NCT03318016

Phase I Trial of Arsenic Trioxide With Cyclophosphamide in Patients With Relapsed/Refractory Acute Myeloid Leukemia

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Version 3.1, Dated October 16, 2018

PROTOCOL TITLE	Phase I Trial of Arsenic Trioxide with Cyclophosphamide in Patients with Relapsed/Refractory Acute Myeloid Leukemia
PROTOCOL / COMIRB NUMBER	17-0754
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VERSION DATE:	October 16, 2018
VERSION NUMBER:	3.1

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STATEMENT OF COMPLIANCE

Protocol Title:	Phase I Trial of Arsenic Trioxide with Cyclophosphamide in Patients with Relapsed/ Refractory Acute Myeloid Leukemia
Protocol / COMIRB #	**17-0754**
Indication:	Relapsed and refractory patients with Acute Myeloid Leukemia (AML)
Investigational Agent:	Arsenic Trioxide
Phase:	I
IND Number:	136665
Protocol Version Date:	09-12-2017

This is an investigator-initiated study. The principal investigator (PI), Daniel Pollyea, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: **Daniel A. Pollyea, MD, MS**

Date: _____

_____
Signature

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
4HNE	4-hydroxynonenal
AE	Adverse Event
ALDH	Aldehyde dehydrogenase
ALDH1A1	Aldehyde dehydrogenase family 1 subfamily A1
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
AST	Aspartate Aminotransferase
ATO	Arsenic Trioxide
BMT	Bone Marrow Transplant
BUN	Blood Urea Nitrogen
Cal	Calcium
CD34+	Human protein encoded by CD34 gene
CFR	U.S. Code of Federal Regulations
CNS	Central Nervous System
CO2	Carbon Dioxide (bicarbonate)
CR	Complete Remission
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRi	Complete Remission with incomplete recovery of blood counts
CRp	Complete Remission with incomplete recovery of platelets
CU	University of Colorado
Cy	Cyclophosphamide
dL	Deciliter
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
DSM	Data Safety Management
DSMC	Data Safety Management Committee
ECOG	Eastern Colorado Oncology Group
EFS	Event Free Survival
EKG	Electrocardiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft vs. Host Disease
HSC	Hemotopoietic Stem Cells
ICH	International Council for Harmonisation
IIT	Investigator-Initiated Trial
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Investigational Review Board

IV	Intravenous
K	Potassium
KASUMI-1	A model of human ALDH1A1
LDH	Lactate Dehydrogenase
LQTS	Long QT Syndrome or QT-prolongation
LSCs	Leukemia Stem Cells
min	Minute
MLFS	Morphologic Leukemia Free State
MTD	Maximum Tolerated Dose
Na	Sodium
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PI	Principal Investigator
PO	Taken by mouth (orally)
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QTc	QT interval corrected
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
UA	Urine Analysis
UAP	Unanticipated Problem
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
WHO	World Health Organization

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PROTOCOL SYNOPSIS

PROTOCOL TITLE: Phase I Trial of Arsenic Trioxide followed by Cyclophosphamide in Patients with Relapsed/Refractory Acute Myeloid Leukemia
INDICATION: Relapsed and refractory patients with AML
STUDY PHASE: I
BACKGROUND AND RATIONALE: Aldehyde dehydrogenase 1A1 (ALDH1A1) is highly expressed in normal CD34+ hematopoietic stem cells (HSCs) but is very low or absent in roughly 25% of human AMLs (termed ALDH1A1$^-$ AML). ALDH1A1 is an important target as it is the primary enzyme responsible for metabolizing a wide range of toxic aldehydes. The differential expression of ALDH1A1 between ALDH1A1$^-$ AML and normal HSCs offers the opportunity to target this subset of AMLs with agents that directly or indirectly generate cytotoxic substrates of ALDH1A1. Laboratory data has demonstrated that compounds including cyclophosphamide (or its active metabolite 4-hydroxypercylophospamide, 4HC) as well as arsenic trioxide (ATO) generate toxic ALDH1A1 substrates that cause DNA damage, apoptosis and cell death in ALDH1A1$^-$ AMLs while HSCs are relatively spared from these effects. In this protocol we propose to test the hypothesis that these agents will be tolerable as well as effective at selectively eliminating AML cells by conducting a phase I study of fixed dose ATO with dose escalated cyclophosphamide (Cy) in patients with relapsed/refractory AML. We will measure ALDH levels and attempt to determine if responsiveness to therapy is determined by ALDH1A1 expression.
STUDY OBJECTIVES: **Primary:** • Determine the maximum tolerated dose (MTD) and toxicity profile of the combination of cyclophosphamide and ATO in subjects with relapsed refractory AML. **Secondary:** • Determine the efficacy of ATO and cyclophosphamide in this population, as defined by response rate, response duration, event-free survival (EFS) and overall survival (OS). • Determine the number of transplant-eligible subjects who are successfully bridged to stem cell transplantation or donor lymphocyte infusion.
STUDY DESIGN: This is an open label phase 1 study of fixed dose ATO and escalating doses of cyclophosphamide using a standard 3+3 dose escalation design. Eligible patients will be adults with relapsed and refractory AML. All subjects will be treated with sequential cycles of 3 days of ATO at 0.15 mg/kg/d IV followed by Cyclophosphamide as a single IV dose on day 4 along with mesna at a dose equal to the cyclophosphamide (for doses ≥1000 mg/m^2) and hydration for a maximum of 6 cycles in the following dose escalation scheme:

- Cohort -1 (3-6 subjects, if needed): Cyclophosphamide 500 mg/m^2
- Cohort 1 (3-6 subjects): Cyclophosphamide 1000 mg/m^2
- Cohort 2 (3-6 subjects): Cyclophosphamide 2000 mg/m^2
- Cohort 3 (3-6 subjects): Cyclophosphamide 3000 mg/m^2
- Cohort 4 (3-6 subjects): Cyclophosphamide 4000 mg/m^2

ATO and Cyclophosphamide will be repeated every 28-42 days. Treatment will be given inpatient for the first cycle, with the option of outpatient treatment for subsequent cycles. Subjects may remain on study in the absence of disease progression or unacceptable toxicity for a maximum six cycles. Toxicity assessments will be performed continuously; DLT determination will be made based on adverse events (AEs) that occur during cycle 1 (day 1-28).

An expansion cohort of ten subjects at the maximum tolerated dose will occur at the conclusion of dose escalation.

STUDY ENDPOINTS

Primary:

- Determination of maximum tolerated dose

Secondary:

- Overall response rate (ORR), defined by: complete remission/complete remission with incomplete recovery of blood counts (CR/CRi), morphologic leukemia free state (MLFS) and partial responses (PR)
- Response/remission duration
- Overall Survival (OS)
- Event Free Survival (EFS)
- Achievement of stem cell transplant or donor lymphocyte infusion in subjects deemed candidates at study entry but unable to receive these maneuvers due to presence of active disease

TOTAL SAMPLE SIZE:

6- 60(dependent on toxicity during dose escalation phase)

SCHEDULE OF STUDY ASSESSMENTS

		ATO	Cyclo-phosphamide[I]	History/ Physical	Hematology Labs	Chemistry Labs	EKG	Screening Activities	Bone Marrow Biopsy	Response Assessment	Safety Assessment	Survival Status
Enrollment/ Screening[B]				X	X	X	X[G]	X	X[C]			
Cycle 1	Days 1-3	X		X[A]	X	X	X					
	Day 4		X	X[A]	X	X						
	Day 14			X[A]	X	X			X			
	Days 28-35			X[A]	X				X[D]	X		
Cycles 2-6[E]	Days 1-3	X		X[A & H]	X[H]	X[H]	X					
	Day 4		X	X[A]								
	Days 28-35								X[F]	X[F]		
30 Days Post Study											X	
Long-term Follow-up[J]											X[K]	X

DEFINITIONS:

History/Physical: Complete or interim medical history, ECOG performance status, toxicity assessment, concomitant medications review, complete physical exam at screening or focused physical examination for subsequent visits and vital signs

Hematology Labs: Complete blood count (includes hemoglobin, hematocrit, red blood cell count, platelet count and white blood cell count with differential)

Chemistry Labs: complete metabolic profile, including Na, K, Cal, CO2, BUN, creatinine, uric acid, glucose, magnesium, phosphorous, total protein, albumin, AST, ALT, alkaline phosphatase, chloride, LDH and total bilirubin

Screening Activities: Prothrombin time (PT) and/or international normalized ration (INR), partial thromboplastin time (PTT), urine pregnancy test to be performed no more than 14 days prior to day 1 of treatment for female subjects of childbearing potential, and echogardiogram with cardiac ejection fraction measurement as per program AML Guidelines.

Bone Marrow Biopsy: Unilateral bone marrow core and aspirate samples. Screening sample to be sent for morphological assessment, cytogenetics, flow cytometry, molecular testing, and tissue banking all as per program AML Guidelines.

Response Assessment: Investigator assessment of response using the European LeukemiaNet criteria (Dohner 2010).

Safety Assessment: Final assessment to assess safety concerns on the study protocol

FOOTNOTES:

[A] History and limited physical exam, focusing on pertitent findings

[B] Includes review of exclusion/inclusion criteria and informed consent. If enrollment and cycle 1 day 1 are ≤ 7 days apart, the history/physical and screening labs performed at enrollment do not need to be repeated on cycle 1 day 1. The screening activities must be completed within 14 days prior to starting study treatment, with the exception of the bone marrow biopsy, which may be performed within 28 days prior to the initiation of the study.

[C] Screening bone marrow biopsy must be followed by study start within 28 days or the screening bone marrow biopsy must be repeated.

[D] Recovery marrow, to be performed as early as D28, when counts have recovered to ANC ≥ 1000 and platelets ≥ 100,000, or by day 35, whichever comes first.

[E] Subsequent cycles begin 28 days after initiation of the previous cycle.

[F] Bone marrow biopsy and response assessments to be performed after each even-numbered cycle; more frequent bone marrow biopsies may occur at the investigator's discretion.

[G] Perform 3 serial EKGs; calculate QTc based on the average, after correction with the Frederica calculation

[H] Required on day 1 only

[I] With Mesna for subjects receiving ≥1000mg/m^2 Cy

[J] With exceptions for patients who die or withdraw consent, all patients will remain in follow up. All subjects will be followed at least quarterly for one year after the last study treatment, and then at least annually until death for a minimum of five years. Subsequently, annual assessments for long-term survivors will occur as long as the study is in follow-up.

[K] Safety data beyond 30 days may be reported if deemed relevant by the investigator.

1 PARTICIPATING SITES

A complete and current listing of investigators, research personnel, research facilities and other study centers (if applicable) participating in this study will be maintained throughout the duration of this study on applicable study required forms such as an *FDA Form 1572*, the *COMIRB Research Personnel Form*, and/or a *UCCC Protocol Contact List*, incorporated herein by reference.

2 INTRODUCTION

2.1 Background and Rationale

Approximately 20,000 people develop Acute Myeloid Leukemia (AML) each year, and the median age at diagnosis is 67. Those who can tolerate it are treated with intensive chemotherapy and patients deemed at high risk for relapse but otherwise fit are further treated with an allogeneic stem cell transplant. Overall about 30-40% of patients with AML can be cured; however, there is great variation in cure rates depending on the underlying biological feastures as well as the age and fitness of the patient. In patients with adverse risk biological features, only 5-10% of patients can be cured.[1]

The most common approach to disease that is refractory to front-line intensive cytoreductive chemotherapy is to attempt another regimen of intensive cytoreductive chemotherapy, which is highly toxic and often ineffective. Patients who relapse during or after consolidation chemotherapy are usually offered stem cell transplantation (SCT), but many patients, including the elderly, who constitute the majority of patients with AML, are not candidates for this intensive approach. Patients who relapse after SCT have very limited options, as few can tolerate a second SCT, and other maneuvers, such as donor lymphocytCTe infusions, are rarely effective. Thus, the majority of AML patients are ultimately faced with relapsed and refractory disease, and when they are, there are few treatment options. It is for these patients that novel approaches would be beneficial.

Aldehyde dehydrogenase 1A1 (ALDH1A1) is an enzyme that is highly expressed in $CD34^+$ hematopoietic stem cells (HSCs) and functions in part to protect HSCs from reactive aldehydes and other toxic compounds.[2,3] We have recently found that ~25% of human AML expresses low to absent levels of ALDH1A1 and many other AMLs express intermediate levels relative to the high levels of ALDH1A1 expressed in normal HSCs. In a review of public databases, $ALDH1A1^-$ AML had improved outcomes with standard AML therapy. This suggested the possibility that $ALDH1A1^-$ AML could be particularly sensitive to drugs that specifically generate toxic substrates of ALDH1A1.[4] In support of this, Kasumi-1, a model of human $ALDH1A1^-$ AML, as well as primary $ALDH1A1^-$ AML samples, were very sensitive to treatment with the reactive aldehyde 4-hydroxynonenal (4HNE), a prototypical toxic ALDH substrate.[5] As 4HNE is not clinically useful due to its short half-life and non-specific toxicity, we screened for compounds that could generate high levels of intracellular 4HNE in AML cells. We found that arsenic trioxide (ATO) was effective at generating intracellular 4HNE and inducing cell death in Kasumi-

1 cells. When ATO was combined with another toxic ALDH substrate, 4-hydroperoxycyclophosphamide (4HC, the in-vitro active metabolite of cyclophosphamide), the combination of ATO and 4-HC was even more effective in killing Kasumi-1 cells along with primary ALDH1A1- AML samples, as well as primary leukemia stem cells (LSCs) detectable in a murine/human xenotransplant model. ATO and 4-HC were also toxic to Kasumi-1 that had been engineered to express ALDH1A1 as well as ALDH1A1 expressing primary AMLs, but less so than ALDH1A1$^-$ AMLs. Our data further suggested that the mechanism of cell killing was at least in part through 4HNE adduction of critical proteins as well as DNA damage caused by both by 4HNE as well as through the effects of the active nitrogen mustard metabolite of cyclophosphamide/4HC.[6] In addition, when ALDH1A1$^-$ AML was established in immunodeficient mice, significant responses were seen with the same cyclophosphamide+ATO treatment combination to be used in this clinical trial. In contrast, normal HSCs were relatively resistant to this therapy (Gasparetto et al, Hematologica, epub March 9, 2017). These observations provide the background for our study hypothesis: Sequential treatment of patients with relapsed/refractory AML with ATO and cyclophosphamide will be effective and well-tolerated, particularly in the ALDH1A1$^-$ subset of patients.

ATO is FDA approved for the AML subtype acute promyelocytic leukemia (APL), and cyclophosphamide has been widely used for decades in the treatment of a variety of cancers as well as other diseases. The toxicity profiles and dosing ranges of both cyclophosphamide and ATO are well known. These primarily consist of cytopenias, hemorrhagic cystits, and at high doses, cardiac toxicity for cyclophosphamide, and cardiac arrhythmias and neuropathies for ATO. However, cyclophosphamide and ATO have not been used in combination, and so we will test the study hypothesis with a phase I clinical trial using cyclophosphamide and ATO at standard dose ranges; we will also perform correlative laboratory studies designed to study potential mechanisms of action and resistance to this combination.

2. 2 Arsenic Trioxide (ATO)

Mechanism of Action

ATO creates reactive oxidative species, causing DNA damage and forming adducts on DNA repair proteins, preventing cellular repair.

Pharmacokinetics and Drug Metabolism

ATO is delivered intravenously. It is immediately hydrolyzed in the blood to the active form, which is then hepatically cleared. Half-life of the active form is 10-14 hours, with peak effect immediately following infusion.

Major Adverse Events

QT prolongation, which can lead to torsade de pointes, a fatal ventricular tachycardia. Close monitoring of EKGs and electrolytes is important, as is minimizing other QT-prolonging medications. Other toxicities include peripheral neuropathies and cytopenias.

2.3 Cyclophosphamide

Mechanism of Action

Cyclophosphamide is an alkylating agent that prevents cell division bycross-linking DNA strands and decreasing DNA synthesis. Its metabolite, aldophosphamide, causes DNA adducts.

Pharmacokinetics and Drug Metabolism

Cyclophosphamide is delivered intravenously, and is metabolized in the liver to acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard. The half-life is 3-12 hours, with peak effect at 2-3 hours. Drug and metabolites are excreted in the urine.

Major Adverse Events

Hemorrhagic cystitis, alopecia, sterility, diarrhea, nausea, vomiting, mucositis, myelosuppression. Cardiotoxicity including hemorrhagic pericarditis and myocarditis can occur at very high doses, but is rare at the doses used in this study.

3 STUDY OBJECTIVES

3.1 Primary Objectives

Determine the maximum tolerated dose (MTD) and toxicity profile of the combination of cyclophosphamide and ATO in subjects with relapsed refractory AML.

3.2 Secondary Objectives

- Determine the efficacy of ATO and cyclophosphamide in this population, as defined by response rate, response duration, event-free survival (EFS) and overall survival (OS).
- Determine the number of transplant-eligible patients who are successfully bridged to stem cell transplant or donor lymphocyte infusion.

4 STUDY DESIGN, ENDPOINTS AND INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open label, phase I study of the sequential combination of ATO and cyclophosphamide in relapsed and refractory patients with AML.

4.1.1 Dosing Schema

Enrolled subjects will receive 3 consecutive days of ATO at a fixed dose of 0.15 mg/kg/d IV followed by Cyclophosphamide on day 4 as a single IV dose along

with Mesna (in subjects receiving ≥1000mg/m^2 Cy) and hydration for a maximum of 6 doses in the following dose escalation schema:

- Cohort -1 (3-6 subjects, if needed): Cyclophosphamide 500 mg/m^2
- Cohort 1 (3-6 subjects): Cyclophosphamide 1000 mg/m^2
- Cohort 2 (3-6 subjects): Cyclophosphamide 2000 mg/m^2
- Cohort 3 (3-6 subjects): Cyclophosphamide 3000 mg/m^2
- Cohort 4 (3 subjects): Cyclophosphamide 4000 mg/m^2

ATO and Cyclophosphamide will be repeated every 28 days. Treatment will be given inpatient for the first cycle, with the option of outpatient treatment for subsequent cycles. Subjects may remain on study in the absence of disease progression or unacceptable toxicity for a maximum six cycles. Toxicity assessments will be performed continuously; DLT determination will be made based on adverse events (AEs) that occur during cycle 1 (day 1-28).

4.1.2 Expansion Cohort

Once the MTD is reached, an expansion cohort of 10 additional subjects will accrue at the MTD dose level.

4.2 Study Endpoints

4.2.1 Primary Endpoint

MTD as determined by the dose limiting toxicities (DLT). MTD is defined in section 6.5.2 and DLT is defined in section 6.5.3.1.

4.2.2 Secondary Endpoints

- ORR defined by: complete remission/complete remission with incomplete recovery of blood counts (CR/CRi), morphologic leukemia free state (MLFS) and partial responses (PR)
- Response/remission duration
- OS
- EFS
- Achievement of stem cell transplant or donor lymphocyte infusion in patients deemed candidates at study entry but unable to receive these maneuvers due to presence of active disease.

5 STUDY ENROLLMENT, WITHDRAWAL AND DURATION

5.1 Selection of Study Population and Enrollment Procedures

All subjects will be screened for eligibility prior to enrollment. The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for screening and subsequent entry into the study. After the

patient has signed and dated the informed consent form, all screening procedures have been completed and clinical eligibility has been confirmed, the patient can be officially enrolled in the study. All subjects must meet the qualifications as outlined below.

5.2 Inclusion Criteria

To be eligible to participate in this study, a patient must meet the following criteria:

1. WHO-confirmed AML, other than APL, with no standard treatment options available
2. Age 18 years or older
3. Relapsed or refractory (resistant) disease, as defined by standard criteria[7]
    - **Relapsed:** Bone marrow blasts ≥5%, reappearance of blasts in the blood, or development of extramedullary disease following achievement of CR/CRi/CRp/MLFS
    - **Refractory** (**resistant**): Failure to achieve CR/CRi/MLFS in subjects who survive ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
4. >14 days since any prior therapy for AML excluding hydroxyurea
5. Willing and able to understand and voluntarily sign a written informed consent
6. Able to adhere to the study visit schedule and other protocol requirements
7. Women of childbearing potential must use an acceptable form of birth control for 28 days prior to beginning study treatment, through the duration of study treatment, and for 3 months after discontinuing study treatment.

5.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from this study:

1. New York Heart Association Class III or IV heart failure
2. Unstable angina pectoris
3. Significant uncontrolled cardiac arrhythmias, including ventricular arrhythmias, congenital long QT syndrome, symptomatic atrial fibrillation, symptomatic bradycardia, right bundle branch block plus left anterior hemiblock or bifasicular block
4. QTc >500 ms, uncorrectable by managing electrolytes and medications, using the QTcF formula in Appendix D.

5. Active acute graft vs. host disease ≥ grade 2 or active extensive chronic GVHD
6. Relapse after allogeneic stem cell transplantation prior to post-transplant day 30
7. Active central nervous system (CNS) involvement of leukemia (lumbar puncture not required to rule out CNS involvement if not suspected)
8. Uncontrolled psychiatric illness that would limit compliance with requirements
9. Pregnant or breast feeding females
10. Laboratory abnormalities:
    a. Either creatinine >2.0 mg/dL or creatinine clearance <30 mL/min
    b. Total bilirubin > 3 x institutional upper limit of normal (ULN) (unless documented Gilbert's syndrome)
    c. AST or ALT > 3 x institutional ULN, unless felt to be due to disease involvement
11. Other medical or psychiatric illness or organ dysfunction or laboratory abnormality which, in the opinion of the investigator, would compromise the subject's safety or interfere with data interpretation.

5.4 Duration of Study

All subjects will be followed at least quarterly for one year after the last study treatment, and then at least annually until death for a minimum of five years. Subsequently, annual assessments for long-term survivors will occur as long as the study is in follow-up.

6 STUDY AGENTS AND TREATMENT

6.1 Drug Administration

The drugs used in this study are standard of care drugs and therefore, any formulation, packaging, storage, supply, preparation and accountability will be in accordance with the study drug label and the institution's current pharmacy policies.

6.1.1 Premedication

Anti-emetic prophylaxis will be given as institutional standard of care prior to administration of cyclophosphamide, such as ondansetron 8 mg IV/PO and dexamethasone 20 mg IV/PO. Other anti-emetic strategies are acceptable and will be tailored to each patient.

No pre-medication regimen is required for ATO.

6.1.2 Arsenic Trioxide

Arsenic trioxide will be administered at 0.15 mg/kg/day IV over 2-3 hours in accordance with standard of care practice, daily for 3 days. The infusion duration may be increased in accordance with institutional policies if a vasomotor infusion reaction is observed. Central line is not required.

6.1.3 Cyclophosphamide and Mesna

Cyclophosphamide will be administered on day 4 in normal saline over 30 minutes to two hours, depending on the dose, and in accordance with standard of care practice. Prior to cyclophosphamide administration for all cohorts except for cohort -1, 500 cc normal saline will be given one hour before cyclophosphamide and 500 cc normal saline will be given one hour after cyclophosphamide or at provider discretion. For all cohorts except for cohort -1, MESNA in normal saline will be given at 20% of the dose of cyclophosphamide starting one hour prior to cyclophosphamide initiation, followed by 80% continuous infusion over 24 hours, started concurrently with the cyclophosphamide infusion.

6.2 Location of Treatments and Supportive Care

Subjects will be admitted to the hospital for cycle 1. Supportive care visits in the outpatient hematology clinic and BMT infusion center after study drug administration will be conducted as needed and per standard of care. Subsequent cycles of chemotherapy may be administered in the outpatient infusion center if deemed appropriate by the investigator.

6.3 Study Treatment Schedule

Potentially eligible subjects will sign consent and undergo screening procedures. Prior to the initiation of therapy subjects will be admitted to the hospital. ATO will be given daily on days 1-3, and cyclophosphamide and Mesna will be given on day 4. Bone marrow biopsies will be performed at screening, on day 14 and at the completion of cycle 1. Sequential cycles may be administered, every 28 days, with the ability to delay subsequent cycles for potential regimen-related toxicity by up to an additional 14 days. A maximum of six cycles may be administered. Treatment will continue until the occurrence of excessive toxicity, relapse, or evidence of refractory disease.

6.4 Concomitant Therapy

6.4.1 Permitted Concomitant Therapy

Transfusion of blood and blood products, antibiotics, antiemetics and other standard supportive care medications are permitted. Filgrastrim will not be routinely used, but will be considered for neutropenic subjects in the setting of an active infection and may be used at the discretion of the investigator. Antibiotics will be used for subjects with known infections or neutropenic

fevers. Hydroxyurea may be used to control blood counts throughout the duration of the study.

6.4.2 Prohibited Concomitant Therapy

Chemotherapy, immunotherapy, and radiotherapy are prohibited. Medications known to prolong the QTc should be changed to other available agents if possible.

6.5 Safety Plan

Subject safety will be assessed by reviewing AEs during planned visits and physical and laboratory examinations from the time the subject receives the first dose of study drug until 30 days after the subject's last study treatment. Tumor lysis syndrome, while unlikely, will be monitored.

6.5.1 Stopping Rules

6.5.1.1 Individual Subjects' Stopping Rules

Subjects may be terminated from the study for the following:

- Non-compliance with the study protocol
- Disease progression
- Subject decides to withdraw from the study
- Achievement of a response that allows discontinuation to proceed to transplant OR achievement of a response in the setting of a subject who does not wish to receive maintenance cycles of therapy
- Receipt of six cycles of therapy
- Related or suspected related ≥ Grade 3 AE that does not resolve or improve by day 42 of a treatment cycle (does not include hematologic toxicity if subjects are un-evaluable; see Appendix B: Definition of Hematological Toxicity)
- Related or suspected related serious adverse event (unless involving hematologic toxicity in an un-evaluable subject)
- Development of unrelated illness which compromises further participation in the study
- Investigator determines that continuation on study is no longer in the best interest of the subject or a change in the subject's condition renders them ineligible for further treatment
- Subject is lost to follow up, or withdraws consent (no further data collection or submission will be expected)
- Subject becomes pregnant
- Subject death

At termination, both concomitant medications and ongoing AEs are to be recorded, including any new AEs reported at the end of the study. Any unresolved AE at discontinuation of the study treatment should be followed until they have resolved or stabilized. Subjects may choose to stop study treatment for any reason without jeopardizing their relationship with healthcare

providers. With exceptions for patients who die or withdraw consent, all patients will remain in follow up.

6.5.1.2 Study Stopping Rules

The study will continue until the MTD is reached, the expanded cohort is enrolled, and the last subject is followed one year beyond receiving the last dose of study drug. Subsequently, subjects will be contacted annually until death for a minimum of five years. The study will be stopped early for futility if 3 or fewer patients out of the first 18 patients achieve a CR/marrow CR.

6.5.2 Dose Escalation

The trial is organized in a standard, phase I, 3+3 design. The first 3 subjects will be assigned to cohort 1. Per standard trial design, if there are 0/3 dose-limiting toxicities (DLT) in this cohort, the next three subjects will be assigned to cohort 2. This will continue until cohort 4. If a cohort has >1 DLT, the next highest cohort with ≤1/6 DLTs will be considered the MTD. If there is >1 DLT event in cohort 1, dose de-escalation to cohort -1 will occur (see Section 5.1.1. Dosing Schema). Once the MTD is established a 10-subject dose expansion will occur to obtain further experience with the AE profile of this regimen prior to a phase 2 study.

6.5.3 Dose Delays and Modification

Sequential cycles may be delayed by up to 14 days; if a greater than 14-day delay is required for toxicity-related concerns, the subject will come off study.

Subjects who experience a ≥ Grade 3 non-hematologic AE can have treatment interrupted for up to 14 days from the expected initiation of the next cycle and can be restarted at the original dose if the abnormality returns to baseline or ≤ grade 1.

Subjects who are evaluable for hematologic toxicity at original screening baseline and do not meet its criteria by day 28 of any given treatment cycle (See Appendix B: Definitions of Hematological Toxicity) may proceed with the treatment cycle. Subjects who were originally evaluable for hematologic toxicity that do meet criteria for hematologic toxicity by day 28 of a treatment cycle may delay initiation of the next cycle for 14 days; if they continue to meet criteria for hematological toxicity they must discontinue the study. If they do not meet criteria for hematologic toxicity by day 42 of a treatment cycle, they may resume treatment. Subjects who were un-evaluable at baseline for hematologic toxicity will be treated on schedule, regardless of count recovery, until they achieve a CR, CRi or MLFS (see Appendix A). After subjects who were un-evaluable for hematologic toxicity at baseline achieve a response, they cannot continue with subsequent cycles of treatment until they no longer meet criteria for hematologic toxicity by day 42 of a given treatment cycle. These subjects will be removed from the study if they continue to meet criteria for hematologic toxicity after day 42 of a treatment cycle.

In the event of QTc prolongation >500 msec, ATO should be held together with any medication known to prolong the QTc interval and electrolytes should be repeated as clinically indicated. The time between discontinuing ATO and normalization of the QTc interval may be several days; doses of ATO should not be made up if missed, and should not be given outside of days 1-3 of a cycle. Once the QTc is ≤460 msec, resume ATO at 0.075 mg/Kg (50%) and continue to monitor QTc. In subsequent cycles, if no further prolongation occurs, resume at full dose.

Prior to the initiation of each cycle, creatinine must be <2.0 mg/dL or creatinine clearance >30 mL/min, total bilirubin must be <3 x institutional ULN (unless documented Gilbert's syndrome), and AST and ALT must be < 3 x institutional ULN, unless felt to be due to disease involvement. The QTc must be ≤500 msec.

Subjects who have disease progression, disease relapse after achieving a response, or those who experience excessive toxicity, as determined by the investigator, will be removed from the study. Subjects who experience a response that allows them to proceed to stem cell transplantation or donor lymphocyte infusion may elect to discontinue the study. Subjects may receive no more than six cycles of therapy on study; cycles may continue past the time of a response as a maintenance strategy.

6.5.3.1 Dose-limiting toxicity (DLT) definition

DLT events will be assessed during cycle 1.

Grade ≥ 3 non-hematologic toxicity, excluding grade ≥ 3 electrolyte or AST/ALT abnormalities that return to baseline within 7 days, will be considered DLT. Grade 4 AST/ALT abnormalities will be considered DLT regardless of the timing of resolution.

QTc prolongation > 500 msec will require repeat testing and correction of reversible causes, such as electrolyte abnormalities or concomitant QTc-prolonging medications. This will be considered a DLT if not related to correctable electrolyte abnormality.

In subjects in whom hematologic toxicity is evaluable, prolonged myelosuppression during the first cycle that lasts longer than 42 days after initiating cycle 1, defined as ANC < 500/μL or platelet count < 10 x 10^9/L with a bone marrow that shows <5% blasts with no evidence of disease, is defined as DLT.

All subjects who receive at least one dose of study drug will be considered eligible for evaluation of DLT.

7 STUDY ASSESSMENTS AND ACTIVITIES

7.1 Schedule of Study Assessments

The time each assessment is performed relative to treatment is shown in the Schedule of Study Assessments..

7.2 Study Activities

7.2.1 Screening Period

Written consent must be obtained before performing any study-specific screening activities. The screening activities outlined in the Schedule of Study Assessments must be completed within 14 days prior to starting study treatment, with the exception of the bone marrow biopsy, which may be performed within 28 days prior to the initiation of study treatment.

7.2.2 Treatment Schedule

Subjects will receive study treatment as detailed in Section 6.1, and assessments will be performed as outlined in the Schedule of Study Assessments. A maximum of six cycles may be administered. Treatment will continue until the occurrence of excessive toxicity, relapse or evidence of refractory disease.

7.2.3 Safety Follow-Up Visit

Safety data will be collected for 30 days after the last study treatment. Safety data beyond 30 days may be reported if deemed relevant by the investigator.

7.2.4 Study Assessments

7.2.4.1 Vital Signs and ECOG Performance Status

All vital signs (blood pressure, pulse, respiratory rate, temperature, oxygen saturation) and ECOG performance status grade (See Appendix C) will be measured during screening and during study visits as specified in the Schedule of Study Assessments.

7.2.4.2 Physical Examination

A complete physical examination, including measurement of height and weight, must be performed during screening (minimum 14 days before beginning study treatment); a more limited exam, focusing on pertitent findings, is permitted at later study time points as specified in the Schedule of Study Assessments.

7.2.4.3 Adverse Events

All AEs will be recorded from the time the informed consent is obtained until 30 days after the last dose of study treatment. In addition, all non-serious AEs

that occur before study drug administration but after informed consent is obtained and are associated with protocol-specific procedures (eg: AEs associated with blood draws performed only for protocol purposes) will be reported. Subjects who experience a non-serious AE considered to be possibly or definitely related to study treatment will be followed until all significant changes have stabilized or returned to baseline, the subject withdraws consent, or death. All SAEs will be followed as described, regardless of their relationship to study treatment. Safety data beyond 30 days may be reported if it is deemed relevant by the investigators.

7.2.4.4 Laboratory Assessments

The following laboratory assessments will be performed at screening and at study visits throughout the course of the subject's participation in the trial. See the Schedule of Study Assessments for specific timing.

- Bone Marrow Examinations: Include core biopsies and aspirations for morphologic assessments and flow cytometry. Initial screening bone marrow aspirate, and selected subsequent aspirates, will be evaluated for cytogenetic and molecular testing.
- Hematology: Hemoglobin, hematocrit, red blood cell count, total white blood cell count with differential, platelet count.
- Chemistries: Albumin, alkaline phosphatase, ALT, AST, bicarbonate (CO2), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, sodium, magnesium, phosphorus, total bilirubin, total protein, LDH.
- Coagulation: Prothrombin time (PT) and/or international normalized ration (INR), partial thromboplastin time (PTT)
- Urine pregnancy test for female subjects of childbearing potential

7.2.4.5 Disease Assessments and Response Criteria

Subjects will have baseline disease assessments by means of a bone marrow examination, which will be repeated on cycle 1 day 14, end of cycle 1, and at the end of each subsequent even-numbered cycle. In addition, subjects will undergo follow-up disease assessments by means of a bone marrow examination at any sign of progressive disease, or as dictated by subsequent bone marrow transplant.

AML response assessments will be based on the LeukemiaNet guidelines[7] (See Appendix A: Definitions of Disease Responses). Briefly, a CR requires <5% bone marrow blasts with an absolute neutrophil count >1.0x10^9/L, platelet count >100x10^9/L and independence from red blood cell transfusions. A CR with incomplete recovery (CRi) requires all the CR criteria with an allowance for residual neutropenia or thrombocytopenia. A morphologic leukemia-free state (MLFS) requires bone marrow blasts <5% without hematologic recovery, and a PR requires all the hematologic criteria of a CR with the exception of a decrease in bone marrow blasts to 5%-25% and a decrease in pre-treatment blast percentage by ≥50%.

7.2.4.6 Correlative Assessments

All bone marrow specimens will be banked for future correlative testing in the University of Colorado Hematological Malignancies Tissue Bank.

7.2.4.7 Cardiac Assessments

3 serial EKGs will be performed at screening and single EKGs will be performed for subsequent visits. The QTc will be calculated based on the average, after correction with the Frederica calculation (see appendix D). Echogardiograms with cardiac ejection fraction measurement will be performed per program AML Guidelines. Please see the Schedule of Study Assessments for specific timing of assessments.

8 SAFETY ASSESSMENTS

AEs and SAEs will be reviewed on an ongoing basis to identify safety concerns, and the investigators can discontinue the study if excessive toxicity is observed.

8.1 Definitions

8.1.1 Definition of Adverse Event

According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (Federal Register. 1997;62(90):25691-25709), Title 21 of the US Code of Federal Regulation (CFR) 312.32, and Investigational New Drug (IND) Safety Reports, an AE is defined as follows:

> "Any untoward medical occurrence in a subject or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any untoward medical occurrence regardless of relationship to the medicinal (investigational) product."

8.1.2 Definition of Serious Adverse Event (SAE)

An adverse event will be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death.

Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	AE that required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating:	AE resulted in substantial and permanent disruption of the patient's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

8.1.3 Definition of an Unanticipated Problem (UAP)

Any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

8.2 Pregnancy

Pregnant subjects will not be included in the trial. If a subject becomes pregnant during the course of the trial, the subject will be withdrawn from the trial and followed until the completion of pregnancy. Pregnancies will not be reported on a pregnancy report form or captured as an SAE, however, they should be documented as an unintended pregnancy per CTCAE.

8.3 Relationship of the Adverse Event to Treatment

The investigator will evaluate the relationship of each AE to study treatment using the following criteria:

Fatal:	AE resulted in death.

Unrelated:	Another cause of the AE is more plausible, a temporal sequence cannot be established with the onset of the AE and administration of the treatment, or a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of treatment, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when treatment is one of several biologically plausible AE causes.
Definitely Related:	The AE is clearly related to use of the treatment.

8.4 Recording Adverse Events

8.4.1 Information to be collected

Whether considered related or not, during the reporting period, all SAEs and non-serious AEs are to be recorded on an AE case report form (CRF). Subjects who terminate the study early will be followed for 30 days after the last dose of study treatment for AEs. Subjects who experience a non-serious AE considered to be possibly or definitely related to study treatment will be followed until all significant changes have returned to baseline or stabilized, the subject dies, or the subject withdraws consent. All SAEs will be followed as described, regardless of their relationship to study treatment. During the reporting period, the following information should be collected:

- Description of the AE, including onset and resolution dates
- Relationship to treatment plan, treatment or other causality
- Action taken, including use of concomitant medications
- If the event is serious, note all criteria that apply

Subjects will be evaluated for AEs at each visit with the NCI-CTCAE version 4.0 used as a guide for the grading of severity. All adverse clinical experiences, whether observed by the investigators or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study, and the subjects' outcomes. The investigators will evaluate each AE for its severity and its relationship to the study. The investigators will appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigators will provide details about the action taken with respect to the study and the subjects' outcomes.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an AE unless an intervention is required (repeat testing to confirm the abnormality is not considered an intervention), the laboratory abnormality results in a SAE, or the AE results in study termination

or interruption/discontinuation of study treatment. Medical conditions present at screening (i.e.: before the study treatment is administered) are not SAEs and will not be recorded on SAE pages of the case report forms. These medical conditions will be adequately documented in the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods will be reported and recorded as AEs.

8.4.2 Recording Serious Adverse Events

- For SAEs, the primary event will be recorded on both an AE CRF and an SAE Report Form; events occurring as a result of the SAE will be described on the SAE Report Form in the narrative description of the case.
- Death is an outcome of an event. The event that resulted in the death will be recorded and reported on both an SAE Report Form and on an adverse event CRF.
- For hospitalizations or surgical or diagnostic procedures, the illness leading to the hospitalization or surgical or diagnostic procedure will be recorded as the SAE, not the procedure itself. The procedure will be captured in the narrative as part of the action taken in response to the illness. Planned surgeries or procedures will not be considered SAEs.

8.5 Reporting Adverse Events

8.5.1 Reporting to the Food and Drug Administration (FDA)

If the FDA determines an IND is necessary, the conduct of the study will comply with all FDA safety reporting requirements. Additionally, in accordance with 21 CFR 312.33 annual reports will be provided to the FDA within 60 days of the IND anniversary date.

8.5.1.1 Format for Adverse Event Reporting

All AE reports will include the subject's number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to the study (fatal relationship, definitely related, possibly related, unrelated), date and time of administration of test medications and all concomitant medications, and subsequent medical treatment provided.

8.5.2 Reporting to the IRB

The Principal Investigator (PI) will notify the IRB of a SAE according to institutional policy.

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected

- Any new finding from tests in laboratory animals in ongoing laboratory studies that suggests a previously unknown significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

The PI will notify the IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The PI must keep copies of all AE information, including correspondence with and the IRB.

8.5.3 Non-serious Adverse Event Reporting Period

Events that occur before informed consent is obtained should be documented as medical history. All non-serious AEs that occur after informed consent is obtained and up to 30 days after administration of the last study treatment will be reported. All non-serious AEs that occur subsequent to the safety follow-up visit and are considered to be pertinent in the opinion of the investigators may be reported.

8.5.4 SAE Reporting Period

All SAEs that occur after informed consent is obtained will be reported up to 30 days after administration of the last study treatment, regardless of relationship to study treatment. All SAEs that occur beyond 30 days after the administration of the last study treatment and are considered pertinent, in the opinion of the investigators, may be reported. Within 24 hours of observing or learning of an SAE, investigators are to report the event, regardless of the relationship of the event to the treatment plan regimen. For initial SAE reports, available case details are to be recorded on an SAE Report Form. At a minimum, the following should be included:

- Subject number and initials
- Date of event onset
- Description of the event
- Study treatment

8.5.5 Reporting a UAP

The study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements, discussed herein.

Events that meet the definition of an unanticipated problem must be reported to COMIRB within 5 days of their occurrence.

Investigators must report the following to COMIRB within 5 days:

- An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, psychological events, drug errors).

- Adverse events which in the opinion of the principal investigator are both unexpected and probably or definitely related to the intervention/ drug or device.
- An unforeseen development that potentially increases the likelihood of harm to participants or others in the future.
- Information that indicates a change to the risks or potential benefits of the research.

Please refer to COMIRB's guidelines for further information regarding submission requirements.

9 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The trial is organized in a standard, phase I, 3+3 design. The first 3 subjects will be assigned to cohort 1. Per standard trial design, if there are 0/3 dose-limiting toxicities (DLT) in this cohort, the next three subjects will be assigned to cohort 2. This will continue until cohort 4. If a cohort has >1 DLT, the next highest cohort with ≤1/6 DLTs will be considered the MTD. If there is >1 DLT event in cohort 1, dose de-escalation to cohort -1 will occur (see Section 5.1.1. Dosing Schema). Once the MTD is established a 10-subject dose expansion will occur to obtain further experience with the AE profile of this regimen prior to a phase 2 study. Summary statistics will be used for the efficacy ednpoints such as ORR, OS and duration of response with 95% exact confidence intervals provided. Adverse Events including type and severity will be summarized for each treatment cohort and the dose expansion cohort at the end of the study. Dropouts will be analyzed under an intent to treat paradigm; that is, all dropouts will be included in the final statistical analysis. In the event that the dropout rate exceeds 33%, if the study sponsor wishes to enroll additional subjects, a modification of the statistical analysis will be required. Additional subjects will not be included after data analysis has commenced."

10 STUDY OVERSIGHT – QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

10.1 Study Auditing

The investigators, or a designated member of the investigators' staff, must be available at some time during audits to review data, resolve any queries and to allow direct access to the subjects' records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. In addition, independent audits will be conducted by the DSMC at the University of Colorado Cancer Center (CU Cancer Center) to ensure monitoring practices

are performed consistently (across all participating sites, if applicable) and that monitors are following the CMP, as defined below.

10.2 Monitoring and Oversight

The Principal Investigator (PI) will be responsible for monitoring the trial per the clinical monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the DSMC at the CU Cancer Center. The DSMC is responsible for ensuring data quality and subject safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at weekly disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The PI will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six-month report by the DSMC will be provided to the PI in a DSMC review letter. The PI will submit to the IRB of record at the time of continuing review.

10.3 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in

compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.4 Data Management

The database that will be utilized for data collection and storage will be OnCore. The PI and study staff will adhere to the reporting requirements of the data to the institutional IRB.

To ensure the privacy and confidentiality of data for this protocol, the data will be stored on a restricted access location on our institution's server. Access to the project directory containing the data will be limited to the investigators and research staff. Information about data security awareness is promoted through user training and education and supplemented by policies and procedures. Password protection will be used for all transactions that involve viewing, editing, and analyzing the data or that provide access to data fields derived from the original source documents.

The investigator maintains the confidentiality standards of each patient enrolled in the study through the assignment of a unique subject identification number that de-identifies the study information from the patient's health information. The key linking subject code to the patient is kept in an additional secure restricted access location on our institution's server that is only accessible to the study staff. No identifying information, such as the patient's name, will be included in the data sets used for reporting the data. Patient medical information obtained for the study is confidential, and may only be disclosed to third parties as permitted in the informed consent form signed by the subject unless permitted or required by law.

10.5 Training of study site personnel

The PI will ensure that study staff are adequately trained on any procedures they will be performing and tasks which they are delegated. The PI will also train study investigators enrolling patients on the details of the protocol (including, but not limited to, recognition of AEs, AE management, eCRFs, study documentation and informed consent).

11 ETHICS / PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The PI will ensure that this study is conducted in full conformity with regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56. ICH E6 may also be followed to the extent it has been adopted by and is in accordance with FDA regulations.

11.2 Institutional Review Board

The protocol, informed consent form(s), Investigator's Brochures/Package Inserts, recruitment materials (i.e., advertisements) and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled.

The IRB will be informed regarding the progress of the study and any changes made to the protocol, and will be updated at least once a year. Any amendment to this protocol must be agreed to by the investigators and written verification of IRB approval will be obtained before any amendment is implemented. All changes to the consent form will be reviewed and approved by COMIRB with a determination regarding whether previously consented subjects need to be re-consented.

The investigators are also responsible for notifying the IRB of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

11.3 Informed Consent Process

11.3.1 Subject Information Documents and Informed Consent Form

Consent forms describing in detail the study agent, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering study procedures.

11.3.2 Consent Procedures and Documentation

The informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a

verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study.

Subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading subjects. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

11.4 Record of Administration

Accurate records will be kept in the source documents of all drug administration, including prescribing and dosing. The investigators must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy (includes copies of CRF's and source documents such as: hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; SAE reports; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches, photographic negatives, microfilm, or magnetic media; x-rays; subject files; records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents) be retained for as long as needed to comply with national and international regulations. By signing the protocol, the investigators agree to adhere to the document/records retention procedures.

11.5 Data Analysis

Data will be reviewed on an ongoing basis in order to determine appropriate subject enrollment, and analyzed at the time of study completion.

11.6 Subject and Data Confidentiality

The subject's medical information obtained in this study is confidential, and disclosure to third parties is prohibited, unless the subject allows information to be shared with his or her personal physician or other appropriate medical personnel responsible for his or her welfare. In compliance with United States federal regulations, data generated by this study will be available for inspection upon request by the IRB, who may review and/or copy relevant medical records

in accordance with the law. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the investigators to obtain such permission in writing from the appropriate individual.

12 REFERENCES

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APPENDIX A

Definition of Disease Responses[7]

Table 5. Response criteria in AML

Category	Definition
Complete remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 × 10^9/L (1000/μL); platelet count > 100 × 10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)†	All CR criteria except for residual neutropenia (< 1.0 × 10^9/L [1000/μL]) or thrombocytopenia (< 100 × 10^9/L [100 000/μL])
Morphologic leukemia-free state‡	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)§	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)‖	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

Definitions of response criteria are based primarily on those given by Cheson et al.[2]

*All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

†The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

‡This category may be useful in the clinical development of novel agents within phase 1 clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

§Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.[112-115]

‖As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 10^4 copies of *ABL1* in accordance with standardized criteria, transcript levels below 12 to 10 copies appear to be predictive for long-term remission.[108-110]

¶In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

APPENDIX B

Definition of Hematologic Toxicity

- For patients with ANC ≥ 500/mm^3 at baseline: Persistent neutropenia (ANC < 500/mm^3) by day 42 of a cycle without evidence of disease progression on bone marrow examination
- For patients with ANC < 500/mm^3 at baseline: Will not be evaluable for neutrophil toxicity. However, the time course and depth of neutropenia will be examined in all patients to see if any trend can be seen related to study drug administration.
- For patients with non-transfused platelet count of >20,000/mm^3 at baseline: Persistent thrombocytopenia (platelet count <20,000/mm^3 or requiring platelet transfusion by day 42 of a cycle) without evidence of progressive disease on bone marrow examination
- For patients with thrombocytopenia (platelet count <20,000/mm^3 or platelet transfusion dependent) at baseline: Will not be evaluable for platelet toxicity. However, time course and depth of thrombocytopenia will be examined in all patients to see if any trend can be seen related to study drug administration.
- Recovery of neutrophils and platelets is defined as ANC > 500/mm^3 and platelets >20,000/m^3.

APPENDIX C

ECOG Performance Status Scale

SCORE	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 house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only 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.
5	Dead

Appendix D

QTc Formula

The corrected QT interval (QTc) is calculated using the following formula (Fridericia)
$QTc = QT/\sqrt[3]{RR}$

where QTc is the corrected QT interval, QT is the measured QT interval and RR is the measured RR interval (all measurements in seconds).

COMIRB
APPROVED
For Use
17-Oct-2018
16-Oct-2019

Principal Investigator: **Daniel A. Pollyea, MD**
COMIRB No: **17-0754**
Version Date: **10.30.2018**

Study Title: **Phase I Trial of Arsenic Trioxide with Cyclophosphamide in Patients with Relapsed/ Refractory Acute Myeloid Leukemia**

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about a combination of two drugs and how well it might work to treat acute myeloid leukemia (AML). The two drugs are called arsenic trioxide (ATO) and cyclophosphamide. Both drugs are thought to work by generating toxic molecules that normal cells can process, but some cancer cells cannot. This leads to a build-up of the toxic substances in the cancer cells which causes cell damage and death. This study is looking at how safe a constant dose of ATO combined with an increasing dose of cyclophosphamide is, to determine the maximum safe dose of the two drugs in treating your type of cancer.

You are being asked to be in this research study because you have been diagnosed with AML that has either relapsed (come back after remission from initial treatment) or is refractory (your cancer did not go into remission with initial treatment). ATO is approved by the U.S. Food and Drug Administration (FDA) to treat a subtype of AML called acute promyelocytic leukemia (APL), but is not approved to treat your specific type of cancer. Cyclophosphamide is approved by the FDA to treat several different types of cancer, including other blood cancers, but is not approved to treat your specific type of cancer. ATO and cyclophosphamide have not yet been studied in combination. Through the rest of this consent form, ATO and cyclophosphamide will be called the "study drugs" when referenced together.

Other people in this study

Up to 60 people from your area will participate in the study.

Initials_____

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

The next section of this form lists what will be expected of you if you join this study.

Study Procedures

While you are taking part in this study, some of the tests and procedures are the same type that would be performed as part of your regular cancer care even if you did not join the study. Some of the tests and procedures are required only for the study, and are identified below as "**research**" procedures.

The first tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

Screening Visit *(within 28 days before treatment)*

- Informed consent – **research**
- Review of medical history
- Complete physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review
- Vital signs
- Blood draw for routine tests, including:
    - Hematology
    - Chemistry (including magnesium, phosphorus and lactate dehydrogenase)
    - Coagulation tests (including PT and PTT/INR)
- Urine pregnancy test (within 14 days prior to starting treatment for women who can become pregnant)
- Electrocardiogram (EKG)
- Echocardiogram
- Bone marrow biopsy

Cycle 1 – Days 1-3 *(each cycle is 28 days)*

- History and limited physical exam
- Performance status
- Toxicity assessment

Initials_____

- Concomitant medications review
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and lactate dehydrogenase)
- EKG
- Receive ATO (IV) – **research**

Cycle 1 – Day 4

- History and limited physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and lactate dehydrogenase)
- Receive cyclophosphamide (IV) – **research**
  If your dose of cyclophosphamide is greater than 1000 mg/m^2, you will also receive the drug mesna (IV). Mesna is used to reduce the risk of inflammation in your bladder and blood in the urine. The mesna is also a **research** procedure.

Cycle 1 – Day 14

- History and limited physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and lactate dehydrogenase)
- Bone marrow biopsy

Cycle 1 – Day 28-35

- History and limited physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review

Initials_____

- Vital signs
- Blood draw for routine tests, including:
  - Hematology
- Bone marrow biopsy
- Response assessment

Cycles 2-6 – Days 1-3

- History and limited physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and lactate dehydrogenase)
- EKG
- Receive ATO (IV) – **research**

In Cycles 2-6, all procedures will be done on Day 1. Only the ATO and EKG will be done on days 2 and 3.

Cycles 2-6 – Days 4

- History and limited physical exam
- Performance status
- Toxicity assessment
- Concomitant medications review
- Vital signs
- Receive cyclophosphamide (IV) – **research**

If your dose of cyclophosphamide is greater than 1000 mg/m^2, you will also receive the drug mesna (IV). Mesna is used to reduce the risk of inflammation in your bladder and blood in the urine. The mesna is also a **research** procedure.

Cycles 2-6 – Days 28-35

- Bone marrow biopsy
- Response assessment

These will only be done on even-numbered cycles, unless your study doctor feels that they should be done more frequently.

Follow-up Visit *(30 days after end of treatment)*

Initials_____

- Safety assessment

The study team will continue to follow up with you once every three months for one year after study treatment, and then at least one time per year for at least five years. Long-term follow up will continue every year as long as the study is open.

How long will I be in the study?

You may continue receiving study drugs for up to 6 cycles or until your doctor determines that you should stop receiving the study drug regimen due to side effects, progression of your disease, or until you decide to stop participating in the study.

You will be followed long term for disease status and survival information.

What are the possible discomforts or risks?

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks of the Study Drugs

Arsenic Trioxide (ATO)

Common (in more than 20 out of 100 people)

- Fatigue
- Fever
- Swelling
- A sudden feeling of cold that may include shivering and sweating
- Chest pain
- Nausea
- Loss of appetite
- Diarrhea, or loose or watery stools
- Vomiting
- Pain in the belly
- Sore throat
- Constipation
- Changes in blood tests, such as low calcium, low magnesium, and increased blood sugar
- Headache
- Trouble falling asleep or staying asleep

Initials_____

- Tingling in the hands or feet
- Dizziness
- Cough
- Trouble breathing
- Nose bleeds
- Low oxygen in the blood
- Inflammation of the skin, which may be red and painful
- Itchy skin
- Increased heart rate and changes in heart rate that may be serious
- Joint, muscle, or bone pain
- Increased number of white blood cells
- Low blood pressure
- Anxiety
- Vaginal bleeding

Less common (in 5 to 20 out of 100 people)

- Generalized pain
- Pain, swelling, or redness at the infusion site
- Weakness
- Bleeding
- Weight gain
- Wight loss
- Upset stomach
- Blistering or peeling of the skin in the mouth, which may be painful and make it difficult to eat, drink, or speak
- Inability to control bowel movements
- Bleeding in the GI tract or gut
- Dry mouth
- Tender or swollen belly
- Changes in liver function tests, which may indicate liver damage
- Changes in blood tests, including high calcium and low blood sugar
- Tremors or convulsions
- Feeling tired or drowsy
- Fluid in the lungs
- Runny nose
- Wheezing or rattling sounds when breathing
- Coughing up blood
- Fast breathing when at rest
- Discolored skin from bruises underneath the skin
- Dry skin

Initials_____

- Red skin
- Increased sweating
- Swelling in the face
- Night sweats
- Small red or purple spots, which may look like a rash
- Darkening of the skin like a suntan
- Rash with round, red, itchy welts
- Heart palpitations or other abnormal changes to heartrate
- Inflammation of the sinuses
- Increased risk of infections
- Back pain, neck pain, or pain in the arms or legs
- Decreased number of red blood cells (anemia), which may cause you to feel weak or faint
- Decreased number of platelets in the blood, which makes it more difficult for blood to clot
- Decreased number of white blood cells, which may make it more difficult for your body to fight infections
- Abnormal blood clots
- Abnormal swelling of the lymph nodes
- Flushed or pale skin
- High blood pressure
- Depression
- Irritated or dry eyes
- Blurred vision
- Kidney damage
- Ear ache or ringing in the ears

Rare (in fewer than 5 out of 100 people)

- An allergic reaction to the drug, which may cause fever, drop in blood pressure, increase in heart rate, and difficulty breathing. This can be serious.
- Acidosis, which may indicate liver or kidney damage
- Coma
- Peeling of the skin, which may be very painful
- Swelling of the eyelids
- Sepsis, a life-threatening condition in which a bacterial infection spreads to the blood.
- Feeling agitated or confused
- Decrease in urine production
- Inability to control the bladder.

Initials_____

Cyclophosphamide

Common side effects of cyclophosphamide include:

- Low white blood cell count, which may lower your ability to right infections
- Nausea
- Vomiting
- Loss of appetite
- Abdominal discomfort or pain
- Thinning or loss of hair

Less common, but serious side effects:

- Decreased bone marrow function, which may reduce the number of white blood cells, platelets, and red blood cells. This can hinder your ability to fight infections, reduce the ability of your blood to clot, and may make you feel tired or weak. In extreme cases, your immune system may not work properly, which can lead to serious and sometimes fatal infections, particularly if bacteria gets into your blood.
- Inflammation of the bladder and urinary tract which may be accompanied by bleeding. If you see blood in your urine, tell your study doctor immediately.
- Inflammation of the heart and build up of fluid around the heart. There is a risk of developing congestive heart failure. There is also a risk of developing an abnormal heart rhythm.
- Inflammation of the lungs, which may progress to respiratory failure in extreme cases. This side effect may sometimes occur months or years after treatment with cyclophosphamide.
- Developing a different type of cancer, including urinary tract cancer, other types of bone marrow cancer, cancer of the lymph nodes, thyroid cancer, or soft tissue cancers.
- Veno-occlusive liver disease, in which blood flow is blocked in small blood vessels in the liver. If not treated, this can be fatal.
- Infertility in both men and women.
- Lowered ability for wound healing.
- Increased sodium in the blood, which may be fatal if not treated.

Mesna

Common (in more than 20 out of 100 people)

- Nausea
- Vomiting
- Constipation
- Decreased white blood cell count, which may lower your ability to fight infections

Initials_____

- Fatigue
- Fever

Less common (in 5 to 20 out of 100 people)

- Loss of appetite
- Decreased platelet count in the blood, which lowers your ability to form blood clots
- Low red blood cell count (anemia), which may cause you to feel tired or weak
- Feeling weak or unusual loss of energy
- Generalized pain, or pain in the abdomen, chest, or back
- Hair thinning or hair loss
- Trouble breathing
- Low potassium in the blood
- Diarrhea
- Dizziness
- Headache
- Excessive sweating
- Blood in the urine
- Redness or swelling at the infusion site
- Swelling in the hands or feet
- Feeling drowsy or tired
- Anxiety
- Confusion

Rare (in fewer than 5 out of 100 people)

- Swelling in the face
- Trouble falling asleep or staying asleep
- Coughing
- Upset stomach
- Pale or flushed skin
- Dehydration
- Allergic reaction to the drug, can be serious and may cause fever, decreased blood pressure, increased heart rate, kidney damage, lack of oxygen in the blood, blood in the urine, nausea, vomiting, and pain
- Rash, including a severe form of rash called Stevens-Johnson syndrome or toxic epidermal necrosis. In the most extreme forms of this reaction, the skin may peel off and be very painful, and this can be life-threatening. Contact your study doctor immediately if you see any unusual rash.

Initials_____

Other Risks of the Study Procedures

Blood tests

Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to: fainting, bleeding, bruising, discomfort, dizziness, infection and/ or pain at the puncture site.

Having an IV inserted in your vein

In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about four or five hours.

Bone marrow biopsy

In this study we will take four samples of bone marrow from your pelvic bone. Before we take each sample, we will give you some numbing medication on the skin outside your pelvic bone (on your hip). After your skin is numb, we will push a special needle into the center of your pelvic bone. Then, we will draw the bone marrow up into the syringe. When we do this, you will have a pulling feeling as the marrow leaves the bone and goes into the syringe. The area around the bone will be sore for a few days.

There is a very small chance that you will be allergic to the numbing medicine. There is also a very small chance that you could bleed or develop an infection.

Electrocardiogram (EKG)

An electrocardiogram (EKG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an EKG from the electrodes or the gel that is used.

Echocardiogram (ECHO)

An echocardiogram (ECHO) is a noninvasive scan of the heart using sound waves. This test will be used to see how well your heart pumps blood. This test has no known risks or side effects.

Risks Associated with Pregnancy

Both of the study drugs ATO and cyclophosphamide are known to cause severe life-threatening birth defects based on the way the drugs work and reports of effects

Initials_____

in pregnant patients and animals. If ATO or cyclophosphamide is taken during pregnancy, they may cause birth defects or death to an unborn baby. Females must not become pregnant while taking ATO or cyclophosphamide.

Both ATO and cyclophosphamide are also present in breast milk and can be transferred to infants by nursing mothers. This can reduce bone marrow function in infants and cause serious and life-threatening side effects in nursing babies.

Risk of Loss of Confidentiality

There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the study drugs and how they work together to treat your type of cancer. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with another experimental therapy.
- You may choose to receive treatment with another approved therapy.
- You may choose to receive comfort/ palliative care.
- You could also choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

The Cancer League of Colorado and the University of Colorado Cancer Center are providing grants of funding support for this research. Dr. Daniel Pollyea is the Sponsor- Investigator of this study. The research grants will pay for the drugs used in this study.

Initials_____

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

You and/ or your health insurance may be billed for the costs of medical care during this study, if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or if you do not have insurance, these costs will be your responsibility.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Pollyea immediately. His phone number is 720-848-8084.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Initials_____

Who do I call if I have questions?

The researcher carrying out this study is Daniel A. Pollyea, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Pollyea at 720-848-8084. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Pollyea with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This Web site will not include information that can identify you. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Initials_____

Daniel A. Pollyea, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- The Cancer League of Colorado and the University of Colorado Cancer Center, organizations who are providing grants of funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Tissue samples and the data with the samples.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens

Initials_____

collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Subject Signature:_____Date: _____

Subject Print Name:_____

Consent form explained by:_____ Date: _____

Print Name: _____

---------- ***Use Only if Applicable*** ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Witness Signature:_____ Date:_____

Witness Print Name: _____

Initials_____

University of Colorado Cancer Center

A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTEF

UCCC Informed Consent Process Documentation

COMIRB# _____ Patient Initials _____ Subject Number _____

Type of ICF (i.e. screening, main, optional) _____

Version date:_____IRB Approval date: _____
(CIRB = protocol version) (CIRB = ICF version date)

The clinical investigator or trained delegate has:

Date	Initials	
		Thoroughly reviewed the study treatments, procedures, risks, schedules and expenses with the patient and/or legal guardian.
		Provided adequate opportunity to read the IRB approved consent and HIPAA form.
		Provided adequate opportunity to consider all options.
		Exchanged information and responded to questions.
		Verified understanding of this information.
		Obtained voluntary agreement to participate in the clinical trial.
		Verified the date of signature on the consent document. Consent was obtained before the subject began participation in the study.
		Provided the patient and/or legal guardian with a copy of the consent document that was given to subject to obtain consent.
		Provided the patient and/or legal guardian with the CCTO Internal Patient Card (If Applicable). If N/A, write N/A next to initials.
		Retained the original signed consent document in the study records.
		This consent form has been sent to Health InforMatics to be added to the participant's medical chart.