INOTUZUMAB OZOGAMICIN VERSUS INVESTIGATOR’S CHOICE OF CHEMOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA*

Inotuzumab ozogamicin is an investigational agent and has not been approved by regulatory agencies.

*This study is not yet open for enrollment.

| INTRODUCTION | • Inotuzumab ozogamicin is an investigational antibody-drug conjugate (ADC) comprised of a monoclonal antibody (mAb) targeting CD22, a cell surface antigen expressed on approximately 90 percent of B-cell malignancies, linked to a cytotoxic agent.  
  
  • CD22 is an important modulator of B-cell lymphocyte function and survival, and is expressed on mature B-cells, which may allow for targeted delivery of the cytotoxic agent.  
    - When inotuzumab ozogamicin binds to the CD22 antigen on malignant B-cells, it is absorbed into the cell, at which point the cytotoxic agent calicheamicin is released to destroy the cell.  
  
  • Studies have shown that adding an ADC targeting CD22, such as inotuzumab ozogamicin, to existing treatments options, may provide additional anti-tumor activity.  
    - The CD22 antigen has also been shown to be expressed on the surface of more than 90 percent of leukemic blasts in a vast majority of B-cell acute lymphoblastic leukemia (ALL) patients.  
    - There is preclinical evidence that a CD22-targeted cytotoxic may provide antitumor activity against CD22 positive ALL.  
  
  • Pfizer is also conducting an open-label, Phase 1 study of inotuzumab ozogamicin to evaluate the safety, tolerability and efficacy at increasing dose levels in patients with relapsed or refractory CD22+ ALL.  |

| RATIONALE | A study published in the February 2012 issue of The Lancet by Dr. Hagop Kantarjian et al. showed an increased overall response rate in patients with refractory or relapsed ALL when treated with 1.8 mg/m2 of inotuzumab ozogamicin intravenously over one hour every 3-4 weeks (the first three adults and three children received 1.3 mg/m2 in the first course). Pfizer has initiated INO-VATE Study 1022 to evaluate the efficacy, in terms of complete responses and overall survival, of inotuzumab ozogamicin versus investigator’s choice of chemotherapy.  
  
  • In 2010, of the estimated 22,000 deaths resulting from leukemia in the United States, ALL accounted for approximately 1,400 cases.  
    - Five-year survival rates for ALL patients (including adults and children) are low; approximately 63 percent.  
    - Survival rates in adults are less favorable, with a five-year survival rate of less than 10 percent, demonstrating an unmet need in this patient population.  |

| OBJECTIVES | • Primary:  
  
  o Response to therapy (percentage of patients achieving a complete response and complete responses with incomplete platelet and/or |

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**neutrophil recovery**

- **Secondary:**
  - Overall survival
  - Progression-free survival
  - Volume of distribution and systemic clearance for inotuzumab ozogamicin in serum
  - Duration of response
  - Rate of stem-cell transplantation
  - Minimal residual disease
  - Cytogenetics
  - Quality of life (European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire, Core-30 and EuroQual-5D Health Questionnaire)

### STUDY DESIGN
INO-VATE ALL Study 1022 is an open-label, randomized, Phase 3 study of inotuzumab ozogamicin compared to a defined investigator's choice of chemotherapy in adult patients with relapsed or refractory CD22+ ALL.°

- **Arm A:** Patients will receive 0.8-0.5 mg/m$^2$ of inotuzumab ozogamicin administered intravenously, weekly, three times per cycle (21-28 days per cycle), for a planned six cycles
- **Arm B:** Patients will receive investigator's choice:
  - **FLAG** (fludarabine, cytarabine and G-CSF): cytarabine administered intravenously 2.0 g/m$^2$ per day (on days 1-6), fludarabine administered intravenously 30 mg/m$^2$ per day (on days 2-6), during a 28 day cycle, for a planned four cycles
  - **High dose cytarabine (HIDAC)**: administered intravenously 3 g/m$^2$ every 12 hours for up to 12 times
  - **Cytarabine administered intravenously 200 mg/m$^2$ per day over seven days and mitoxantrone 12 mg/m$^2$ administered intravenously, days 1-3, during a 15-20 day cycle, for a planned four cycles

### SELECTED ELIGIBILITY CRITERIA
- **Selected Inclusion Criteria:**°
  - Males and females 18 years or older
  - CD22 expression
  - Adequate liver and renal functions
- **Selected Exclusion Criteria:**°
  - Isolated extramedullary disease
  - Active central nervous system disease

### NUMBER OF PATIENTS
- This trial intends to enroll approximately 292 patients in U.S. and ex-U.S. clinical trial sites.
1. Boni J et al. Modeling the Pharmacokinetic/Pharmacodynamic Platelet Response of Inotuzumab Ozogamicin, a Novel Antibody Drug Conjugate, Administered Alone or in Combination with Rituximab in Patients with Non-Hodgkin’s Lymphoma. Accepted Poster Presentation at the European Society of Medical Oncology 2010 Annual Meeting, October 8-12, 2010, Milan, Italy.


