blasts in the vast majority of patients (>90%).

Population≥

Patients 18 years old or older with relapsed or refractory B cell acute lymphoblastic leukemia (ALL) due to receive either salvage 1 or 2 therapy

Inclusion Criteria

1. Relapsed or refractory CD22-positive ALL (≥ 5% marrow blasts, assessed by morphology; ie, M2 or M3 marrow) due to receive either salvage 1 or salvage 2 therapy and for which either arm of randomized study therapy offers a reasonable treatment option;
2. Ph+ ALL patients must have failed treatment with at least 1 second or third generation tyrosine kinase inhibitor and standard multi-agent induction chemotherapy;
3. Patients in Salvage 1 with late relapse should be deemed poor candidates for reinduction with initial therapy;
4. Patients with lymphoblastic lymphoma and bone marrow involvement ≥5% lymphoblasts by morphologic assessment;
6. ECOG performance status 0-2;
7. Adequate liver function
8. Serum creatinine □1.5 x upper limit of normal (ULN) or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min;

Exclusion Criteria

1. Isolated extramedullary relapse (ie, testicular or CNS);
2. Burkitt's or mixed phenotype acute leukemia based on the WHO 2008 criteria
3. Active central nervous system (CNS) leukemia within 28 days. Prophylactic intrathecal medication is not a reason for exclusion
4. Prior chemotherapy within 2 weeks before randomization with the following exceptions:

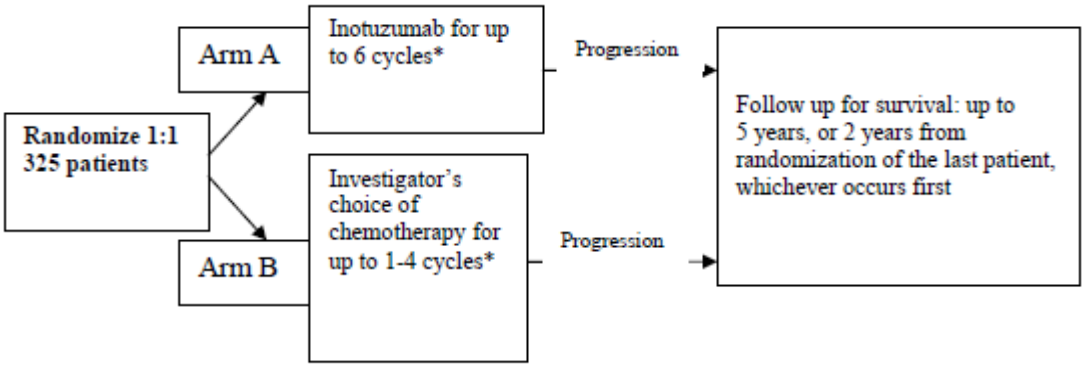
a. To reduce the circulating lymphoblast count or palliation: ie, steroids, hydroxyurea or vincristine;

b. For ALL maintenance: mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors.

5. Prior monoclonal antibodies within 6 weeks of randomization, with the exception of rituximab which must be discontinued at least 2 weeks prior to randomization;
6. Prior allogeneic hematopoietic stem cell transplant (HSCT) or other anti-CD22 immunotherapy 4 months before randomization. Patients must have completed immunosuppression therapy for treatment of GvHD prior to enrollment.
7. Peripheral absolute lymphoblast count 10,000 /L (treatment with hydroxyurea and/or steroids/vincristine is permitted within 2 weeks of randomization to reduce the WBC count);
8. Known systemic vasculitides, primary or secondary immunodeficiency
9. Current or chronic hepatitis B or C infection as evidenced by hepatitis B surface antigen and anti-hepatitis C antibody positivity,
10. Major surgery within 4 weeks before randomization;
11. Unstable or severe uncontrolled medical condition
12. Concurrent active malignancy other than non-melanoma skin cancer, carcinoma in situ of the cervix, or localized prostate cancer that has been definitely treated with radiation or surgery. Patients with previous malignancies are eligible provided that they have been disease free for ≥2 years;
13. Cardiac function, as measured by left ventricular ejection fraction (LVEF) that is less than 45%, or the presence of New York Heart Association (NYHA) stage III or IV congestive heart failure
14. Patients with active heart disease
15. QTcF >470 msec (based on the average of 3 consecutive ECGs);
16. Myocardial infarction 6 months before randomization;
17. History of clinically significant ventricular arrhythmia, or unexplained syncope not believed to be vasovagal in nature, or chronic bradycardic states such as sinoatrial block or higher degrees of AV block unless a permanent pacemaker has been implanted;
18. Uncontrolled electrolyte disorders that can compound the effects of a QTc prolonging drug (eg, hypokalemia, hypocalcemia, hypomagnesemia);
19. History of chronic liver disease (eg, cirrhosis) or suspected alcohol abuse;
20. History of hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS);
21. Administration of live vaccine 6 weeks before randomization;
22. Evidence of uncontrolled current serious active infection (including sepsis, bacteremia, fungemia) or patients with a recent history (within 4 months) of deep tissue infections such as fascitis or osteomyelitis;
23. Patients who have had a severe allergic reaction or anaphylactic reaction to any humanized monoclonal antibodies;

Studi Flow Diagram

Figure 4. Study Flow Diagram



ARM B, investigator's choice, will be FLAG