INO-VATE ALL STUDY 1022: A PHASE 3 STUDY OF 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,[1] a cell surface antigen expressed on approximately 90 percent of B-cell malignancies,[2] linked to a cytotoxic agent.[1]
	• CD22 is an important modulator of B-cell lymphocyte function and survival,[3] and is expressed on mature B-cells, which may allow for targeted delivery of the cytotoxic agent.[4]
	  ○ 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.[1]
	• Studies have shown that adding an ADC targeting CD22, such as inotuzumab ozogamicin, to existing treatments options, may provide additional anti-tumor activity.[5]
	  ○ 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 lymphomblastic leukemia (ALL) patients. [6]
	  ○ There is preclinical evidence that a CD22-targeted cytotoxic may provide antitumor activity against CD22 positive ALL.[6]
	• 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.[7]

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),[8] 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.[9]
	• In 2010, of the estimated 22,000 deaths resulting from leukemia in the United States, ALL accounted for approximately 1,400 cases.[10]
	  ○ Five-year survival rates for ALL patients (including adults and children) are low; approximately 63 percent.[11]
	  ○ 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.[12]

OBJECTIVES	• Primary:[7] ○ Response to therapy (percentage of patients achieving a complete response and complete responses with incomplete platelet and/or

	neutrophil recovery)
	• Secondary:[7]
	  ○ 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 of refractory CD22+ ALL.[7]
	  ○ 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), flurdarabine administered intravenously 30 mg/m^2 per day (on days 2-6), during a 28 day cycle, for a planned four cycles
	  ○ High dose cytrabine (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:[7]
	  ○ Males and females 18 years or older
	  ○ CD22 expression
	  ○ Adequate liver and renal functions
	• Selected Exclusion Criteria:[6]
	  ○ 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.
[2] Leonard J et al. Epratuzumab, a Humanized Anti-CD22 Antibody, in Aggressive Non-Hodgkin's Lymphoma: a Phase I/II Clinical Trial Results. *Clinical Cancer Research.* 2004; 10: 5327-5334.
[3] Dorner T. Targeting CD22 as a Strategy for treating systemic autoimmune diseases. *Therapeutics and Clinical Risk Management.* 2007; 3: 953-959.
[4] DiJoseph J et al. Antibody-Targeted Chemotherapy with CMC-544: a CD22-Targeted Immunoconjugate of Calicheamicin for the Treatment of B-Lymphoid Malignancies. *Blood.* 2004; 1-3: 1807- 1814.
[5] DiJoseph JF. Antitumor Efficacy of a Combination of CMC-544 (Inotuzumab Ozogamicin), a CD22-Targeted Cytotoxic Immunoconjugate of Calicheamicin, and Rituximab against Non-Hodgkin's B-Cell Lymphoma. *Clin Cancer Res.* 2006; 12: 242-250.
[6] DiJoseph JF, Dougher MM, Armellino DC, et al. Therapeutic potential of CD22-specific antibody-targeted chemotherapy using inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia. Targeted therapy of ALL with CMC-544 (inotuzumab ozogamicin). Nature Leukemia. 2007; 21, 2240-2245.
[7] Clinicaltrials.gov. Study Evaluating Inotuzumab Ozogamicin in Acute Lymphocytic Leukemia. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01363297?term=inotuzumab&phase=0&rank=3. Accessed April 12, 2012.
[8] Kantarjian H. et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a Phase 2 study. *The Lancet.* February 21, 2012.
[9] Clinicaltrials.gov. A Study of Inotuzumab Ozogamicin Versus Investigator's Choice of Chemotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia. Available here: http://www.clinicaltrials.gov/ct2/show/NCT01564784?term=inotuzumab&rank=7. Accessed March 30, 2012.
[10] American Cancer Society: Detailed Guide – Acute Lymphocytic Leukemia. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003109-pdf.pdf. Accessed April 28, 2011.
[11] National Cancer Institute: SEER Stat Fact Sheets: Acute Lymphocytic Leukemia. Available at: http://seer.cancer.gov/statfacts/html/alyl.html. Accessed April 28, 2011.
[12] Fielding A. et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2006; 944-950.