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SWOG

A PHASE I STUDY OF INOTUZUMAB OZOGAMICIN (NSC-772518) IN COMBINATION WITH CVP (CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISONE) FOR PATIENTS WITH RELAPSED/REFRACTORY CD22-POSITIVE ACUTE LEUKEMIA (INCLUDING B-ALL, MIXED PHENOTYPIC LEUKEMIA, AND BURKITT'S LEUKEMIA)

NCT #01925131

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AGENTS:

IND-Exempt Agents:
Cyclophosphamide (Cytoxan®) (NSC-26271)
Prednisone (NSC-10023)
Vincristine (Oncovin) (NSC-67574)

SWOG-Held IND Agents:
Inotuzumab Ozogamicin (PF-05208773, CMC 544) (NSC-772518) (IND-119281)

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TABLE OF CONTENTS

1.0 OBJECTIVES

1.1 Primary Objective

a. To assess the safety of inotuzumab ozogamicin in combination with cyclophosphamide, vincristine and prednisone (CVP) and to determine the maximum tolerated dose (MTD) of inotuzumab ozogamicin in this regimen for patients with relapsed or refractory CD22+ acute leukemia (B-ALL, mixed phenotype, and Burkitt's).

1.2 Secondary Objective

a. To estimate the preliminary activity [response rate: complete remission (CR) + complete remission with incomplete count recovery (CRi)] of this combination in the expansion cohort.

b. To estimate the frequency and severity of toxicities of this combination in this patient population.

2.0 BACKGROUND

Relapsed/refractory ALL has a dismal prognosis. At the time of relapse, cytotoxic therapy is often ineffective in achieving a second remission and the overall survival for patients is 7% at 5 years. *(1)* CD22 is a transmembrane glycoprotein of the immunoglobulin superfamily located on B-lymphocytes. Approximately 90% of all B-ALLs express CD22. *(2)* CD22 binds to a sialic acid bearing ligand and serves as an adhesion molecule. *(3)* CD22 is rapidly internalized after binding with an antibody, making it an attractive target for anti-CD22 antibody-drug conjugates. *(4)* Inotuzumab has demonstrated promising single agent activity in relapsed/refractory ALL in a Phase II trial. *(5)* The response rate was 57%, and included both complete response (CR) and complete response with incomplete count recovery (CRi). The patient group was poor risk, with the majority of patients (73%) in salvage 2 or 3; 14% of patients had undergone prior allogeneic hematopoietic stem cell transplant. The most frequent adverse events during course one of treatment (n=49) were fever (Grade 1-2 in 20 patients, Grade 3-4 in nine), hypotension (Grade 1-2 in 12 patients, Grade 3 in one) and hepatotoxicity (bilirubin: Grade 1-2 in 12 patients, Grade 3 in two; elevated aminotransferase: Grade 1-2 in 27 patients, Grade 3 in one). *(6)* The degree of myelosuppression observed was based on initial platelet/granulocyte counts. Among six patients with platelet counts of 100×10^9/L or higher before treatment, two developed Grade 1-2 thrombocytopenia, one Grade 3, and one Grade 4. Among 11 patients with platelet counts 50-99×10^9/L, three developed Grade 3 thrombocytopenia and eight Grade 4 after treatment was started. *(7)* Among 25 patients with absolute granulocyte counts of 1×10^9/L or higher before therapy, three developed Grade 3 neutropenia and 19 Grade 4 during treatment with inotuzumab ozogamicin. *([8])*

Inotuzumab ozogamicin has demonstrated very encouraging activity in two trials of patients with relapsed/ refractory ALL. *(9,10)* In both studies, patients were heavily pre-treated and the response rates are much higher than those observed with standard salvage chemotherapy or Marqibo® (which was recently FDA approved for this disease). Given this, a Phase III study of inotuzumab is ongoing, comparing this agent to standard salvage therapy, and will likely lead to FDA approval of this drug for relapsed ALL. Although the response rates are encouraging, there are still patients who are refractory, and patients not proceeding to transplant are still relapsing. Therefore, there is a need to improve on the current results with single agent inotuzumab. The next step once this drug is approved will be to evaluate combination therapy to improve the above outcomes, and also to potentially move this drug to the upfront setting in poor risk patients (i.e. elderly patients with ALL). The maximum tolerated dose of inotuzumab based on both lymphoma and ALL studies is 1.8 mg/m^2 every 3-4 weeks. *(11,12)* Two different schedules of

inotuzumab have been evaluated: a weekly schedule, and the once every 3-4 week schedule. *(13)* The weekly schedule appears to be equally efficacious and less toxic; therefore, this schedule will be used for this current trial. *(14)* In the current trial, the dose of CVP is kept constant, and the dose of inotuzumab ozogamicin is escalated up to the MTD (total of 1.8 mg/m^2 if total dose is calculated). No studies have previously been conducted with this combination in the acute leukemia population. In lymphoma, a study was performed combining Rituximab/CVP with inotuzumab ozogamicin, where the inotuzumab ozogamicin was given on an every 3 week schedule (not weekly). In this trial, the MTD of inotuzumab ozogamicin was 1.8 mg/m^2 every 3 weeks. *(15)* Because acute leukemia is a different disease, and because this study uses a different dosing schedule with a "break" on Day 8 in the first 3 dose levels, it is possible that a higher dose of inotuzumab ozogamicin may be able to be administered. The previous backbone chemotherapy regimen (clofarabine/cytarabine) was decided against due to concerns of increased toxicity with an aggressive re-induction regimen.

The single-agent response rates with inotuzumab ozogamicin are likely to be improved by combining the drug with other active agents. Cyclophosphamide (C), vincristine (V), and prednisone (P) are all active agents in ALL. Pre-clinical studies have also demonstrated superior anti-tumor activity when inotuzumab ozogamicin is co-administered with CVP. *(16)* Because this trial is a Phase 1 design and since Burkitt's and mixed phenotype leukemias can also express surface CD22, these patients will also be included in this study.

Inclusion of Certain HIV+ Patients

Since HIV-positive patients are immunocompromised and most are treated with already myelosuppressive antiretroviral regimens, and since there is insufficient data on the safety of this regimen in HIV-positive patients, patients with HIV infection will be excluded from this study if they do not meet the parameters that are felt will allow safe participation. HIV infected patients with sufficient CD4 cell count, acceptable viral load and who are not receiving the myelosuppressive agents zidovudine or stavudine will be included in this study (see Section 5.2r).

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	9	13
Not Hispanic or Latino	8	17	25
Total Ethnic	12	26	38
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	0	2	2
Black or African American	1	3	4
Native Hawaiian or other Pacific Islander	0	1	1
White	10	19	29
Racial Category: Total of all Subjects	12	26	38

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, cyclophosphamide, prednisone and vincristine are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, inotuzumab ozogamicin is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. PHARMACOLOGY

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which are thought to cross-link to tumor cell DNA. These metabolites interfere with the growth of rapidly proliferating susceptible malignant cells.

b. PHARMACOKINETICS

1. Distribution: Concentrations reach a maximal plasma concentration in 2-3 hours following an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%.

2. Metabolism: Cyclophosphamide undergoes liver metabolism to active metabolites by a mixed function microsomal oxidase system.

3. Elimination: Cyclophosphamide is eliminated primarily in the form of metabolites, but 5-25% percent of unchanged drug is excreted in the urine. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

c. ADVERSE EFFECTS

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Cyclophosphamide		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Leukopenia	
	Thrombocytopenia	

CARDIAC DISORDERS		
	Facial Flushing	Congestive heart failure
GASTROINTESTINAL DISORDERS		
	Nausea	
	Vomiting	
	Anorexia	
	Diarrhea	
	Mucositis	
	Stomatitis	
METABOLISM AND NUTRITION DISORDERS		
Amenorrhea	Sterility	SIADH
NERVOUS SYSTEM DISORDERS		
	Headache	
RENAL AND URINARY DISORDERS		
		Hemorrhagic cystitis
		Urinary fibrosis
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Nasal congestion occurs when I.V. doses are administered too rapidly; patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing during or immediately after the infusion	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	Skin rash	
	Nail changes	

Adverse events occurring in < 1%, postmarketing, and/or case reports:

Acute respiratory distress syndrome, anaphylactic reactions, arrhythmias (with high-dose [HSCT] therapy), cardiac tamponade (with high-dose [HSCT] therapy), CHF (with high-dose [HSCT] therapy), darkening of skin/fingernails, dizziness, dyspnea, heart block, hemorrhagic colitis, hemorrhagic myocarditis (with high-dose [HSCT] therapy), hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, hyponatremia, interstitial pneumonitis, interstitial pulmonary fibrosis (with high doses), jaundice, malaise, mesenteric ischemia (acute), methemoglobinemia (with high-dose [HSCT] therapy), myocardial necrosis (with high-dose [HSCT] therapy), neutrophilic eccrine hidradenitis, pulmonary infiltrates, radiation recall, renal tubular necrosis, reversible posterior leukoencephalopathy syndrome (RPLS), secondary malignancy, SIADH, Stevens-Johnson syndrome, thrombocytopenia (immune mediated), toxic epidermal necrolysis, toxic megacolon, veno-occlusive liver disease, weakness

2. Pregnancy and Lactation: Pregnancy Category D. Cyclophosphamide can cause fetal harm when administered to pregnant women and such abnormalities have been reported following therapy in pregnant women including ectrodactaly. Normal infants have also been born to women treated with cyclophosphamide, including the first trimester. If this drug is used during pregnancy, or if the patient becomes pregnant while

taking (receiving) cyclophosphamide, the patient should be informed of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration.

3. Drug Interactions:

Refer to package insert or manufacturer website for the most complete and up to date information.

Due to potential drug interactions, a complete patient medication list, including cyclophosphamide, should be screened prior to initiation of cyclophosphamide. Of note, cyclophosphamide is a major substrate of CYP2B6 and moderately induces CYP2B6 and CYP2C9.

d. DOSING & ADMINISTRATION

1. Dosing – See treatment plan (Section 7.2).

2. Refer to package insert for drug administration.

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Cyclophosphamide for injection, USP is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials for single dose use.

2. Cyclophosphamide is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.2 Inotuzumab Ozogamicin (PF-05208773, CMC-544) (NSC-772518) (IND-119281)

a. PHARMACOLOGY

Mechanism of Action: Inotuzumab ozogamicin is a CD22-specific cytotoxic immunoconjugate in which humanized anti-CD22 mAB (G544) is covalently attached to NAc-gamma calicheamicin DMH. This novel approach known as antibody-targeted chemotherapy involves specific delivery of a cytotoxic agent to tumor cells in the form of a conjugate with a monoclonal antibody via its binding to a tumor associated antigen. The cytotoxic agent NAc-gamma calicheamicin DMH is a derivative of calicheamicin methyl trisulfide, a highly potent enediyne class of DNA-damaging cytotoxic natural products synthesized by *Micromonospora echinospora*, ssp. *calichensis*. A bifunctional hybrid linker attaches the cytotoxic agent to the ε-amino groups of the lysines in the antibody and contains an acid-labile bond. Upon binding to the tumor antigen, the conjugate is internalized. In the acidic lysosomal compartment the hydrazone bond is hydrolyzed, with the possible assistance of esterases, releasing NAc-gamma calicheamicin DMH (referred to calicheamicin) from the antibody. The drug is assumed to diffuse into the nucleus and bind the cellular DNA and, after activation with glutathione and likely assistance by glutathione-S-transferases, the eneidyne war-head causes DNA strand breaks leading to cell death.

b. PHARMACOKINETICS

1. Absorption: Inotuzumab ozogamicin peak concentrations were generally observed at or shortly after termination of infusion. Cmax appeared to increase with dose but was unaffected by differences in treatment period. After treatment with 1.8 mg/m2 once every 4 weeks, Cmax ranged from 559 ng/mL to 969 ng/mL with moderate intersubject variability between the studies.

2. Distribution: Steady-state volume of distribution ranged (4.06 to 6.24 L). AUC on Day 1 ranged from 14039 ng•h/mL to 22300 ng•h/mL, but increased to a range of 28390 ng•h/mL to 54,800 ng•h/mL after 2 to 3 cycles for subjects treated once every 4 weeks. A commensurate decrease in clearance was observed in all 3 studies suggesting that exposures by Day 29 may not be at steady state, and subsequent cycles of treatment may result in further changes in drug clearance.

   Peak total calicheamicin concentrations were observed typically within 3-4 hours after start of inotuzumab ozogamicin infusion. As seen with inotuzumab ozogamicin, total calicheamicin mean Cmax appeared to increase with dose and apparent clearance decreased over time.

   Concentrations of free calicheamicin were much lower than those of other analytes and in 2 studies were not detected and pharmacokinetic parameters were not calculated. In the other study, mean Cmax values ranged from 1.30 to 3.18 ng/mL.

   As was observed in the inotuzumab ozogamicin and total calicheamicin datasets, G544 AUC values increased with treatment period and dose in 2 studies and increased with treatment period alone in the other study. Apparent clearance of G544 appeared to decrease with treatment period as well.

3. Metabolism: In vitro studies in human hepatocytes demonstrate that the cytochrome P450 (CYP) enzyme 3A4 contributes to the metabolism of NAc-γ calicheamicin DMH.

4. Elimination: Terminal half-life of inotuzumab ozogamicin was reported in 2 studies, ranging from 18.8 hours to 51.7 hours in one study and 44 hours in the other. Terminal half-life of calicheamicin at steady state was approximately 173 hours, however ranged from 79.8 hours on day 1 to 285 hours on Day 85 in one study. Terminal half-life of G544 increased with dose and treatment period in 2 studies and increased with treatment period alone in other study

ADVERSE EFFECTS

1. Human data

Version 2.0, October 5, 2018 [1]

Adverse Events with Possible Relationship to Inotuzumab ozogamicin (PF-05208773) (CTCAE 5.0 Term) [n= 422]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
Febrile neutropenia		
GASTROINTESTINAL DISORDERS		
	Abdominal distension	
Abdominal pain		
	Ascites	
	Constipation	
	Diarrhea	
	Mucositis oral[2]	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
Fever		
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (venoocclusive liver disease)	
INFECTIONS AND INFESTATIONS		
Infection[3]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
Aspartate aminotransferase increased		
Blood bilirubin increased		
		Electrocardiogram QT corrected interval prolonged
GGT increased		
	Lipase increased	
	Lymphocyte count decreased	
Neutrophil count decreased		

Adverse Events with Possible Relationship to Inotuzumab ozogamicin (PF-05208773) (CTCAE 5.0 Term) [n= 422]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Platelet count decreased		
	Serum amylase increased	
White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperuricemia	
	Hypokalemia	
		Tumor lysis syndrome
NERVOUS SYSTEM DISORDERS		
Headache		
VASCULAR DISORDERS		
Hemorrhage[4]		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Mucositis oral may include the following: Aphthous ulcer, Mucosal inflammation, Mouth ulceration, Oral pain, Oropharyngeal pain, and Stomatitis.

[3] Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4] Hemorrhage may include the following: Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eyelid bleeding, Gastrointestinal hemorrhage, Gastritis hemorrhagic, Gingival bleeding, Hematemesis, Hematochezia, Hemotympanum, Hematuria, Hemorrhage intracranial, Hemorrhage subcutaneous, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Lip hemorrhage, Lower gastrointestinal hemorrhage, Mesenteric hemorrhage, Metrorrhagia, Mouth hemorrhage, Muscle hemorrhage, Oral mucosa hematoma, Petechiae, Post procedural hematoma, Rectal hemorrhage, Shock hemorrhagic, Subcutaneous hematoma, Subdural hematoma, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.

Adverse events reported on inotuzumab ozogamicin (PF-05208773) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that inotuzumab ozogamicin (PF-05208773) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Left ventricular systolic dysfunction
EYE DISORDERS - Eye disorders - Other (blindness unilateral)
GASTROINTESTINAL DISORDERS - Colitis; Gastrointestinal disorders - Other (intestinal ischemia); Pancreatitis; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Generalized edema; Malaise; Multi-organ failure; Pain
HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Hepatic failure; Hepatobiliary disorders - Other (biliary cirrhosis); Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic function abnormal); Portal hypertension
INVESTIGATIONS - Blood lactate dehydrogenase increased; Creatinine increased; Investigations - Other (blood fibrinogen increased); Investigations - Other (fibrin D dimer increased); Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hyperglycemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dysgeusia; Paresthesia; Presyncope; Somnolence; Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Cough; Oropharyngeal pain; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Inotuzumab ozogamicin (PF-05208773) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Specific Adverse Reactions of Note: Initial reviews of electrocardiogram (ECG) monitoring data from two ongoing studies evaluating inotuzumab ozogamicin in indolent Non-Hodgkin's Lymphoma (NHL) patients revealed a prolongation of QTc. Although no serious treatment-related cardiac events have been reported to date and prolonged QTc is not considered an adverse event for this study, close monitoring of the QTc interval is being performed in ongoing studies until the clinical effects on QTc are better characterized.

2. Pregnancy and Lactation: There have been no human studies of inotuzumab ozogamicinin in pregnant women and no reports of exposure utero. Fertility studies of inotuzumab ozogamicin in rats and rabbits revealed potential for embryo-fetal and maternal toxicity. Inotuzumab ozogamicin was not teratogenic in rats or rabbits.

   Pregnant or breastfeeding women should not receive inotuzumab ozogamicin. Female and male subjects biologically capable of having children are required to use a reliable method of birth control during treatment and for 90 days after the last dose of inotuzumab ozogamicin.

3. Drug Interactions: In vitro studies in human hepatocytes demonstrate that the cytochrome P450 (CYP) enzyme 3A4 contributes to the metabolism of NAc-γ calicheamicin DMH. However, inhibition or induction of CYP3A4 is unlikely to result in significant drug-drug interactions in humans. In addition, it is unlikely that inotuzumab ozogamicin will

interact with the clearance of concomitant medications that are substrates for CYP enzymes.

Due to the potential risk of prolongation of QTc, patients should not be given medications with a known risk of Torsades de Pointes. See Section 8.0, Toxicities to be Monitored and Dosage Modifications.

c. DOSING & ADMINISTRATION

1. Dosing – See treatment plan (Section 7.2).

2. Inotuzumab ozogamicin should be administered by intravenous infusion over 1 hour. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

d. PREPARATION, STORAGE & STABILITY

1. Preparation: All preparations are recommended to be carried out in a laminar flow hood or bio-safety cabinet (Class II-IV) using aseptic technique for sterile products and handling precautions for hazardous drugs.

Calculate the appropriate number of vial(s) of inotuzumab ozogamicin required to obtain the total dose.

Remove the required vial(s) from storage and allow vial(s) to warm to room temperature.

For 1 mg/vial product supplied in 10 mL vial, reconstitute the contents of each vial with 1 mL Sterile Water for Injection (USP) using polypropylene syringes. For 4 mg/vial product supplied in 10 mL vial, reconstitute with 4 mL USP. The final concentration of the reconstituted drug solution is 1 mg/mL. Gently swirl each vial until dissolution of the drug.

Remove the calculated volume of inotuzumab ozogamicin for further dilution into an intravenous (IV) bag. A foil covering is required over the syringe barrel containing reconstituted inotuzumab ozogamicin if transfer to the infusion bag is not performed immediately. Further dilute inotuzumab ozogamicin into infusion bags containing sodium chloride 0.9% to achieve a final volume of 50 mL. Cover the infusion preparation in the IV bag with an amber bag or ultraviolet (UV) protective covering. Gently mix the contents of the bag by inversion. Avoid vigorous agitation and foaming.

Infusion bags made of PVC or polyolefin (polypropylene and/or polyethylene) are recommended. Tubing lines with or without an in-line filter are acceptable. Tubing lines made of PVC (DEHP or non-DEHP containing) or polyolefin (polypropylene and/or polyethylene) are recommended. The infusion line should be primed and flushed using sodium chloride 0.9%.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particles or discoloration are observed, do not use the vial(s) and notify the study monitor.

2. Storage: Inotuzumab ozogamicin should be stored refrigerated (2-8^{O}C) and protected from light.

3. Stability: The administration of inotuzumab ozogamicin must be completed by 8 hours from reconstitution. Bacteriostatic water for injection containing benzyl alcohol or any other preservative should NOT be used for reconstitution of inotuzumab ozogamicin.

e. HOW SUPPLIED

1. Inotuzumab ozogamicin is supplied as a white, unpreserved, lyophilized cake in a 10 mL Type I amber glass vial with a rubber closure and aluminum flip-top cap. Each vial contains 1 mg or 4 mg of inotuzumab ozogamicin (refer to the package label for strength).

2. Inotuzumab ozogamicin will be supplied free of charge for this protocol by Pfizer, Inc.

3. Drug ordering: Drug orders must be submitted by faxing the Inotuzumab Ozogamicin Drug Request Form to Pfizer at the number listed on the order form. The form can be found on the SWOG website (www.swog.org). Initial drug orders of 1 carton (6 vials) should be submitted at the time of IRB approval; **do not wait until patient is registered to order drug or it may not arrive in time to treat.** It is recommended that 1 carton of drug be kept on site at all times to ensure that drug is available when needed, as subsequent orders may also take up to a week to process. Pfizer will ship the drug Monday through Friday during regular business hours. If ordering on a Friday, pharmacy personnel must be available to take Saturday delivery since drug requires refrigeration. Emergency shipments may be made if necessary, but may still take at least 3 days to process.

   NOTE: A current IRB approval must be on file with Pfizer in order for drug to be shipped at any time. Sites should submit initial IRB approval and annual IRB approval renewals upon receipt to avoid unnecessary drug ordering delays. Approvals may take up to 2 weeks to process. Approvals should be submitted to Pfizer by e-mail to IIR-Oncology@Pfizer.com.

4. Drug Handling and Accountability

   Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

5. Drug Return and/or Disposition and Expiration

   a. Drug Disposition: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

   b. Drug Expiration: If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first). Any updates on drug expiration information will be distributed to sites as necessary.

6. Questions about drug orders or shipping should be directed to IIR-Oncology@Pfizer.com.

3.3 Prednisone (NSC-10023)

a. PHARMACOLOGY

Prednisone decreases inflammation by inhibiting the migration of polymorphonuclear leukocytes; at high doses it suppresses adrenal function. The antitumor effects may be due to inhibition of glucose transport, phosphorylation, or induction of cell death of immature lymphocytes.

b. PHARMACOKINETICS

1. Absorption: 50-90% after oral administration

2. Distribution: Protein binding: 70%; volume of distribution (Vd): 0.4 – 1L/kg.

   Metabolism: Converted from prednisone to prednisolone (active drug) hepatically.

3. Elimination: Half-life (normal renal function): 3.5 hours

c. DOSING & ADMINISTRATION

1. Dosing – See treatment plan (Section 7.2).

2. Refer to package insert for drug administration.

d. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

e. HOW SUPPLIED

1. Formulation and dose form available: oral solution, 1 mg/mL (5 mL, 120 mL, 500 mL); concentrated oral solution, 5 mg/mL (30 mL); oral tablet, 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg.

   Prednisone is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.4 Vincristine (Oncovin) (NSC-67574)

a. PHARMACOLOGY

The mechanism of action of vincristine is thought to be due to inhibition of microtubule formation in the mitotic spindle. This leads to arrest of dividing cells during the metaphase stage.

b. ADVERSE EFFECTS

c. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse REACTIONS.

Adverse Events with Possible Relationship to Prednisone		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Increase in absolute granulocyte count		Leukemoid reaction
Decrease in lymphocyte count		
Decrease in monocyte count		
CARDIAC DISORDERS		
Hypertension		
EYE DISORDERS		
		Cataracts
		Glaucoma
GASTROINTESTINAL DISORDERS		
Disorder of GI tract		Gastrointestinal perforation
		Gastrointestinal ulceration
		Pancreatitis
IMMUNE SYSTEM DISORDERS		
At risk for infection		
INFECTIONS AND INFESTATIONS		
Oropharyngeal candidiasis		Pulmonary tuberculosis
INVESTIGATIONS		
Hypernatremia	Hypokalemia	
	Hyperuricemia	
METABOLISM AND NUTRITION DISORDERS		
Body fluid retention	Hyperglycemia	Cushing's syndrome
Decreased body growth		Primary adrenocortical insufficiency
		Diabetes mellitus
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Osteoporosis	Myopathy	Aseptic necrosis of bone
NERVOUS SYSTEM DISORDERS		
		Pseudotumor cerebri
PSYCHIATRIC DISORDERS		
Depression		Mental status changes
Euphoria		Personality changes
		Mania
		Hallucinations
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		

Atrophic condition of skin	Petechiae	Kaposi's sarcoma
Acne	Ecchymosis	
Impaired skin healing	Dermatitis	
	Facial erythema	
	Hirsutism	
	Increased sweating	

Adverse events occurring in < 1%, postmarketing, and/or case reports: staphylococcal scalded skin syndrome, disseminated varicalla-zoster virus, hyperthyroidism, porphyria, abnormal lipids, extrapyramidal sign, lung abscess, aspergillosis, interstitial pneumonia, pulmonary nocardiosis, decreases in cardiac function.

1. Pregnancy and Lactation: Pregnancy Category C. Adverse events have been observed with corticosteroids in animal reproduction studies. Prednisone and prednisolone cross the human placenta. Prednisone enters breast milk. American Academy of Pediatrics rates it as compatible.

2. Drug Interactions:

Prednisone is a minor substrate of CYP3A4 and induces both CYP2C19 and CYP3A4 weakly/moderately. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including prednisone, should be screened prior to initiation of prednisone.

d. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Within 15-30 minutes of injection, 90% of the drug is distributed from the blood into tissues where it is tightly bound.

3. Metabolism: Extensively metabolized by the liver via CYP3A4

4. Elimination: Terminal half-life: 85 hours (range, 19-155 hours); 80% excreted in feces, 10-20% excreted in urine.

e. ADVERSE EFFECTS

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Vincristine		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Leukopenia	
	Thrombocytopenia	
CARDIAC DISORDERS		
	Edema	
	Hyper-/hypotension	
	Myocardial ischemia	

	Angina	
EYE DISORDERS		
	Cortical blindness	Optic atrophy
	Nystagmus	
GASTROINTESTINAL DISORDERS		
Constipation	Hepatoxicity	Acute pancreatitis
		Paralytic ileus
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Back pain	
	Bone pain	
	Gait instability	
NERVOUS SYSTEM DISORDERS		
Peripheral neuropathy		Seizures
		Vocal cord palsy
RENAL AND URINARY DISORDERS		
	SIADH	
	Acute uric acid nephropathy hemolytic uremic syndrome	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Bronchospasm	Acute Respiratory Distress
	Dyspnea	
	Pharyngeal pain	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		

2. Pregnancy and Lactation: Pregnancy Category D. It is not know whether vincristine is excreted in human breast milk.

3. Drug Interactions:

Refer to package insert or manufacturer website for the most complete and up to date information.

Due to potential drug interactions, a complete patient medication list, including vincristine, should be screened prior to initiation of vincristine. Of note, vincristine is a CYP3A4 and P-glycoprotein substrate.

f. DOSING & ADMINISTRATION

1. Dosing – See treatment plan (Section 7.2).

2. Refer to package insert for drug administration.

g. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

h. HOW SUPPLIED

1. Formulation and dose form available: Injection, solution 1mg/mL (1 mL, 2 mL).

   Vincristine is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

a. Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume minus the volume of fibrosis.

2. Blasts: Blasts characteristic of L1, L2, L3, or mixed phenotype leukemia are included in the calculation of blast percentages. *([17,18])*

3. Marrow Blast Percentage: Bone marrow blast percentage is calculated as the percentage of blasts among all nucleated marrow cells except mature lymphocytes and plasma cells.

b. Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL) is defined by the following:

   The differential diagnosis of ALL is based on the presence of FAB L1, L2, or L3 morphology with negative staining for myeloperoxidase or Sudan Black (myeloid pattern), negative staining for non-specific esterase (myeloid pattern), and the presence of lymphoid-associated antigens. *(12,13)* In the setting of relapsed or refractory disease, ALL is defined as ≥ 5% lymphoblasts in the bone marrow at least 4 weeks after the initiation of Induction therapy.

c. Mixed lineage ALL (ML-ALL) is defined by a lack of cytochemical markers of myeloid differentiation, and by the presence of immunophenotypic markers suggesting both lymphoid and myeloid differentiation.

d. M0 and mixed lineage AML can be misdiagnosed as acute lymphoblastic leukemia. Mixed lineage AML is eligible if the blasts are surface CD22+. M0 cases are not eligible. . Definitions for these 2 types of acute leukemias which are not included in the FAB classification are as follows:

1. AML without differentiation (M0): Acute leukemia without differentiation by conventional morphologic/cytochemical studies but myeloid by immunophenotypic criteria. *(14)* Cases meeting the following criteria based on B-lymphoid markers CD19 and CD22, T-lymphoid markers CD3, CD7, CD5, CD2 and myeloid markers CD33, CD13, and CD15 are considered M0:

   a. Negative cytochemical staining for myeloperoxidase, Sudan black, and nonspecific esterase (myeloid pattern) by light microscopy, no Auer rods, and not M7.

   b. Lymphoid markers negative:

      B: CD19 negative, CD22 negative*

T: CD3 negative (mandatory), and at least 2 of the following (CD7, CD5, CD2) negative **

c. Myeloid markers positive (at least one):

Myeloid: CD33, CD13, CD15

* If positive for either CD19 or CD22, but also positive for 2 myeloid antigens, then the case is M0.
** If positive for CD7, CD5, or CD2, then:
- the other 2 must be negative
- at least 2 myeloid markers must be positive

2. Mixed lineage AML (ML-AML): blast has cytochemical markers of myeloid differentiation and has immunophenotypic markers suggesting both lymphoid and myeloid differentiation.

e. WHO Classification of ALL, with the following additions and classifications. *(19,20,21)*

	ICD-O Code	FAB Equivalent
Precursor B-cell neoplasm		
Precursor B lymphoblastic Leukemia	9836/3	L1, L2
Burkitts Leukemia	968713	L3
Precursor T-cell neoplasms		
Precursor T lymphoblastic leukemia	9837/3	L1, L2

f. fBurkitt's leukemia: L3 morphology with previous documentation of the t(8;14) translocation.

g. For any of the relapsed/ refractory acute leukemias (mixed lineage, biphenotypic, Burkitts, ALL), >=5% blasts must be present in the bone marrow.

4.2 Staging Criteria

Staging criteria are not applicable to this protocol.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 28, or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related/Previous Therapy Criteria

a. Patients must have a diagnosis of relapsed or refractory CD22-positive acute leukemia including B-ALL, mixed phenotype leukemia (biphenotypic), or Burkitt's leukemia based on WHO classification. Patients with bilineal leukemia are excluded.

b. Patients must have evidence of acute leukemia in their peripheral blood or bone marrow. Patients must have ≥ 5% blasts in the peripheral blood or bone marrow within 14 days prior to registration. At least ≥ 20% of those blasts must be CD22-positive (surface) based on local immunophenotyping and histopathology.

c. Patients must be refractory or have relapsed following prior Induction therapy.

A standard Induction regimen is defined as any program of treatment that includes vincristine and prednisone or dexamethasone, cytarabine/anthracycline, or high dose cytarabine.

d. For sites with the B1931022 pharmaceutical trial open, precursor B-cell ALL patients from that site may be eligible for **S1312** providing they meet the following criteria:

1. Patient is in second salvage or more and **B1931022** has been considered and ruled out as a treatment option;

OR

2. Patient was treated on the standard of care arm of **B1931022** and failed therapy.

e. Patients may have received prior allogeneic transplant or autologous transplant. However, patients with prior allogeneic bone marrow transplant will be eligible only if both of the following conditions are met:

1. The transplant must have been performed ≥ 90 days prior to registration

2. The patient must not have ≥ Grade 2 acute graft versus host disease (GvHD) or either moderate or severe limited chronic GvHD within 14 days prior to registration.

f. Patients known to have Ph+ ALL must have either failed treatment or been intolerant to treatment with at least one second or third generation tyrosine kinase inhibitor.

g. Patients must not have received prior treatment with inotuzumab ozogamicin. Previous treatment with other anti-CD22 antibodies must have been completed at least 90 days prior to registration.

h. Patients must have Zubrod Performance Status 0-2 (see Section 10.10).

i. Patients must not have received any chemotherapy, investigational agents, or undergone major surgery within 14 days prior to registration with the following exceptions:

1. Monoclonal antibodies must not have been received for 1 week prior to registration.

2. Chimeric antigen receptor (CAR) T-cells must not have been received for 28 days prior to registration.

3. Steroids, hydroxyurea, vincristine, 6-mercaptopurine, methotrexate, thioguanine and intrathecal chemotherapy are permitted within any time frame prior to registration. FDA-approved tyrosine kinase inhibitors may also be administered until 1 day prior to start of study therapy (C1, D1).

4. All drug-related toxicities must have resolved to ≤ Grade 2.

5.2 Clinical/Laboratory Criteria

a. Patients must not have a systemic bacterial, fungal, or viral infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement despite appropriate antibiotics or other treatment).

b. Patients must not have any other serious concurrent disease or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or other organ system that would put the patient at undue risk of undergoing therapy.

c. Patients must not have active CNS involvement (by clinical evaluation). Patients with previous documented history of CNS involvement of acute leukemia, or with clinical signs or symptoms consistent with CNS involvement of acute leukemia, must have a lumbar puncture which is negative for CNS involvement of acute leukemia. The lumbar puncture must be completed within 14 days prior to registration. Patients with no previous history of documented CNS involvement and with no clinical signs or symptoms consistent with CNS involvement are not required to have completed a lumbar puncture before registration. Note that treatment with intrathecal therapy is recommended during protocol treatment but CNS analysis during treatment is not required.

d. Patients must be ≥ 18 years of age.

e. Patients must have a peripheral blast count < 25,000/uL within 2 days prior to registration. (Treatment with hydroxyurea and steroids is permitted to bring the countdown.)

f. Patients must have serum creatinine ≤ 2 x institutional upper limits of normal (IULN) within 7 days prior to registration.

g. Patients must have bilirubin ≤ 2 x IULN within 7 days prior to registration (unless the bilirubin is primarily unconjugated).

h. Patients must have < Grade 2 neuropathy (sensory/motor) within 7 days prior to registration.

i. Patients must have SGOT **and** SGPT ≤ 2.5 x IULN within 7 days prior to registration.

j. Patients with a history of a serious allergic or anaphylactic reaction to humanized monoclonal antibodies are not eligible.

k. Patients must not have a history of chronic or active hepatitis B or C infection. Patients must have negative Hepatitis B and C serologies performed within 28 days prior to registration.

l. Patients must not have evidence or history of veno-occlusive disease or sinusoidal obstruction syndrome.

m. Patients must not have a cardiac ejection fraction < 45% or the presence of New York Heart association stage III or IV heart failure within 14 days prior to

registration (see Appendix 18.1). Either ECHO or MUGA may be used to determine ejection fraction.

n. Patients must not have a myocardial infarction within 6 months prior to registration.

o. Patients must not have a history of clinically significant arrhythmia, prolonged QTc interval, or unexplained syncope not thought to be vasovagal in nature within 6 months prior to registration.

p. Patients must not have a screening QTcF interval > 500 milliseconds (by Fridericia calculation) based on the average of triplicate EKG performed within 7 days prior to registration. Note that triplicate EKG is required at other timepoints (see Section 7.1f).

q. Patients must not have a history of chronic liver disease (or cirrhosis).

r. Patients who are known to be HIV+ are eligible providing they meet all of the following additional criteria within 28 days prior to registration:

1. CD4+ cells ≥ 350/mm^3 (nadir)

2. Viral load of < 50 copies HIV mRNA/mm^3 if on cART or < 25,000 copies HIV mRNA if not on cART

3. No zidovudine or stavudine as part of cART

Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

s. Patients with evidence of extramedullary disease at diagnosis will have CT scan of the chest, abdomen and pelvis to obtain baseline values within 28 days prior to registration. See Section 7.1j for additional CT/MRI time points during treatment.

t. Patients must have complete history and physical examination within 28 days prior to registration.

u. Patients must not be pregnant or nursing due to the unknown teratogenic effects of the study drug on an unborn child. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

v. Prior malignancy other than acute leukemia is allowed, provided it is in remission and there is no plan to treat the malignancy at the time of registration.

w. Pretreatment cytogenetics must be performed on all patients. Collection of pretreatment specimens must be completed within 14 days prior to registration to **S1312**. Specimens must be submitted to the site's preferred CLIA-approved cytogenetics laboratory (see Section 9.0). Reports of the results must be

submitted as described in Sections 14.0 and 15.3. Note that cytogenetics are required at other timepoints (see Section 9.0).

5.3 Regulatory Criteria

a. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.5 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

c. Patients planning to enroll in this study must first have a slot reserved in advance of the registration. All site staff will use OPEN to create a slot reservation (see Section 13.2 for OPEN slot reservation instructions).

6.0 STRATIFICATION FACTORS

Stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Advani at 216/445-9354 or Dr. Michaela Liedtke at 650/498-6000. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and General Considerations

a. Pre-medication 0.5-2.0 hours prior to inotuzumab ozogamicin is required. The recommended pre-medication is: acetaminophen: 650 mg oral, diphenhydramine 50 mg oral or IV, and hydrocortisone 50-100 mg IV. However, hydrocortisone alone or acetaminophen/diphenhydramine can be administered.

b. Granisetron is recommended but not required prior to administration of cyclophosphamide (drugs that increase the risk of *Torsades de pointes* such as ondanstetron should not be administered; see www.azcert.org/medical-pros/drug-lists/bycategory.cfm#).

c. One liter of IV fluids is also recommended but not required because of the cyclophosphamide.

d. Hydroxyurea may be administered concurrently with study drug until the white blood cell count has come down to a reasonable level (as deemed by the treating physician).

e. Patients experiencing tumor lysis should be treated with appropriate supportive measures per local standard and at the discretion of the treating physician.

f. Patients must undergo triplicate EKG prior to drug administration on Day 1 of Cycles 2 and 4. Electrolytes (K and Mg) must be corrected prior to the first EKG on each day. For QTcF > 500 (by Fridericia Calculation) on any EKG, the Study Chair must be contacted to discuss whether the patient may continue on protocol therapy. The EKG Results Form must be submitted documenting the results (see Section 14.4c).

g. Prophylactic intrathecal chemotherapy is recommended as follows: Methotrexate 12 mg intrathecally once during each cycle; CSF sampling does not need to be performed.

h. At the discretion of the treating physician, patients may be removed from protocol therapy at any time to receive transplant. Due to concerns of veno-occlusive disease (VOD), a one month lapse between the last dose of inotuzumab and the initiation of transplant is recommended.

i. See Sections 8.3d-8.3f for required laboratory values prior to each dose of inotuzumab ozogamicin.

j. Patients with evidence of extramedullary disease at diagnosis will have CT scan or MRI of the chest, abdomen and pelvis within 28 days prior to registration, then every 3 months for 2 years then every 6 months until 3 years after initial registration.

7.2 Treatment

a. This study will be conducted as a Phase I dose finding study with an expansion cohort treated at the maximum tolerated dose (MTD). The protocol will be revised to include the MTD prior to opening the expansion cohort.

The protocol will be revised to include the MTD which will be used in the expansion cohort once it has been determined. In order to avoid delay in activating the expansion cohort, a memorandum will be distributed instructing sites of the dose level that will be used in the expansion cohort (the MTD) to allow accrual to continue pending distribution of the full revision incorporating the MTD.

NOTE: Effective with Revision #8, the MTD has been determined to be Dose Level 5 (see Section 7.2b). Therefore, patients enrolled in the expansion cohort will be treated at Dose Level 5.

A maximum of 6 cycles of treatment will be administered.

Agent	Dose	Route	Day [c]	Schedule*
Cyclophosphamide [b]	750 mg/m^2	IV	1	every cycle
Vincristine [b]	1.4 mg/m^2 (max 2 mg)	IV	1	every cycle
Prednisone [d]	100 mg	PO	1-5	every cycle
Inotuzumab ozogamicin [b]	Dose Level 5 [a]	IV	1, 8, 15	every cycle

* 1 cycle = 28 days

[a] In the initial MTD-finding cohort, patients were treated at an assigned dose, based on the dose escalation schema in Section 7.2b and the DLT definition in Section 7.3. In the expansion cohort, patients are treated at Dose Level 5 (the MTD).

[b] May be given through the same IV line. Order of administration is at the discretion of the treating physician. Dose may be given ± 2 days from scheduled administration date.

[c] See Sections 7.1f and 7.1g for EKG and prophylactic chemotherapy guidelines during treatment.

[d] Prednisone may also be administered via IV at the investigator's discretion.

b. Inotuzumab Ozogamicin Dose Escalation Schema

Dose Level	Day 1 dose (mg/m^2)	Day 8 dose (mg/m^2)	Day 15 dose (mg/m^2)
1	0.4	0	0.4
2	0.6	0	0.4
3	0.8	0	0.4
4	0.8	0.4	0.4
5	0.8	0.5	0.5

c. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.3.

2. Only DLTs occurring during Cycle 1 will be used to guide dosing determination of inotuzumab ozogamicin.

3. Patients will be considered evaluable for DLT if they receive inotuzumab ozogamicin at the assigned dose for Cycle 1, or if they develop a DLT. If for any reason a patient does not develop a DLT and does not receive the full assigned inotuzumab dose, the patient will be considered not evaluable for DLT and will be replaced.

Note that for the purposes of this study, prolonged myelosuppression (lasting longer than 35 days beyond the most recent dose of inotuzumab ozogamicin) will be considered a DLT (see Section 7.3b). Therefore, in order to be considered evaluable for DLT, patients with myelosuppression after Cycle 1 must remain on the study for at least 35 days beyond the last dose of inotuzumab ozogamicin, or until myelosuppression is no longer present (whichever is first).

d. MTD Determination Scheme

1. Begin at Dose Level 1 (see Section 7.2b).

2. Enroll 3 patients at the current dose level and evaluate for toxicity. Enroll additional patients as required until 3 evaluable patients have been enrolled.

3. If 0 of the initial 3 evaluable patients experience a DLT, stop enrollment at this dose and continue to next dose level.

4. If only 1 of the initial 3 evaluable patients at the current dose level experience a DLT, expand enrollment until 6 evaluable patients have been enrolled or a second patient experiences a DLT.

5. If 2 or more evaluable patients experience a DLT at the current dose level:

   a. If the current dose level is Dose Level 1, the study may be permanently closed.

   b. If fewer than 6 evaluable patients have been enrolled in the next lower dose level, expand that dose level until 6 evaluable patients have been enrolled, then return to Section 7.2d.4 above.

6. If 1/6 evaluable patients experience a DLT at the current dose level:

   a. If 2 or more evaluable patients have already experienced a DLT at the next dose level then the current dose level is the MTD.

   b. If the current dose level is Dose Level 5, then this is the recommended dose level for the expansion cohort.

   c. If neither of the above apply, continue to the next dose level.

Only one dose level of inotuzumab ozogamicin will be open at a time. Adverse events and accrual monitoring are done routinely by the Study Chairs and Study Statisticians. A mandatory conference call for study teams with active patients will take place twice a month.

Once the MTD has been determined, a temporary closure will occur in order to assess dose and to evaluate the safety profile more fully. All toxicities will be captured and described. If the regimen is considered safe, an expanded cohort of patients will be treated at the MTD. (A total of 12 patients will be treated in the expansion cohort.)

7.3 DLT Determination

For this protocol, DLT will be defined as any of the following events occurring during the first cycle of treatment that are possibly, probably or definitely attributable to inotuzumab ozogamicin, cyclophosphamide, vincristine, or prednisone. However, Grade 3 or 4 toxicities due to pre-existing conditions that are exacerbated by the steroids will not be considered DLTs.

a. Any Grade 4 or greater non-hematologic toxicity with the exception of nausea and vomiting (if manageable with supportive care measures), and toxicities secondary to neutropenia and sepsis.

b. Prolonged myelosuppression, defined as: absolute neutrophil count (ANC) < 500/uL or platelet count < 25,000/uL in a bone marrow with < 5% blasts and no evidence of leukemia that lasts longer than 35 days beyond the most recent dose of inotuzumab ozogamicin.

c. Any Grade 3 non-hematologic toxicity (excluding peripheral neuropathy and hyperglycemia, and toxicities secondary to neutropenia, thrombocytopenia and sepsis) that does not resolve to Grade 2 or better by 7 days beyond the most recent dose of inotuzumab ozogamicin or is determined to be clinically significant irrespective of duration.

d. Any Grade 3 or higher elevation of SGOT/SGPT or bilirubin lasting ≥ 7 days.

e. Any inotuzumab ozogamicin-related toxicity resulting in permanent discontinuation of inotuzumab ozogamicin (e.g., no recovery to ≤ NCI CTCAE Grade 1 or baseline non-hematologic inotuzumab ozogamicin related toxicity within 28 days of scheduled day of dosing, except as noted above). Note: Alopecia is not considered a DLT.

f. Expedited reporting is required for adverse events that occur within 30 days of the last administration of inotuzumab ozogamicin (see Section 16.0 for expedited reporting requirements).

7.4 Criteria for Removal from Protocol Treatment

a. Progression (see Section 10.7). Exception: Patients experiencing only isolated CNS disease may continue on protocol treatment, with appropriate intrathecal therapy, at the discretion of the treating physician.

b. Unacceptable toxicity.

c. Patient requires more than 2 inotuzumab ozogamicin dose reductions or discontinuation of inotuzumab.

d. Treatment delay for any reason > 28 days.

e. Completion of 6 cycles of protocol treatment.

f. Patient begins another non-protocol treatment (i.e., allogeneic transplant).

g. The patient may withdraw from the study at any time for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Dose delays/modifications will be made for inotuzumab ozogamicin and vincristine. No dose reductions are allowed for cyclophosphamide or prednisone.

b. Doses of cyclophosphamide and prednisone may be delayed but should not be omitted. However, for inotuzumab ozogamicin, dose delays of > 7 days within a cycle will result in omission of the dose. The patient will remain eligible to receive the subsequent planned doses, assuming that all dosing criteria are met.

c. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction. Doses will not be reduced for alopecia.

d. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

e. Once a dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

f. If any study drug must be permanently discontinued the patient will be removed from protocol therapy.

8.3 Inotuzumab Ozogamicin Dose Delays

- Dose delays due to inotuzumab ozogamicin-related toxicity ≤ 7 days during a treatment cycle are permitted.
- **Dose delays of > 7 days within a cycle will result in omission of the dose**; the subject remains eligible to receive the subsequent planned dose assuming all dosing criteria are met.
- Dose delays due to inotuzumab ozogamicin-related toxicity > 28 days at the end of a treatment cycle (i.e., delay of Day 1 dosing) will result in permanent discontinuation of study treatment.

If the patient does not meet the criteria outlined below on the day of scheduled the administration of the dose will be delayed.

a. No evidence of progressive disease (PD) prior to the administration of each dose of inotuzumab ozogamicin defined in Section 10.7 within a cycle. Exception: Patients experiencing only isolated CNS disease may continue on protocol treatment, with appropriate intrathecal therapy, at the discretion of the treating physician.

b. Prior to the start of each cycle, the patient has a decrease in blast percentage or stable disease (i.e., not more than a 50% increase in blast percentage) based on the most recent bone marrow evaluation. NOTE: If biopsy was dry tap at baseline, the estimate of the blast count obtained on the baseline biopsy may be used for comparison. This must be documented on the **S1312** Treatment Summary Form.

c. Recovery to Grade 1 or baseline non-hematologic inotuzumab ozogamicin-related toxicity (except as outlined in Section 8.3d, not including alopecia or hyperglycemia) prior to each dose of inotuzumab ozogamicin and prior to each cycle.

d. Prior to each dose of inotuzumab ozogamicin and prior to each cycle, serum bilirubin ≤ 1.5 x ULN, and SGOT/SGPT and alkaline phosphatase ≤ 2.5 x ULN (or if elevated due to tumor, bilirubin ≤ 2 x ULN). Isolated SGOT or alkaline phosphatase elevations need not result in dose delays if not related to hepatobiliary organs (e.g., alkaline phosphatase elevations due to bone involvement).

e. Prior to each dose of inotuzumab ozogamicin and prior to each cycle, serum creatinine ≤ 2 x ULN or estimated creatinine clearance ≥ 40 mL/min as calculated using the institutional standard method.

f. Blood count requirements must be met per the following:

- Prior to the start of each cycle, for subjects with pre-treatment ANC ≥ 1,000/uL; ANC ≥ 1,000/uL.
- Prior to the start of each cycle, for subjects with pre-treatment platelets ≥ 50,000/uL; platelets ≥ 50,000/uL.
- Subjects with pre-treatment ANC < 1,000/uL and/or platelets < 50,000/uL; ANC and platelets must recover to baseline values obtained for the prior cycle, or ANC ≥ 1,000/uL and platelets ≥ 50,000/uL, or the most recent bone

marrow must demonstrate stable or improved disease, and the ANC and platelets are believed to be low due to disease, not inotuzumab ozogamicin.

NOTE: There are no ANC or platelet count requirements for Cycle 1 Day 1, as dosing criteria are relative to pre-treatment values. Doses given within a treatment cycle (i.e., Days 8 and/or 15) need not be delayed due to neutropenia or thrombocytopenia.

g. QTcF ≤ 500 msec (average of 3 EKGs) on Day 1 of Cycles 2 and 4. For QTcF > 500 on any EKG, the Study Chair (Dr. Advani at 216/445-9354 or Dr. Michaela Liedtke at 650/498-6000) must be contacted to discuss whether the patient may continue on protocol therapy.

8.4 Dose Modifications

a. General Inotuzumab Ozogamicin Dose Reduction

Refer to the appropriate row in the table based on the starting date.

	Starting Dose (mg/m^2) (Dose Level 0)				Reduction Dose Level -1				Reduction Dose Level -2		
Assigned Dose Level	**D1**	**D8**	**D15**		**D1**	**D8**	**D15**		**D1**	**D8**	**D15**
Dose Level 1	0.4	0	0.4		Remove patient from protocol treatment						
Dose Level 2	0.6	0	0.4		0.4	0	0.4		Remove patient from protocol treatment		
Dose Level 3	0.8	0	0.4		0.6	0	0.4		0.4	0	0.4
Dose Level 4	0.8	0.4	0.4		0.8	0	0.4		0.6	0	0.4
Dose Level 5	0.8	0.5	0.5		0.8	0.4	0.4		0.8	0	0.4

Patients experiencing a DLT or a treatment interruption due to inotuzumab-related toxicity ≥ 14 days may resume dosing at the next lower dose level (if a lower dose level is available) for the subsequent cycle once adequate recovery is achieved (i.e., if a patient is being treated on Dose Level 2, Reduction Dose Level -1, they would be treated at Dose Level 2, Reduction Dose level -2; see table). Dose reductions to the next lower dose level (if a lower dose level is available) should also be considered for patients with CRi, whose platelet counts have not recovered to values obtained prior to the start of the previous cycle.

Patients requiring more than two dose reductions will be withdrawn from treatment.

b. Dose Modifications for Inotuzumab Ozogamicin Infusion Reactions

For patients experiencing infusion reaction, infusion should be slowed or stopped at the discretion of the treating physician. The infusion may be restarted and/or the rate re-escalated if felt safe by the treating physician. It is recommended that the infusion be given at a reduced rate following any infusion reaction. Questions regarding dose modification for infusion reactions should be directed to the Study Chair (see Section 8.7).

Patients may be medicated during treatment as indicated in the judgment of the treating physician to control potential infusion or hypersensitivity responses (including with steroids).

For anaphylactic reactions, appropriate medical measures (e.g., epinephrine, antihistamines, hydrocortisone, and IV fluids) should be taken. Such a subject should not receive additional study drug and should be discontinued from protocol therapy.

If a patient has an infusion reaction to inotuzumab ozogamicin that requires permanent discontinuation of inotuzumab, they may continue treatment with CVP but will be considered off protocol treatment and unevaluable for response. Additional medical support should be administered at the discretion of the treating physician.

c. Vincristine Dose Reduction

Toxicity	Dose Reduction
≥ Grade 2 neuropathy OR ≥ Grade 2 bilirubin (unless primarily unconjugated)	Hold vincristine until toxicity has resolved to ≤ Grade 1, then resume at full dose. Do not make up missed doses.

8.5 Concomitant Medications

a. Concomitant medications to treat other medical conditions (antibiotics, antiemetics are allowed during protocol treatment with the exceptions in Sections 8.5b and 8.5d.

b. Medications known to predispose to *Torsades de pointes* are prohibited (see http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm#--).

If sedation will be utilized for bone marrow biopsies, drug(s) with the least potential for Torsades de pointes should be used. Propofol is specifically contraindicated; however, acceptable alternatives include (but are not limited to) midazolam and fentanyl.

c. It is recommended but not required that inhibitors or inducers of cytochrome P450 not be given during protocol treatment (see Appendix 18.2).

d. Concurrent therapy with radiation, chemotherapy (other than in the protocol), or prednisone > 20 mg every other day (other than what is written in the protocol) is prohibited.

8.6 G-CSF Guidelines

Secondary prophylaxis/use of G-CSF may be implemented if clinically indicated after the first or later dose of investigational product in accordance with ASCO guidelines unless the patient has a mixed phenotype leukemia; patients with mixed phenotype leukemia may not receive G-CSF. All G-CSF use must be documented on the appropriate treatment summary form.

8.7 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Advani at 216/445-9354 or Dr. Michaela Liedtke at 650/498-6000.

8.8 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

	Pre	Cycle 1				Cycle 2				C3	C4	C5	C6	Prog	Follow Up β
	Tx	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4						
REQUIRED STUDIES															
History / Physical Exam	X	D1				D1				D1	D1	D1	D1	X	X
Weight / Performance Status %	X	D1				D1				D1	D1	D1	D1		
Toxicity Notation €	X	X	X	X	X	X	X	X	X	X	X	X	X		X
LABORATORY STUDIES															
CBC, Diff Plts €	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine €	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bilirubin €	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SGOT/SGPT €	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Alkaline Phosphatase €	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hep B/Hep C Serology	X														
Lumbar Puncture ƒ	X														
Neuropathy Assessment	X	D1				D1				D1	D1	D1	D1	X	
Disease Assessment – PB/BM Asp/Biopsy ¥	X			X				X			X		X		
Cytogenetics/FISH Δ	X			X											
X-RAYS / SCANS															
EKG $	X					D1					D1				
ECHO or MUGA	X														
CT or MRI #	X				P Tx					P Tx			P Tx		X
TREATMENT															
Cyclophosphamide		X				X				X	X	X	X		
Inotuzumab Ozogamicin		X	X	X		X	X	X		X	X	X	X		
Prednisone		X				X				X	X	X	X		
Vincristine		X				X				X	X	X	X		

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0. Click here for Footnotes

Footnotes:

€ Days 1, 8, 15 and 22 of each cycle (not counting dose delays).

ƒ For patients with previous documented history of CNS involvement of acute leukemia, or with clinical signs or symptoms consistent with CNS involvement of acute leukemia. May be performed during intrathecal chemotherapy at the discretion of the treating physician.

¥ Performed between Days 21-25 of Cycles 1, 2, 4 and 6. Due to the frequency of biopsies, sedation is encouraged (see Section 8.5b).

Δ Pretreatment and after completion of treatment Cycle 1 (Day 21-25). FISH is optional.

% Patient to be weighed prior to treatment of each cycle.

$ EKG must be performed in triplicate at each indicated time point. Electrolytes must be corrected prior to the first EKG each day. (See Sections 5.2p and 7.1f.)

Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis performed pre-study, after completion of Cycles 1, 3, and 6 treatment, then every 3 months for 2 years, and then annually until 3 years after initial registration.

β Follow up tests will be performed every 2 months for the first year from registration, every 3 months for the second year, then every 6 months for the third year, unless otherwise noted.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in http://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

Note: For all sites of extramedullary disease present prior to treatment, subsequent disease measurements must be made using the same techniques as at baseline.

10.1 Extramedullary Disease

a. Measurable Extramedullary Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. **Note**: CT scans remain the standard for evaluation of nodal disease.

b. Non-measurable Extramedullary Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (e.g., lab values).

c. Extramedullary Disease Status:

C1. Complete disappearance of all measurable and non-measurable extramedullary disease with the exception of lesions for which the following must be true: for patients with at least one measurable lesion, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses ≥ 1 cm and ≤ 1.5 cm in GTD at baseline must have regressed to < 1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable.

All disease must be assessed using the same technique as at baseline.

C2. Patient does not qualify for C1 status.

10.2 Complete remission (CR)

a. < 5% marrow aspirate blasts. Blasts can be ≥ 5% if the blasts are found to be recovering myeloid cells.

b. Neutrophils ≥ 1,000/uL, platelets > 100,000/uL, and no blasts in the peripheral blood.

c. C1 Extramedullary disease status (see Section 10.1c).

10.3 Complete remission with incomplete platelet recovery (CRi)

Same as CR but absolute neutrophil count (ANC) may be < 1,000/uL and/or platelet count may be ≤ 100,000/uL.

10.4 Partial remission (PR)

Improvement or no worsening of acute leukemia, as indicated by all of the following:

a. No blasts in the peripheral blood

b. Neutrophils ≥ 1,000/uL and platelets > 100,000/uL

c. Either or both of the following:

1. At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥ 5% and ≤ 25%.

2. C2 extramedullary disease status (see Section 10.1c).

10.5 Treatment Failures

Patients who fail to achieve CR, CRi, or PR following Induction will be classified according to the type of failure:

a. Resistant Disease: patient survives ≥ 7 days following completion of initial treatment course and has persistent leukemia in the most recent peripheral blood smear or bone marrow and/or persistent disease involvement at any extramedullary site after completion of therapy.

b. Death during Aplasia: patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-Induction bone marrow without leukemic blasts.

c. Indeterminate:

1. Patient survives < 7 days after completion of initial treatment course.

2. Patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post induction bone marrow examination or extramedullary disease examination.

10.6 Relapse from CR or CRAppearance of leukemic blasts in the peripheral blood.

a. Appearance of extramedullary disease.

b. ≥ 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia). If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is ≥ 5% but < 20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is ≥ 5% is necessary to establish relapse.

10.7 Progression

Doubling of peripheral blasts with an absolute increase > 5 x 10^9 and/or the appearance or progression of extramedullary disease within a treatment cycle; or prior to the start of each cycle, > 50% increase in blast percentage in the bone marrow. Note that patients experiencing only isolated CNS disease may continue on protocol treatment, with appropriate intrathecal therapy, at the discretion of the treating physician.

10.8 Overall Survival (OS)

Overall survival will be measured from the day of registration on study until death from any cause with observations censored on the day of last contact for patients not known to have died.

10.9 Relapse-Free Survival (RFS)

RFS will be defined only for patients who achieve CR or CRi and will be measured from the date the patient first achieves CR or CRi until relapse from CR/CRi or death from any cause. Observations will be censored on the day of last contact for patients not known to have relapsed from CR/CRi or to have died.

10.10 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT DESCRIPTION

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

The primary objective will be to determine the maximum tolerated dose (MTD) of inotuzumab ozogamicin in combination with CVP in patients with relapsed or refractory acute leukemia. The regimen will be considered safe and the MTD determined if the dose-limiting toxicity rate is < 33%.

This will be a dose escalation clinical trial using a standard 3+3 design. Section 7.2 provides the details of the study design. There will be five dose levels. The starting dose level is Dose Level 1. No patients will be enrolled in the next dose level until the toxicity is fully assessed after the completion of 1 cycle in at least 3 patients enrolled at the previous dose level. The maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of dose-limiting toxicities (DLT) is < 33%. The cohort of the MTD (or proposed dose for the expansion cohort) will be at least 6 patients before the enrollment is opened in the expansion cohort.

11.2 Maximum Tolerated Dose

Once the MTD has been determined, a temporary closure will occur in order to assess dose and to evaluate the safety profile more fully. If the regimen is considered safe, an expanded cohort of patients will be treated at the MTD (an additional 12 patients will be treated at the MTD; see Section 7.2). Non-dose limiting toxicities will be captured and described in the expansion cohort. With 12 patients, the probability of any particular

toxicity can be estimated to within at most ±28% (95% confidence interval). Any toxicity having a true occurrence rate of 15% or more is very likely to be observed in at least one patient (probability ≥ 85%).The response rate (CR/CRi) will be evaluated in a preliminary manner given the small number of patients in the expansion cohort.

11.3 Accrual

The study will be open in a limited number of institutions, with an expected accrual of 3-30 patients in the Phase I portion and 12 additional patients in the expansion cohort (see Section 7.2). Assuming that 5% of patients enrolled will be ineligible, approximately 38 patients will be required. Based on **S0530** and **S0910**, the estimated accrual rate is 1.5 B-ALL patients per month. SWOG does not have recent experience accruing patients with mixed phenotypic leukemia or Burkitt's leukemia, but we expect this accrual rate to be conservative and the actual accrual rate could be higher because of the wider eligibility. Estimated accrual time is up to 21 months for the initial Phase I portion and up to 4 months for the expansion cohort.

11.4 Data and Safety Monitoring

See Section 15.2 for a description of conference calls for safety monitoring.

There is no formal data and safety monitoring committee for Phase I studies. Adverse events and accrual monitoring are done routinely by the Study Chairs and Study Statisticians. Accrual and adverse event listings are posted real time. A conference call between the study team and participating investigators takes place every other week to discuss enrollment, patient progress, adverse events, DLTs, and dose escalation/de-escalation decisions. Formal toxicity reports are published Group-wide every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor serious adverse events on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment).

13.2 Slot Reservation

Patients planning to enroll on this study must first have a slot reserved in advance of the registration, even if the site plans to enroll right away.

All site staff will use OPEN to create a slot reservation. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench. Please refer to the 'Slot Reservation Quick Reference Site User Guide' within the OPEN tab on the CTSU members' website under 'Training and Demonstration Materials' for detailed instructions.

The individual making the slot reservation for the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Patient Initials

e. Patient's Date of Birth

f. ZIP Code

g. Gender (select one):
- Female Gender
- Male Gender

Slot reservations expire within 11 calendar days. A warning e-mail will be sent 48 hours before the expiration date. The reservation can be renewed any time before it expires as long as at least 1 slot is still available. After it expires, a new slot reservation must be changed for the patient before they can be enrolled to this trial. Reservations may also be withdrawn at any time. If a reservation is withdrawn, the SWOG Statistical Center should be notified (leukemiaquestion@crab.org).

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. Rave® may also be accessed via the SWOG CRA Workbench. Go to a SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After logging on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. Registering individual is entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. Registering individual is associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Sites local Web User Administrator has added the registering individual as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please e-mail technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1312 Onstudy Form

S1312 Baseline Disease Assessment Form

Pathology Report

b. WITHIN 28 DAYS AFTER REGISTRATION:

Submit the following:

Cytogenetics and/or FISH Reports from lab (whichever are performed)

Mutational Analysis and Cytogenetics Report Forms

CT Scan Reports (if extramedullary disease is found)

c. WITHIN 7 DAYS AFTER DAY 1 EKG RESULTS OF CYCLES 2 AND 4

Submit the EKG Results Form

d. EVERY 14 DAYS DURING PROTOCOL TREATMENT:

Submit the **S1312** Adverse Event Form **(Submit every 7 days during Cycle 1; see Section 15.1 for Rapid Reporting requirements.)**

e. WITHIN 28 DAYS AFTER CYCLE 1 OF TREATMENT:

Submit the following:

Mutational Analysis and Cytogenetics Report Forms

Cytogenetics and/or FISH Reports from lab

f. WITHIN 7 DAYS AFTER EACH CYCLE OF TREATMENT (1 cycle = 28 days):

Submit the following:

S1312 Treatment Form

ALL Disease Assessment Form (Including assessment of extramedullary disease for all patients who had extramedullary disease at baseline.)

g. WITHIN 14 DAYS AFTER KNOWLEDGE OF RESPONSE OR RELAPSE:

Submit the following:

ALL Disease Assessment Form documenting the date of and evidence for response or relapse. (Including a response, resolution, or relapse of extramedullary disease for all patients who had extramedullary disease at baseline.)

h. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT

Submit the following:

Off Treatment Notice

S1312 Treatment Form

S1312 Adverse Event Form

i. AFTER THE PATIENT IS OFF TREATMENT, EVERY 2 MONTHS FOR THE FIRST YEAR, EVERY 3 MONTHS FOR THE SECOND YEAR, THEN EVERY 6 MONTHS FOR THE THIRD YEAR AFTER REGISTRATION

Submit the following:

Leukemia Follow-Up Form

S1312 Transplant Form (if patient received HCT)

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH

Submit the Notice of Death **and all of the items listed in Section 14.4f (**if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Rapid Reporting

RAPID REPORTING OF TREATMENT-RELATED DOSE-LIMITING TOXICITIES

This trial requires that Adverse Events be reported every 7 days for patients who have initiated treatment during Cycle 1 and then every 14 days during subsequent cycles.

Institutional participation in the trial requires the identification of a contact CRA and back-up CRA. **Prior to registration of the first patient, each institution must provide the**

contact and back-up CRA names, e-mail addresses, and phone numbers to the SWOG Data Operations Center. Institutions will be responsible for keeping this information up-to-date and must notify the study Protocol Coordinator (Cara Laubach: claubach@swog.org), of any changes.

The contact CRA and back-up CRA will receive weekly e-mails including a list of the Adverse Event forms that are overdue, currently due, or due in the next week. These e-mails will include a reply-to address and phone number to contact the Data Operations Center when questions arise.

15.2 Mandatory Conference Calls

A mandatory conference call for study teams with active patients will take place twice a month. The call will update participants on the current status of the trial and will include representatives from the study team, investigators from all participating institutions and representatives from Pfizer. At this time any serious toxicities encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of important study decisions via e-mail.

Institutional participation on these calls requires the identification of an investigator contact and a CRA contact. **Prior to registration of the first patient, each institution must provide the contact names, e-mail addresses, and phone numbers to the SWOG Data Operations. Institutions will be responsible for keeping this information up-to-date and must notify the study Protocol Coordinator (Sandi Fredette: sfredette@swog.org), of any changes of any changes.** The investigator and the contact CRA will receive e-mail reminders with the conference call information.

15.3 Cytogenetics and FISH (REQUIRED)

Specimens for cytogenetic (and FISH if possible) analysis must be submitted to the site's preferred local CLIA-approved laboratory.

a. Diagnostic/pre-treatment specimens (bone marrow aspirate, or peripheral blood if dry tap) obtained within 14 days prior to registration must be submitted for cytogenetic (and FISH if possible) analysis. Use of SWOG approved laboratories is encouraged, but not mandatory.

b. Specimen collection and submission instructions and a list of approved laboratories can be accessed on the SWOG Cytogenetics webpage (www.swog.org/Members/ClinicalTrials/Specimens/Cytogenetics.asp).

c. The S1312 Cytogenetics Lab Report Form must be submitted to the laboratory along with the specimen. The laboratory will then return the completed form with the results. E-mail contact information for the Data Manager must be provided to the lab performing the cytogenetics studies. The Institution will complete the Mutational Analysis and Cytogenetics Report Form via Medidata Rave® using the information provided by the lab.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research

Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at: http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210/614-8808, or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification

that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study inotuzumab ozogamicin. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse events that Occur on Studies under an Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Inotuzumab Ozogamicin.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210/614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited monitoring for this trial:

- Dose Limiting Toxicities (DLTs) outlined in Section 7.3.

- Potential causes of drug-induced liver injury:

  - Subjects with SGOT or SGPT and total bilirubin baseline values within the normal range who subsequently present with SGOT or SGPT ≥ 3 times the upper limit of normal concurrent with a total bilirubin ≥ 2 times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the upper limit of normal or not available.

  - For subjects with pre-existing SGOT or SGPT OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    For subjects with pre-existing SGOT or SGPT baseline values above the normal range: SGOT or SGPT ≥ 2 times the baseline values and ≥ 3 times the upper limit of normal, or ≥ 8 times the upper limit of normal (whichever is smaller).

    Concurrent with:

    For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or ≥ 3 times the upper limit of normal (whichever is smaller).

- Veno-occlusive disease/sinusoidal obstructive syndrome: For this study, VOD/SOS is defined as:

a. The occurrence of 2 of the following 3 clinical criteria:

Total serum bilirubin level > 34 µmol/L (> 2.0 mg/dL).

- An increase in liver size from baseline or development of right upper quadrant pain of liver origin.

- Sudden weight gain > 2.5% during any 72-hour period after infusion of investigational product because of fluid accumulation or development of ascites.

AND

- The absence of other explanations for these signs and symptoms.

OR

b. Development of bilirubin elevation, weight gain, or hepatomegaly plus histologic abnormalities on liver biopsy demonstrating hepatocyte necrosis in zone 3 of the liver acinus, sinusoidal fibrosis, and centrilobular hemorrhage, with or without fibrosis of the terminal hepatic venules. Elevation of portal pressure (> 10 mm Hg) is useful in the diagnosis of VOD/SOS.

3. For this study, the adverse events listed below do **not** require expedited reporting via CTEP-AERS:

- Neutropenic fever
- Grade 4 cytopenias (unless they qualify as a DLT)

g. *Reporting Secondary Malignancy, including AML/ALL/MDS*

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210/614-0006 or mail to the address below.

    - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
    - (if available) a copy of the cytogenetics report

    SWOG
    ATTN: SAE Program
    4201 Medical Drive, Suite 250
    San Antonio, Texas 78229

    NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. Reporting Pregnancy, Fetal Death, and Death Neonatal

- **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

  Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

- **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

- **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

  A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or

chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

i. Pfizer-Direct Additional SAE Reporting Requirements

1. Pregnancy Reporting

In the event that a study participant or the partner of a study participant becomes pregnant while the participant is on study treatment, additional reporting of pregnancy information to Pfizer is requested.

In the event of such a pregnancy, the site must make reasonable efforts to obtain consent from the study participant and/or their partner for pregnancy reporting. The additional consent is the responsibility of the site and must take place according to local Institutional Review Board requirements. A sample consent template is included as Appendix 18.3.

If consent is obtained, information about the pregnancy and the outcome of the pregnancy must be reported via the Pfizer Exposure During Pregnancy (EDP) Supplemental Form. The form must be submitted directly to Pfizer according to the instructions on the Investigator-Initiated Research Reportable Event Cover Sheet. The form and cover sheet are available on the protocol abstract page of the SWOG website (www.swog.org).

Institutional support for this additional data collection and submission may be obtained by submitting the Pregnancy Reporting Reimbursement Form which is available on the protocol abstract page. Note that this additional support is available ONLY to institutions submitting the Pfizer Exposure During Pregnancy Supplemental Form. Pregnancy and outcome information submitted via CTEP-AERS performed in accordance with NCI guidelines as part of regular adverse event reporting requirements is not reimbursed.

2. Additional Reporting Requirements

The additional events listed below will be considered SAEs by Pfizer and should be reported directly to Pfizer via the Pfizer SAE Report Form. The form should be submitted directly to Pfizer according to the instructions on the Investigator-Initiated Research Reportable Event Cover Sheet. The form and cover sheet are available on the protocol abstract page of the SWOG website (www.swog.org).

a. Exposure during breastfeeding

Exposure during breastfeeding occurs if an infant child may have been exposed through breast milk to the investigational agent by a female taking the agent and is reportable regardless of whether there is an associated SAE in the infant or child.

b. Occupational exposure

Occupational exposure is defined as an exposure to the investigational agent as a result of one's occupation and must be reported regardless of whether there is an associated SAE.

Occupational exposure is not specifically listed on the SAE Report Form; therefore, it should be reported primarily by use of the narrative field of the form. The narrative should clearly state that occupational exposure is being reported, and that no patient is involved in the event. The report should include detailed information about how and when the exposure took place, and whether any adverse effects occurred.

Note that reporting occupational exposure requires consent of the individual who was exposed to the drug. In the event of occupational exposure, the site must make reasonable efforts to obtain consent from the exposed individual for reporting. The additional consent is the responsibility of the site and must take place according to local Institutional Review Board requirements. A sample consent template is included as Appendix 18.4.

Institutional support for this additional data collection and submission may be obtained by submitting the Pfizer-Additional SAE Reporting Reimbursement Form which is available on the protocol abstract page. Note that this additional support is available ONLY to institutions submitting the Pfizer SAE Report Form. SAEs submitted via CTEP-AERS performed in accordance with NCI guidelines as part of regular adverse event reporting requirements are not reimbursed.

3. For additional information regarding Pfizer-direct reporting requirements as outlined above, refer to the Pfizer Safety Reporting Training Materials on the protocol abstract page of the SWOG website (www.swog.org). Note that the training materials are provided as a supplement to the protocol information and specifically to supplement information regarding the Pfizer-direct additional reporting requirements. Reporting information provided in the protocol takes precedence over information provided in the supplemental reporting requirements. Questions regarding reportability of Pfizer-direct additional events should be directed to Alison Randall at Pfizer (alison.randall@pfizer.com).

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 New York Heart Association Classifications

18.2 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

18.3 Pfizer-Direct Pregnancy Reporting Consent

18.4 Pfizer-Direct Occupational Exposure Reporting Consent

18.1 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.2 T Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

CYP2D6	
Substrates	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, o-demelhylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (o-demethylation)	Propafenone
Dihydrocodeine	Propranolol

Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluosetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Haiofantrine	Tamoxifen
Haioperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (o-desmethylation)
Meperidine	Yohimbine
Methadone	

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam

Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	
Carbamazepine	Diazepam (minor; hydroxylation, N-demethylation)
Cevimeline	
Cerivastatin	Nefazodone
Digitoxin	Nelfinavir
Diltiazem	Nevirapine
Disopyramide	Nicardipine
Docetaxel	Nifedipine
Dolasetron	Niludipine

Donepezil	Nimodipine
Doxorubicin	Nisoldipine
Doxycycline	Nitrendipine
Dronabinol	Omeprazole (sulfonation)
Enalapril	Ondansetron
Erylhromycin	Oral contraceptives
Estradiol	Orphenadrine
Ethinyl estradiol	Paclitaxel
Ethosuximide	Pantoprazole
Etoposide	Pimozide
Exemestene	Pioglitazone
Dofetilide (minor)	Pravastatin
Felodipine	Prednisone
Fentanyl	Progesterone
Fexotenadine	Proguanil
Finaxteride	Propafenone
Fluoxetine	
Flutamide	
Substrates	
Glyburide	Quercetin
Granisetron	Quetiapine
Halofantrine	Quinidine
Hydrocortixone	Quinine
Hydroxyarginine	Repaglinide
Ifosfamide	Retinoic acid
Imipramine	Rifampin
Indinavir	Risperidone
Isradipine	Ritonavir
Itraconazole	Salmeterol
Ketoconazole	Saquinavir
Lansoprazole (minor)	Sertindole
Letrozole	Sertraline

Levobupivicaine	Sibutramine
Lidocaine	Sildenafil citrate
Loratadine	Simvastatin
Losartan	Sirolimus
Lovastatin	Sufentanil
Methadone	Tacrolimus
Mibefradil	Tamoxifen
Miconazole	Temazepam
Midazolam	Teniposide
Mifepristone	Terfenadine
Mirtazapine (N-demethylation)	Testosterone
Montelukast	Tetrahydrocannabinol
Navelbine	Theophylline
Toremifene	Tiagabine
Trazodone	Tolterodine
Tretinoin	Vincristine
Triazolam	Warfarin (R-warfarin)
Troglitazone	Yohimbine
Troleandomycin	Zaleplon (minor pathway)
Venlafaxine (N-demethylation)	Zatoestron
Verapamil	Zileuton
Vinblastine	Ziprasidone
	Zolpidem
	Zonisamide

INDUCERS	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
INHIBITORS	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem	Propoxyphene
Dirithromycin	Quinidine
Disulfiram	Quinine
Entacapone (high dose)	Quinupristin and dalfopristin
Erythromycin	Ranitidine
Ethinyl estradiol	Ritonavir

Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

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18.3 Pfizer-Direct Pregnancy Reporting Consent

* NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

  - This template Pfizer-direct pregnancy reporting consent is provided as a tool to be used in the event that a female study participant or the female partner of a male study participant becomes pregnant while the study participant is on study treatment. This consent is not mandatory for all patients, only those who will submit additional pregnancy information to Pfizer. Sites may use local pregnancy reporting consent forms providing that they include adequate information as provided in this document, and pregnancy reporting consent is obtained in some written and IRB approved form prior to reporting pregnancy information to Pfizer. *Note that patients consent to pregnancy prevention as part of the clinical trial consent, so pregnancy events are not expected during the trial.*
  - This template has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. It is suggested that sections of this document that are in bold type be used in their entirety.

* These notes for investigators are instructional and should not be included in the informed consent form given to the prospective participant.

Pfizer-Direct Pregnancy Reporting Consent

What is the purpose of this consent form?

You are either a study participant or the partner of a study participant that took the drug inotuzumab ozogamicin as part of the study **S1312**, and you or your partner have become pregnant. Pfizer, the drug's manufacturer, is trying to learn more about how the drug affects the developing baby and the pregnancy. They would like to collect information about you, your pregnancy, the baby's development during the pregnancy, and the outcome of the pregnancy. This will help them to better inform future patients who receive the drug about what their pregnancy risks might be.

The purpose of this consent form is to ask your permission for your doctor/nurse to collect this information and provide it to Pfizer.

The information they will ask for is as follows:

FEMALES

- What are the first date of your last menstrual period and estimated date of conception?
- When during your pregnancy was the first exposure to the drug?
- Do you have any other risk factors that would affect the pregnancy (high blood pressure, diabetes, history of abnormal pregnancy, etc.)?
- Did you smoke, drink alcohol, or use any illegal drugs during the pregnancy?
- How many previous pregnancies and children have you had, and were there any problems?
- Outcome of the pregnancy (birth, stillbirth, miscarriage, etc.)?

- Was the baby born with any abnormalities?
- Is the baby male or female, and what is his/her length, weight and head measurement?

MALES

- Age, date of birth and occupation
- Do you have any other risk factors that would affect the pregnancy (AIDS, exposure to toxins, family history of abnormal pregnancy, etc.)
- Did you take any drugs (e.g. over the counter or prescription medications) during the mother's pregnancy?
- Did you smoke, drink alcohol, or use any illegal drugs during the pregnancy?

Your personal identifying information will not be provided to Pfizer. Your SWOG patient ID will be the only identifying information sent. Pfizer will not have access to the secure study database for **S1312** that links SWOG patient IDs to patient identifying information.

If you consent, your study doctor/nurse will gather this information on a form and send it to Pfizer. The information will be sent over a secure system. The doctor/nurse may need to ask you questions to get the necessary information. Pfizer will put your information into a database with the information from others who have provided pregnancy information, and analyze it to see if and how the drug has affected the reported pregnancies. They will need to collect this information throughout your pregnancy – at the time you initially learn of the pregnancy, at the time of any event during the pregnancy, and at the end of the pregnancy.

If you do not sign this consent, it will not affect your or your partner's treatment on the **S1312** study.

By signing this consent form you are agreeing to allow the information about you, your pregnancy, and your baby's development during the pregnancy to be sent to Pfizer.

What possible risks are there?

If you provide this information, you may be asked sensitive or private questions about you and your pregnancy which you normally do not discuss. You may have some emotional discomfort from answering these questions.

There is also a possible risk that your personal information might be compromised. Secure programs and procedures are in place to protect your personal information, your personal information is not provided to Pfizer, and we will do our best to make sure that personal information is kept private.

However, we cannot guarantee total privacy. There is a chance that some of your personal information may be given out as required by law. If any

information that is sent to Pfizer is published or presented at scientific meetings, your name and personal identifying information will not be used.

Can I stop providing information?

You can decide to stop providing information to Pfizer at any time. However, information that has already been sent cannot be taken back. If you decide to stop, no further information about you, your pregnancy, or the pregnancy outcome will be sent to Pfizer.

Signature

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in this study.

Participant's signature_____

Date of signature_____

18.4 Pfizer-Direct Occupational Exposure Reporting Consent

* NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

- This template Pfizer-direct occupational exposure consent is provided as a tool to be used in the event that any site personnel is/are exposed to the investigational agent inotuzumab ozogamicin in their occupational duties related to **S1312**. This consent is not mandatory for all site personnel, only those who will submit occupational exposure information to Pfizer. Sites may use local occupational exposure reporting consent forms providing that consent is obtained in some written and IRB approved form prior to reporting occupational exposure information to Pfizer.
- This template has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. It is suggested that sections of this document that are in bold type be used in their entirety.

* These notes for investigators are instructional and should not be included in the informed consent form given to the prospective participant.

Pfizer-Direct Pregnancy Reporting Consent

What is the purpose of this consent form?

You have been exposed to the investigational agent inotuzumab ozogamicin as part of your occupational duties with the study **S1312**. Pfizer, the drug's manufacturer, is trying to learn more about occupational exposure frequency and effects. They would like to collect information about you and your exposure to the drug. This will help them to better inform future healthcare providers about the risks of occupational exposure and proper drug handling.

The purpose of this consent form is to ask your permission for your site to collect this information and provide it to Pfizer.

They would like information about when and how you were exposed to the drug, and what, if any, side effects you may have experienced.

Your personal identifying information will not be provided to Pfizer.

If you consent, your site personnel will gather this information and send it to Pfizer. The person completing the report may need to ask you questions to get the necessary information. Pfizer will put your information into a database with the information from others who have provided the same information, and analyze it to learn more about occupational exposure events.

If you do not sign this consent, it will not affect your employment or your duties related to the **S1312** study.

By signing this consent form you are agreeing to allow the information about your occupational exposure to be sent to Pfizer.

What possible risks are there?

If you provide this information, you may be asked questions about the exposure and any side effects you experienced that you do not want to discuss. You may have some emotional discomfort from answering these questions.

Since your personal information is not collected on the reporting form and is not provided to Pfizer, there should be no risk of your personal information being given out.

Can I stop providing information?

Once an exposure event has been reported to Pfizer, the information cannot be recalled. You can, however, decide not to provide information about any subsequent exposure events that occur.

Signature

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to allow my occupational exposure information to be provided to Pfizer.

Participant's signature_____

Date of signature_____

Informed Consent Model for S1312

Readability Statistics:		
Flesch Reading Ease	62.1	(targeted above 55)
Flesch-Kincaid Grade Level	8.4	(targeted below 8.5)

Consent Form

Study Title for Study Participants:
Testing the Addition of Inotuzumab Ozogamicin to Usual Chemotherapy in Relapsed and Refractory Acute Leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
S1312, A Phase I Study of Inotuzumab Ozogamicin (NSC-772518) in Combination with CVP (Cyclophosphamide, Vincristine, Prednisone) for Patients with Relapsed/Refractory CD22-Positive Acute Leukemia (Including B-ALL, Mixed Phenotypic Leukemia, and Burkitt's Leukemia)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

What is the usual approach to my leukemia?

You are being asked to take part in this study because you have an acute leukemia that has either come back or not gone away after treatment. People who have this type of cancer and choose not to participate in a study are usually either treated with high doses of chemotherapy or get comfort care. Comfort care does not treat the cancer but helps to lessen the symptoms.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- you could decide not to be treated
- or you could get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It

does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Why is this study being done?

The purpose of this study is to test the safety of the experimental drug inotuzumab ozogamicin at different doses to find out what effects, if any, it has on people. The researchers also want to determine the effects, good and/or bad, of adding inotuzumab ozogamicin to regular chemotherapy with cyclophosphamide, vincristine and prednisone (CVP). While researchers hope that adding inotuzumab ozogamicin will be a better treatment, there is no proof of this. Between 6 to 38 patients will take part in this study.

What are the study groups?

Different doses of the study drug inotuzumab ozogamicin will be given to several study participants in combination with CVP chemotherapy. The first several study participants will receive the lowest dose. If the drug does not cause serious side effects, it will be given to the next several study participants at a higher dose. The doses will continue to increase for every group of study participants until side effects occur that require the dose to be lowered. Then the study is stopped. When the maximum dose is reached, the study will be expanded to an additional 12 patients to learn more about that dose before it is stopped.

You will get up to 6 cycles of treatment. Each cycle is 28 days long. You will receive drug on some days, and other days will be rest days. After the complete 28 day cycle, you will start the next cycle as soon as your side effects have gotten better enough. One treatment cycle is outlined in the chart below.

Drug	How is Drug Given?	What Days is Drug Given?
Cyclophosphamide	Into your vein	1
Vincristine	Into your vein	1
Prednisone	By mouth	1-5
Inotuzumab Ozogamicin	Into your vein	1, 8, 15

How long will I be in this study?

You will receive the study drugs for about 6 months. After you finish the study drugs, your doctor will continue to watch you for side effects and follow your condition until 3 years after you start the study.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and scans that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following extra tests and scans to find out if you can be in the study:

- 3 EKGs to test heart function

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests and scans. They are not part of the usual approach for your type of cancer.

During the study:

- Bone marrow aspirate and biopsy near the end of the first month, second month, fourth month and sixth month of treatment
- EKGs to test heart function 2 months and 4 months after you start the study.

Neither you nor your health care plan/insurance carrier will be billed for these extra tests and scans before the study or during the study.

What risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You may also have the following discomforts:

- **Spend more time in the hospital or doctor's office.**
- **Be asked sensitive or private questions about things you normally do not discuss.**
- **May not be able to take part in future studies.**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach.

Here are important things to know about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, and some may never go away.**

- **Some side effects may make it hard for you to have children.**
- **Some side effects may be mild. Other side effects may be very serious and even result in death.**

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- **If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.**
- **Your study doctor will work with you to treat your side effects.**
- **Your study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of CVP Chemotherapy (Cyclophosphamide, Vincristine and Prednisone)

COMMON, SOME MAY BE SERIOUS **In 100 people receiving CVP, more than 20 and up to 100 may have:**
• **Hair loss** • **Nausea, vomiting, loss of appetite** • **Constipation** • **Sores in mouth** • **Infection, especially when white blood cell count is low** • **Absence of menstrual period which may decrease the ability to have children** • **Blood in urine** • **Pain or redness at the site of vincristine injection** • **Numbness and tingling of fingers or toes** • **Headache, jaw pain and/or muscle pain** • **Weakness and difficulty walking** • **Swelling of lower legs** • **Increased blood pressure** • **Belly pain** • **White patches in the mouth or throat (thrush)** • **Weakening of bones** • **Feelings of sadness or excitement** • **Skin problems such as acne and slower wound healing**

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving CVP, from 4 to 20 may have:**
• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions** • **Loss or absence of sperm which may lead to an inability to father children** • **Stuffy nose** • **Fluid around the heart** • **Anemia which may cause tiredness, or may require transfusion** • **Drooping eyelids** • **Hoarseness** • **Increased blood sugar** • **Skin problems such as reddening, peeling, flaking, abnormal hair growth or increased sweating**

RARE, AND SERIOUS In 100 people receiving CVP, 3 or fewer may have:
• Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • A new cancer including cancer of bone marrow (leukemia) or skin/lymph nodes (Kaposi's sarcoma) caused by chemotherapy • Swelling of the body including the brain which may cause dizziness, confusion • Scarring of the lungs • Seizure • Vision problems such as cataract or glaucoma • Sores or ulcers in the gastrointestinal tract • Swelling of the pancreas • Severe lung or bone infection • Diabetes • Changes in personality or hallucinations

Possible Side Effects of Inotuzumab Ozogamicin

COMMON, SOME MAY BE SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Belly pain • Nausea • Tiredness, fever • Bruising, bleeding • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), from 4 to 20 may have:
• Bloating, constipation, diarrhea, vomiting • Fluid in the belly which may cause swelling • Sores in the mouth which may cause difficulty swallowing • Chills • Damage to the liver which may cause yellowing of eyes and skin • Loss of appetite

RARE, AND SERIOUS In 100 people receiving inotuzumab ozogamicin (PF-05208773), 3 or fewer may have:
• **Reaction during or following a drug infusion which may cause rash, low blood pressure** • **Change in the heart rhythm** • **Kidney damage which may require dialysis**

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. You should continue pregnancy prevention for at least 90 days after stopping study drugs.

What possible benefits can I expect from taking part in this study?

While we hope adding inotuzumab ozogamicin will be helpful to your cancer, there is no evidence of this. This study may help us learn things that may help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The inotuzumab ozogamicin will be supplied at no charge while you take part in this study. The cost of getting the inotuzumab ozogamicin ready and giving it to you is not covered by the study, so you or your insurance company may have to pay for this. Cyclophosphamide, vincristine and prednisone are not paid by the study sponsor so you or your insurance company may have to pay for these. It is possible that the inotuzumab ozogamicin may not continue to be supplied free while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of managing any side effects. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

(paragraphs below added 3/25/15)
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://m.cancer.gov/topics/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured or hurt because I took part in this study?

If you feel you have been injured or hurt as a result of taking part in the study, it is important that you tell the study doctor. You will get medical treatment if you are injured or hurt as a result of taking part in this study.

The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance coverage, you would be responsible for any costs. Even though you are in a study, you keep all of your legal rights to receive payment for injury caused by medical errors.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the

researchers will do their best to make sure that any information that is released will not identify you. There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor (SWOG) and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION: This section is about optional studies you can choose to take part in.

Circle your choice of "yes" or "no" for future contact below.

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the *main study* and any additional studies where I circled 'yes'.*)*

Participant's (or legally authorized representative's) signature_____

Date of signature_____