Clinical Protocol

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Official Title: A Phase II Study of the Efficacy and Pharmacogenomics of Cladribine-based Salvage Chemotherapy in Patients With Relapse/Refractory and Secondary Acute Myeloid Leukemia (AML) and High Risk Myelodysplastic Syndrome (MDS)

NCT03150004

CLINICAL STUDY PROTOCOL

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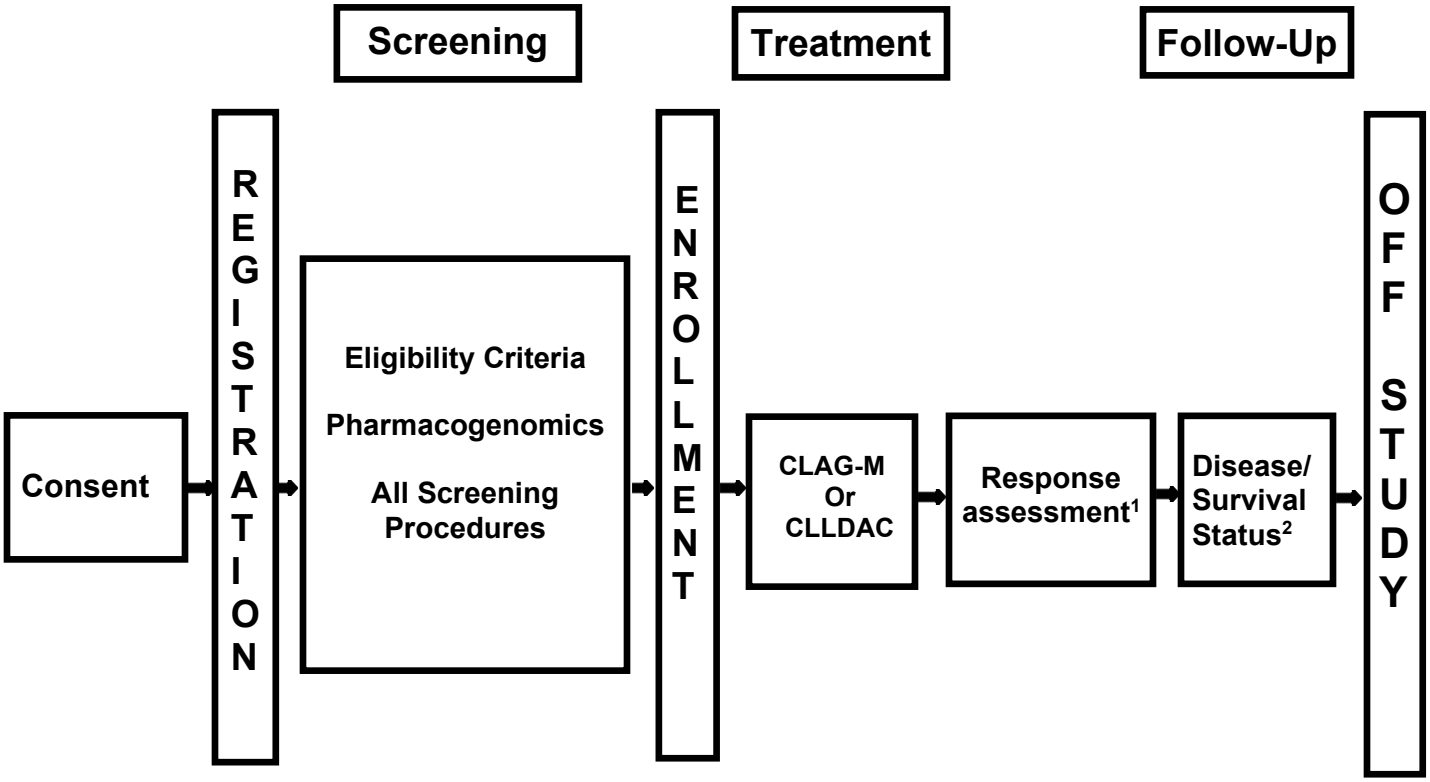
PROTOCOL SUMMARY

Title	A Phase II Study of the Efficacy and Pharmacogenomics of Cladribine based Salvage Chemotherapy in Patients with Relapse/Refractory and secondary Acute Myeloid Leukemia (AML) **and high risk Myelodysplastic Syndrome (MDS)**
OnCore Identifier	IITATALLAHCLAGM-AML
Principal Investigator	Ehab Atallah, MD
Study Sites	Froedtert & the Medical College of Wisconsin
Clinical Trial Phase	Phase II
Study Disease	Acute myeloid leukemia (AML) and myelodysplastic syndrome
Main Eligibility Criteria	**Inclusion criteria** 1. Age ≥18 years at the time of informed consent. 2. Morphologically documented primary Acute Myeloid Leukemia (AML) or AML secondary to Myelodysplastic Syndrome (MDS) myeloproliferative neoplasm (MPN) or therapy related AML (t-AML), as defined by World Health Organization (WHO) criteria. Patients with high risk MDS after failure of hypomethylating agents are also eligible 3. Patients must meet one of the following criteria: • In first or subsequent relapse or refractory status, with or without prior hematopoietic stem cell transplant (HSCT) OR • Patients with MDS or MPN transformed to AML will be eligible even if they had not received prior therapy for AML. • Patients with high risk MDS after failure of hypomethylating agents are also eligible 4. Eastern Cooperative Oncology Group (ECOG) performance score 0–3. 5. **CLAG-M arm only:** Patients must meet the following clinical laboratory criteria: • Total bilirubin ≤ 1.5 X the upper limit of the normal range (ULN) (if elevated, then complete a direct bilirubin), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 X ULN unless related to AML or Gilbert syndrome or hemolysis • Calculated creatinine clearance ≥30 mL/min • LVEF ≥ 45%

Main Eligibility Criteria (continued)	**Exclusion Criteria:** 1. Acute Promyelocytic Leukemia. 2. Pregnant or breast-feeding women. 3. Participation in clinical trials with other investigational agents not included in this trial throughout the duration of this trial.
Study Rationale	The optimal treatment regimen for relapsed/refractory AML and high risk MDS progressing after hypomethylating agents is unknown. Although several chemotherapy options are available, there is no universally accepted regimen to date. Cladribine based salvage regimens have been frequently used at our center. However, it is uncertain to predict which patients are likely to respond to cladribine based salvage or experience treatment related toxicities. While studies have demonstrated that achievement of MRD negative CR is likely to be associated with a better OS, there is limited prospective data evaluating the role of MRD in the setting of relapsed/refractory disease.. Through this study, we aim to demonstrate the influence of achieving MRD negative CR on survival of patients with relapsed/refractory AML/high risk MDS treated with Cladribine based salvage therapy. In addition to the conventionally used predictive factors, we aim to incorporate pharmacogenomics to assess the efficacy and toxicity of therapy.
Primary Objectives	To determine the complete remission (CR) rate and achievement of minimal residual disease (MRD) negativity after treatment with Cladribine based salvage chemotherapy regimen in patients with relapse/refractory AML/high risk MDS.
Secondary Objectives	1. To determine the progression free survival (PFS) and overall survival (OS) of patients treated with a cladribine based salvage chemotherapy regimen. 2. To study the pharmacogenomics of patients receiving a cladribine based salvage and determine its influence on survival, CR rate and MRD negativity. 3. Determination of disease- or patient-related factors that predict MRD negativity and survival with a cladribine based salvage regimen.
Study Design	This is a prospective phase II clinical study planned to be conducted at the Medical College of Wisconsin (MCW). After meeting the study criteria and enrollment, patients will be treated with a cladribine based salvage regimen and followed at periodic intervals to determine the primary and secondary objectives as mentioned above.

Study Agent/ Intervention Description	Patients will be started on CLAG-M or CLLDAC, which consists of the following: • Cladribine 5mg/m^2 IV on days 1–5; • Cytarabine 2 gm/m^2 IV on days 1–5, or 20mg/m2 SC on days 1-10; • (CLAG-M only) Mitoxantrone 10mg/m^2 IV on days 1–3; • (CLAG-M only) G-CSF at a dose of 300 µg on days 1-5.
Number of Subjects	90 patients
Subject Participation Duration	Patients treatment cycle is 30 days.
Duration of Follow up	Patients will be followed for relapse and/or survival every 3 months (+/- 2 weeks) for up to 4 years from the end of treatment.
Estimated Time to Complete Enrollment:	August 2027
Statistical Methodology	Baseline characteristics will be analyzed using descriptive statistics. Progression-free survival (PFS) will be calculated from the first day of remission after therapy until documentation of another relapse. Overall survival (OS) will be calculated from the first day of salvage therapy until death. PFS and OS analyses will be done by Kaplan- Meier method with log rank test. Multivariate analysis using Cox proportional hazard regression method will be used to analyze the determinants of MRD negative CR, OS, and PFS. All analyses will be done with a significant p value < 0.05. With an expected accrual rate of 10 patients per year, and accrual time of 9 years, we anticipate an eventual accrual of 90 patients. With a projected CR rate of 60% after treatment and a further anticipated MRD-negative rate of 60%, 36% of the study population is anticipated to be in MRD-negative CR. Based on binomial proportions, there will be between 23 and 41 MRD-negative patients with a 95.3% confidence, and an expected 22 MRD-positive CR patients for comparison.
Safety Assessments	Analyses will be performed for all patients having received at least one dose of study drug. The study will use the common terminology criteria (CTCAE) v4.0 for reporting of adverse events.
Efficacy Assessments	Assessment of MRD negative CR rate through bone marrow aspirate/biopsy and multi-color flow cytometry; Assessment of Pharmacogenomics through Affimetry DMET assay
Unique Aspects of this Study	This is the first study to evaluate the rate of MRD negativity and the role of pharmacogenomics in determining treatment outcomes of patients with relapsed/refractory AML/high risk MDS treated with cladribine based salvage therapy.

SCHEMA



1. MRD assessment will be performed on patients achieving CR or CRp.
2. Patients will be followed for relapse and/or survival every 3 months (+/- 2 weeks) for up to 4 years from the end of treatment

STUDY CALENDAR

Period/ Procedure	Screening	Treatment[20]					
Study Day/Visit Day	**Day – 30 to day 0 (enrollment)**	**Day 1**	**Day 8 (+/- 5 days)**	**Day 15 (+/- 5 days)**	**Day 22 (+/- 5 days)**	**Day 30/ EOT (+/- 5 days)[17]**	**Follow-up q3 months for 4 years[14]**
Informed consent	x						
AE assessment[6]	x	x	x	x	x	x	
Concomitant medications	x[2]	x	x	x	x	x	
Treatment/Drug Administration							
CLAG-M or CLLDAC[7]		x					
Clinical procedures							
Physical exam	x	X[19]	x	x	x	x	
Vital signs[15]	x	X[19]	x	x	x	x	
Medical history	x	X[19]					
Disease assessment	x[4]					x[13]	X[18]
ECOG Performance status	x	X[19]				x	
Minimal Residual Disease (MRD)						x[12]	
Survival Status							x
Laboratory procedures							
CBC w/ Diff and platelet count[1]	x[3]	x[8,19]	x	x	x	x	X[18]
Pharmacogenomics[11]	x						
Blood chemistry[1, 5]	x[3]	x[8,19]	x	x	x	x	
Pregnancy test (HCG)[9]	x						
Bone marrow aspiration/biopsy	x[16]					x[10, 16]	
Imaging procedures							
Cardiac Assessment (ECHO or MUGA)	x[3]						

1. Must be performed within 7 days prior to enrollment
2. Capture baseline medications taken within 7 days prior to day 1 and follow concomitant medications continuously until day 30.
3. Any results falling outside of the reference ranges may be repeated at the investigator's discretion.
4. Capture baseline blast percentage in bone marrow at the diagnosis of relapsed/refractory AML or MDS. Assessment is based off the previously completed bone marrow biopsy and blast count from recent peripheral blood count.
5. Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), calculated creatinine clearance (Cockcroft-Gault formula)

6. AEs will be followed from consent to 30 days' post last dose.
7. Treatment will be administered on an inpatient or outpatient (CLLDAC arm only) basis. Refer to section 7.
8. Completed within 24 hours of day 1.
9. Serum or Urine pregnancy test completed within 14 days prior to enrollment for women of child bearing potential.
10. Repeat BM study should be obtained after the completion of therapy at day 30 or when absolute neutrophil count (ANC) recovers to >1000 cells/cu.mm or when the treating physician determines that it is clinically indicated. If a second cycle of CLLDAC is administered, a repeat BM study should be performed at day 30 of cycle 2, or when the treating physician determines that it is clinically indicated.
11. For specimen collection instruction see appendix 3. This sample can be collected after a patient consents through day 5.
12. MRD assessment by flow cytometry will be performed on patients achieving CR or CRp. The sample will be collected and processed per institutional guidelines. Refer to section 15.1.
13. Patients responding to therapy (Refer to sections 13.3 and 14) may be subsequently considered for allogeneic stem cell transplantation or further consolidation chemotherapy based on the discretion of the treating clinician. Those with PR or no response could be given additional chemotherapy at the treating physician's discretion and patient's tolerability. Refer to sections 13 & 14. Day 30/EOT disease assessment may be delayed at the treating physician's discretion.
14. Patients will be followed for relapse and/or survival every 3 months (+/- 2 weeks) for up to 4 years from the end of treatment.
15. Vital signs: height, weight, blood pressure, pulse rate, respiratory rate, & temperature. Height is only required at screening.
16. If peripheral blasts are present, a bone marrow aspiration/biopsy is not required and should be performed at the discretion of the treating physician.
17. If patient discontinues treatment early and or progresses/relapses then end of treatment (EOT) assessments can be completed prior to starting other therapy. If a patient has disease progression/relapse then patient will be followed per follow-up requirements.
18. Patients will be followed for survival. CBC and Diff can be captured anytime since last follow up visit, if possible around time of SoC bone marrow biopsies. Patient do not need to be seen by treating physician during the follow-up period. Physician visits to be done only per SOC. All disease assessments (i.e. Bone Marrow Biopsies) should be captured on follow up CRF. If disease assessment or CBC w/ diff not done as part of routine care, this will not result in a protocol deviation.
19. If patient is consented and enrolled same day, Screening and Day 1 assessments can occur on the same day. This will not result in a protocol deviation.
20. Patients who fail to achieve a CR/CRi after the first 30-day cycle may receive a second cycle of CLLDAC, per the discretion of the treating physician. Patients who receive this second cycle should begin cycle 2 no later than 49 days after cycle 1. If a second CLLDAC cycle is administered, the above calendar events will be followed for cycle 2.

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LIST OF ABBREVIATIONS

2-CdA	Cladribine
AE	adverse event
AML	Acute myeloid leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BM	bone marrow
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CLAG-M	Cladribine, Cytarabine, G-CSF, Mitoxantrone
CLLDAC	Cladribine, low dose cytarabine
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CSF	cerebral spinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee

DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FC	flow cytometry
FCBP	female of childbearing potential
FDA	Food and Drug Administration
FLAG	Fludarabine, Cytarabine, G-CSF
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HCT	Hematocrit
HDAC	High-dose Cytarabine
HGB	Hemoglobin
HSCT	Hematopoietic stem cell transplant
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LVEF	left ventricular ejection fraction
MCWCC	Medical College of Wisconsin Cancer Center
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
NCI	National Cancer Institute

ORR	overall response rate
OS	overall survival
PD	disease progression
PFS	progression-free survival
PO	per os (by mouth, orally)
PR	partial response
RBC	red blood cell (count)
RFS	Relapse free survival
RNA	Ribonucleic acid
RR-AML	Relapsed/Refractory AML
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SRC	Scientific Review Committee
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
t-AML	therapy related AML
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risks to subjects or others
WBC	White blood cell (count)
WHO	World Health Organization

1 BACKGROUND

1.1 Acute Myeloid Leukemia (AML) and high risk myelodysplatic syndrome (MDS)

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal expansion of myeloid blasts in peripheral blood, bone marrow and other tissues. In United States, it is the most common form of acute leukemia in adults. Most patients with AML are older adults with a median age of 67 years and one-third of them being older than 75 years [1]. Thus, as the “baby boomer” generation ages, the incidence of AML is on rise. In addition, prior chemotherapy and radiation to treat other malignancies contribute to the rising incidence of therapy related AML. About 20,000 new AML cases are diagnosed each year in United States with more than 10,000 patients dying with this disease. The five-year overall survival of AML is about 26% with younger patients having a higher survival rate (more than 50%) than older adults (~10% for patients 65–74 years) [2]. Despite achieving a complete remission (CR) rate of 60-80% with initial induction therapy, more than 50% of AML patients sustain disease relapse and 10-40% of patients have primary refractory disease [3, 4]. Patients who do not achieve adequate response with initial induction chemotherapy have primary refractory AML. Treatment response of patients with relapsed/refractory AML is variable and factors such as age, cytogenetics, prior stem cell transplantation and duration of first CR have been proposed as important prognostic factors [5]. Factors such as old age and chemotherapy resistance impose significant challenges in achieving second complete remission. All patients with AML are best managed within the context of an appropriate clinical trial.

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant hematopoietic stem cell disorders that are characterized by ineffective blood cell production and a variable risk of transformation to acute myeloid leukemia (AML). Hypomethylating agents such as decitabine and azacitidine are the current mainstay of therapy for patients with high-risk myelodysplastic syndromes (MDS). Unfortunately, when MDS progresses despite these agents, the outcomes for these patients remain dismal with a median OS 5.6 months [6]. Management of MDS after failure of hypomethylating agents is an area of unmet need for research with no standard of care treatments. These patients are often best managed in the context of clinical trials.

1.2 Salvage Chemotherapy and Cladribine based regimens

Several chemotherapy regimens are available for the treatment of patients with relapsed/refractory myeloid malignancies. Many of these combinations are dose-intensive and have not been directly compared against each other. Hence the choice is primarily based upon individual clinical experience. Importantly, a patient's chance of responding to a particular regimen is influenced not only by prior exposure to chemotherapy but also by other patient- and disease-associated factors. Commonly used regimens in this setting include:

1. Re-induction with cytarabine and daunorubicin that could produce CR in approximately 50% of patients with a first remission greater than one year [5, 7]. However, this is often limited by the chances of anthracycline induced cardiotoxicity with cumulative exposure (as it is also commonly used in initial induction therapy).
2. High-dose cytarabine (HDAC) regimen using 2 to 3 g/m^2 every 12 hours for 8 to 12 doses may be effective in 35- 40% of patients’ resistant to conventional dose cytarabine [8]. Toxicity such as cerebellar dysfunction is prohibitively high in patients with age > 60 years.

3. Mitoxantrone, cytarabine with or without etoposide is a commonly used regimen to treat RR- AML [9-15]. In a study by Amadori et al. 32 patients with RR-AML were treated with salvage MEC therapy (mitoxantrone 6 mg/m2 intravenous (IV) bolus, etoposide 80 mg/m2 IV for a period of 1 hour, and cytarabine (Ara-C) 1 g/m2 IV for a period of 6 hours daily for 6 days) [12]. Overall, 21 patients (66%) achieved a complete remission (CR), two (6%) died of infection during induction, and nine (28%) had resistant disease. Age greater than 50 years was the only factor predictive for a significantly lower response rate. The median remission duration was 16 weeks and median overall survival was 36 weeks. In another series of 47 patients with RR- AML, the combination of mitoxantrone (5 mg/m^2 per day for five days) and intermediate-dose cytarabine (0.5g/m^2 IV every 12 hours for six days) resulted in a complete remission rate of 62%, but the median duration of remission was only 3.7 months [14]. Ninety-six percent of those achieving CR eventually relapsed.
4. Fludarabine, cytarabine, plus G-CSF (FLAG) has been reported to have complete remission rates of 45 -55% in patients with RR-AML [16,17]. Studies including older adults have reported mild nonhematologic toxicity most commonly included mucositis. Median survival was over 16 months for those with late relapse (ie, >6 months after stopping chemotherapy), but was only three months for those with early relapse or refractory disease [16].
5. Given the aggressive nature of high risk MDS progressing after hypomethylating agents, these patients are sometimes managed with AML based chemotherapy regimens, especially if they are candidates for allogeneic stem cell transplantation. Many prior studies have included both patients with AML and high risk MDS while evaluating the efficacy of chemotherapy regimens in this setting as described below. A study by DeWitte et al. evaluated the role of idarubicin and cytarabine based chemotherapy in 50 patients with MDS and AML (originating from antecedent MDS) [18]. They noted a complete remission rate of 54% with this regimen and median OS of 14 months. Another study by Ossenkoppele et al. evaluated the efficacy of fludarabine, cytarabine, G-CSF (FLAG) chemotherapy in patients with high risk MDS and AML and noted a complete remission rate of 71% and OS of 39% at 24 months [19]. A study by Parker et al. investigated the efficacy of FLAG-idarubicin chemotherapy in patients with high risk MDS and AML and noted complete remission rate of 63% in these patients [20].
6. A commonly used salvage chemotherapy regimen for relapsed-refractory AML at our center is CLAG-M (cladribine, cytarabine, G-CSF, Mitoxantrone). A phase II study was reported by Wierbozwska et al. about this regimen in 2008 [21]. One hundred and eighteen patients with RR-AML were included. Sixty-six patients (58%) achieved CR after one or two courses of CLAG-M, 49 (35%) were refractory, and 8 (7%) died early. WBC >10 g/L and age > 34 years were factors associated with increased risk of treatment failure. The probability of 4-year overall survival was 14% (95% CI 4-23%) and 4-year disease free survival was 30% for all 66 patients in CR (95% CI 11-49%). Poor karyotype was the only factor associated with decreased probability of DFS. A retrospective study by Price et al. compared two commonly used regimens in RR-AML - CLAG and MEC [22]. The complete response rate (CR) was found to be 37.9% for CLAG (n = 97) and 23.8% for MEC (n = 65) (P = 0.048), with a median overall survival of 7.3 and 4.5 months, respectively (P = 0.05). In primary refractory disease, CR rate was 45.5% for CLAG and 22.2% for MEC (P = 0.09), with median overall survival of 11 and 4.5 months, respectively (P = 0.07). In patients with relapsed AML, CR rate was 36.8% with CLAG and 25.9% with MEC (P = 0.35) and median OS was 6.7 and 6.7 months, respectively (P = 0.87). The combination of purine nucleoside analogue with cytarabine increases the intracellular

accumulation of Ara-C-5′ triphosphate (ara-CTP) that causes cytotoxic effect in leukemic blasts. Addition of granulocyte-colony stimulating factor (G- CSF) further improves the effects of purine nucleoside analogue in combination with Ara-C by activating the leukemic cells and making them susceptible to chemotherapy's effect. Our center has seen good clinical results using this regimen and is often the choice of therapy for RR-AML.

7. CLAG-M has also been studied in patients with myelodysplastic syndrome who have failed hypomethylating agent therapy and progressed to AML [23]. In a retrospective study by Jaglal et al. in patients with myelodysplasia who failed azanucleosides and progressed to AML, the efficacy of CLAG-M induction (28 patients) was compared against standard 3+7 induction chemotherapy (24 patients). Response rates and median overall survival were 64% and 202 days (95% CI 37-367 days) in CLAG-M group versus 29% and 86 days (95% CI 36-136) in 3+7 group, respectively. There was no significant difference in the mortality or serious adverse effects between the two groups. The combination of cladribine, cytarabine, mitoxantrone (in escalating doses) and G-CSF was recently evaluated in a phase I/II clinical study by Halpern et al. in patients with relapsed or refractory AML and other high-grade myeloid neoplasms (≥10% myeloblasts in blood and/or marrow) such as MDS [24]. They reported a response rate (CR, CRi) of 57% among 60 patients enrolled in this study. Hence, these studies emphasize the rationale to prospectively investigate chemotherapy based strategies in patients with high riks MDS progression after hypomethylating agent therapy.Not all patients are "fit" for salvage chemotherapy with CLAG-M. Cladribine, with low dose ara-C (CLLDAC), has shown promise in "unfit" AML patients. Kadia et al studied Cladribine and low-dose cytarabine as front-line therapy for elderly patients with AML [25]. This trial enrolled patients who would not be considered fit for intensive chemotherapy, with regimens including CLAG-M. Impressively, in this difficult to treat patient group, one to two cycles of Cladribine, along with low-dose cytarabine, resulted in a CR rate of 58%, with an additional 9% achieving a CR with incomplete count recovery. Total response rate was 68%. Similarly, the regimen with cladribine and low dose cytarabine has been studied in patients with relapsed/refractory AML or MDS. A retrospective study by Wisniewski et al. described the role of cladribine and low dose cytarabine in patients with relapsed/refractory AML/MDS [26]. They reported the outcomes on 16 patients with relapsed/refractory AML/high risk MDS/chronic myelomonocytic leukemia (CMML) treated with this regimen and noted that it was well tolerated with no treatment related deaths. A complete remission (CR or CRi) was achieved in 56% of patients and the median time to response was 1 cycle. Median progression-free survival was 8 months, and the median OS reached 10.6 months. Although there are no prospective studies that have been reported with this regimen in the relapse/refractory setting, the efficacy noted in prior studies warrant prospective evaluation of this regimen as being proposed in this study .

1.3 Chemotherapy Overview

Cladribine is a chlorodinated derivative of adenine which is converted intracellularly to the cladribine triphosphate, which is believed to compete with adenine triphosphate in DNA synthesis. Cladribine was found to have marked activity against hairy leukemia and was approved for this use in the United States in 1993.

For detailed information on cladribine, please see Section 9, Pharmaceutical Information.

Cytarabine

Cytarabine is also known as ara-C (arabinofuranosyl cytidine) or cytosine arabinoside. It kills the leukemic cells by interfering with the DNA synthesis. Cytosine normally combines with a deoxyribose, to form deoxycytidine, a component of DNA. Cytosine arabinoside is similar to human cytosine deoxyribose (deoxycytidine) and gets incorporated into DNA and causes cell death. It is one of the oldest and most commonly used drug approved for the treatment of AML.

For detailed information on cytarabine, please see Section 9, Pharmaceutical Information.

Filgrastim (G-CSF)

Filgrastim is a granulocyte colony-stimulating factor (G-CSF) analog used to stimulate the proliferation and differentiation of granulocytes. It is produced by recombinant DNA technology and is commonly used to treat neutropenia in patients with malignancy. Rationale for using filgrastim in CLAG-M is to stimulate leukemic cells to enter the active phase of cell cycle, making them susceptible to chemotherapy's effect.

For detailed information on filgrastim, please see Section 9, Pharmaceutical Information.

Mitoxantrone

Mitoxantrone is an anthracycline class chemotherapeutic agent with cytotoxic effects. It inhibits type II topoisomerase and disrupts DNA synthesis and repair. It has been approved for the treatment of AML and is commonly used in combination with various chemotherapeutic agents. Mitoxantrone is a cardiotoxic drug and needs adequate left ventricular ejection fraction before starting therapy.

For detailed information on Mitoxantrone, please see Section 9, Pharmaceutical Information.

1.4 Response Predictors

There is no prospective data to identify those patients who would respond well to a cladribine based regimen. New strategies, such as minimal residual disease (MRD) monitoring is emerging to assess the response to therapy [27,28]. Similarly, pharmacogenomics of the chemotherapeutic agents have been used previously to identify those patients who would have a favorable response to therapy [29-32]. In this novel study, we aim to determine the role of MRD monitoring and pharmacogenomics assay to predict the response to therapy in patients with relapsed refractory AML/high risk MDS planned to be treated with a Cladribine based regimen.

1.5 Minimal (also termed "Measurable") Residual Disease Monitoring

Relapse results from residual leukemic cells that remain following the achievement of morphological "complete" remission. Subclinical levels of residual leukemia are termed minimal residual disease (MRD) and can be evaluated using more sensitive assays such as multicolor flow cytometry. A large retrospective study by Chen et al. included data from 245 adults with AML (of which 81 had RR-AML) who achieved CR, CRp, or CR with incomplete blood count recovery (CRi) after induction therapy [28]. They found that the rate of MRD positivity increases

from 19% in patients who achieved CR to 54.2% in patients with CRp and 60.9% in patients with CRi. Additionally, patients with MRD positive CR had inferior outcomes to therapy as compared to patients with MRD negative CR. Even though this study included a large cohort, it was retrospective and did not exclusively describe the MRD rates and outcomes in relapsed/refractory patients. Hence, it is truly worth exploring prospectively the rate of MRD negative CR achieved with Cladribine based salvagechemotherapy and its influence on long-term outcomes.

1.6 Pharmacogenomics

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology and genomics to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. Studies have shown that patients with AML could have the response and toxicity to chemotherapy predicted using pharmacogenomic assay for specific genes [29-32]. A study by Green et al. described the association between ABCB1 gene polymorphism and its effect on survival [30]. Patients with 1236C/C or 2677G/G genotypes showed poorer survival than patients with other genotypes. Both these genotypes were significantly influenced the survival along with age, NPM1 and FLT3 mutation status. In vitro cytotoxicity studies demonstrated that leukemic cells from 1236T/T and 2677T/T patients were significantly more susceptible to mitoxantrone, and tended to be more susceptible to etoposide and daunorubicin, but not to cytarabine. In another study, Cao et al. found that another gene called RRM1 was highly expressed in patient with features indicative of a high relapse hazard and RRM1 single nucleotide polymorphism (SNP) rs1042919 and promoter SNP rs1561876 were associated with intracellular 1-β-D-arabinofuranosyl-CTP levels, response after remission induction therapy, risk of relapse and overall survival in AML patients receiving cytarabine and cladribine [32]. In addition to these studies, there is a database available to describe the potential genes that could influence the chemotherapeutic drug's course in humans after administration [33]. Hence, this forms a reasonable background to utilize this strategy to find the correlation between the patient's pharmacogenomic profile and the response/toxicity to chemotherapy.

2 HYPOTHESIS AND OBJECTIVES

2.1 Primary Objectives

To determine the complete remission (CR) rate and achievement of minimal residual disease (MRD) negativity after treatment with a salvage cladribine based chemotherapy regimen in patients with relapse/refractory AML/high risk MDS.

2.2 Secondary Objectives

1 To determine the progression free survival (PFS) and overall survival (OS) of patients treated with salvage cladribine based chemotherapy in the same patient population.

2 To study the pharmacogenomics of patients receiving salvage cladribine based chemotherapy and determine its influence on survival, CR rate and MRD negativity in the same patient population.

3 Determination of disease- or patient-related factors that predict MRD negativity and

survival after salvage cladribine based chemotherapy.

3 STUDY DESIGN

3.1 General Description

This is a prospective, phase II clinical study aimed at determining the efficacy of salvage cladribine based chemotherapy in the management of relapse/refractory AML/high risk MDS. Study participants will be recruited at the Froedtert & the Medical College of Wisconsin. After meeting the study criteria and enrollment, patients will be treated with salvage cladribine based chemotherapy and followed at periodic intervals to determine the primary and secondary endpoints as mentioned below.

3.2 Number of Subjects

Ninety subjects will be enrolled in this study.

3.3 Primary Endpoint(s)

To determine the rate of MRD negative CR in patients with relapsed/refractory AML/high risk MDS.

3.4 Secondary Endpoint(s)

1. Determination of the overall survival (OS) and progression free survival (PFS) in patients with relapsed/refractory AML/high risk MDS treated with cladribine based salvage therapy

2. Determination of disease- or patient-related factors that predict MRD negativity and survival with cladribine based salvage, including pharmacogenomics.

3. Determination of the role of pharmacogenomics in predicting the development of treatment related toxicities with cladribine based salvage therapy.

3.5 Randomization

Randomization does not apply to this study

3.6 Study Completion

The study will reach completion approximately 2027.

4 PATIENT SELECTION

Eligibility Criteria

The written informed consent must be obtained from the patient prior to enrollment and any study specific procedures. Patients must have baseline evaluations performed prior to enrollment and the first study drug dose. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria

1. Age ≥18 years at the time of informed consent.

2. Morphologically documented:
   - primary acute myeloid leukemia (AML) or
   - AML secondary to myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN), or
   - therapy-related AML (t-AML), as defined by World Health Organization (WHO) criteria (Appendix 5).
   - Patients with high risk MDS after failure of hypomethylating agents are also eligible.

3. Patients must meet one of the following criteria:
   - In first or subsequent relapse or refractory status, with or without prior hematopoietic stem cell transplant (HSCT) OR
   - Patients with MDS or MPN transformed to AML will be eligible even if they had not received prior therapy for AML.
   - Patients with high risk MDS after failure of hypomethylating agents

4. Eastern Cooperative Oncology Group (ECOG) performance score 0–3.

5. It is not known what effects this treatment has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

   Female patients must meet one of the following:
   - Postmenopausal for at least one year before the screening visit, or
   - Surgically sterile, or if they are of childbearing potential, agree to practice two effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable contraception methods.)

Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last study drug dose, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

6. Ability to understand a written informed consent document, and the willingness to sign it.

7. Patients must meet the following clinical laboratory criteria:

   - **CLAG-M arm only:** For abnormalities in liver function tests, elevation thought to be due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis would not be treated as exclusion criteria.

Organ and Marrow Function Table	
Adequate bone marrow function:	
Absolute neutrophil count	≥1,000/cmm Unless related to AML
Platelets	≥75,000/cmm Unless related to AML
Adequate hepatic function:	
Total bilirubin	≤ 1.5 x the upper limit of the normal range (ULN) (if elevated, then complete direct bilirubin).
AST(SGOT)/ALT	Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN
Adequate renal function:	
Creatinine clearance	≥ 30 mL/min
Cardiac:	
Resting left ventricular ejection fraction	≥45%

- **CLLDAC arm only**:

Organ and Marrow Function Table	
Adequate bone marrow function:	
Absolute neutrophil count	≥1,000/cmm Unless related to AML
Platelets	≥75,000/cmm Unless related to AML

4.2 Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Acute promyelocytic leukemia.
2. Active infection not well controlled by antibacterial or antiviral therapy.
3. Pregnant or breast-feeding women.
4. Participation in clinical trials with other investigational agents not included in this trial, throughout the duration of this trial. , participation of follow-up portion of another clinical trial will not exclude patient from participation

5 STUDY PROCEDURES

5.1 Study Entry Procedures

Required Preregistration Screening Tests and Procedures

The study-specific assessments are detailed in this section and outlined in the Study Calendar. Screening assessments unless otherwise specified must be performed within 30 days prior to enrollment. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. All on-study visit procedures are allowed a window of ± 5 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated.

All patients who are consented will be registered in OnCore®, the MCW Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements. Once a patient has been consented they will be assigned a screening ID that will be used to identify them throughout the study.

5.2 Pretreatment Period

The screening procedures and assessments must be completed within 30 days (unless otherwise specified on the study calendar) of enrollment.

- Informed consent
- Physical examination
- Vital signs
- Medical history
- Disease assessment (Appendix 5)
- ECOG Performance status
- Complete blood count (CBC) with differential and platelet count

- Blood chemistry assessment, including:
- Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), calculated creatinine clearance (Cockcroft- Gault formula)
- Serum or urine pregnancy test within 14 days prior to enrollment for women of child bearing potential
- Cardiac assessment (ECHO or MUGA)
- Serum sample pharmacogenomics (can be collected from consent to day 5)
- Bone marrow aspiration/biopsy- If peripheral blasts are present, a bone marrow aspiration/biopsy is not required and should be performed at the discretion of the treating physician.
- Adverse events
- Concomitant medications (baseline medications taken within 7 days of Day 1)

5.3 Study Procedures during Treatment

Patients must meet eligibility criteria on cycle 1 day 1 to be treated. Patients must be enrolled prior to treatment. A subject will be considered enrolled onto the study once they have signed consent, have successfully met all screening criteria, the eligibility criteria has been reviewed and accepted by the PI or a sub-investigator. Any eligibility questions should be directed to Dr. Atallah at eatallah@mcw.edu.

Study Procedures, Cycle 1 Day 1*

- Physical examination
- Vital signs
- Medical History
- ECOG Performance status
- Adverse events
- Concomitant medications
- CBC with differential and platelet count (completed within 24 hours of day 1) Blood chemistry assessment, including (completed within 24 hours of day 1): Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, calculated creatinine clearance (Cockcroft- Gault formula)

  *If patient is consented and enrolled on the same day, Screening and Day 1 assessments can occur on same day. This will not result in a protocol deviation

Study Procedures during Treatment

The following procedures are done days 8, 15, and 22.

- Physical examination
- Vital signs
- Adverse events

- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including: Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, calculated creatinine clearance (Cockcroft- Gault formula)

5.4 Day 30/End of Treatment Procedures

To be completed day 30 (+/- 5 days) (unless otherwise specified on the study calendar). If patient discontinues treatment early and or progresses/relapses then end of treatment (EOT)/day 30 assessments can be completed prior to starting other therapy.

- Disease assessment (Section 14)
- MRD (Section 15.1)
- Physical examination
- Vital signs
- ECOG Performance status
- Adverse events
- Concomitant medications
- CBC with differential and platelet count
- Blood chemistry assessment, including: Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, calculated creatinine clearance (Cockcroft- Gault formula)
- Repeat bone marrow aspiration/biopsy will be obtained after the completion of therapy at day 30 or when absolute neutrophil count (ANC) recovers to >1000 cells/cu.mm or when the treating physician determines that it is clinically indicated. If peripheral blasts are present, a bone marrow aspiration/biopsy is not required and should be performed at the discretion of the treating physician.

5.5 Follow-Up Visits

Patients will be followed for relapse and/or survival every 3 months (+/- 2 weeks) for up to 4 years from the end of treatment. If a patient has disease progression/relapse, then patient will be followed per follow-up requirements. The following procedures will be captured at the follow-up visit(s):

- Disease assessment (Section 14)* Patients do not need to be seen by treating physician during the follow-up period. Visits to occur only per SOC.
- CBC with differential and platelet count* at time of SoC Bone Marrow Biopsies, if applicable, otherwise as close to follow up window as possible.
    - Collected once during each 3-month follow up period.

*If not done as part of routine care, this will not result in a protocol deviation

6 STUDY WITHDRAWAL PROCEDURES

Duration of Therapy

Patients enrolled in the study and treated with therapy will remain in the study up to 4 years from the end of therapy.

In the absence of treatment delays due to adverse events, study treatment may continue for the protocol specified time frame until:

- Disease progression
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration
- Patient decides to withdraw from the study
- Significant patient noncompliance with protocol
- Unacceptable adverse event(s)

In the event that a patient withdraws from the study after screening and consenting, additional patients will be screened and recruited to match the deficit.

7 TREATMENT PLAN

Treatment will be administered on an inpatient basis for CLAG-M, and on an inpatient or outpatient basis for CLLDAC.

CLAG-M Regimen Description (Cycle = 30 days)

Study Drug	Premedication; precautions	Dose	Route	Schedule
G-CSF*	None	300 µg	Subcutaneous	Days 1-5*
Cladribine*	Monitor for and report infection	5 mg/m^2	Intravenous over 2 hours	Days 1–5
Cytarabine*	Monitor for neurological toxicity	2 gm/m^2	Intravenous over 4 hours	Days 1–5
Mitoxantrone*	Monitor for cardiovascular toxicity	10 mg/m^2	Intravenous	Days 1–3

* Treatment given per institutional guidelines. Deviations from suggested infusion times above will not result in protocol deviations.

G-CSF can be given prior to enrollment per treating physician discretion, but remaining CLAG-M

should be given after enrollment. Intrathecal chemotherapy can be given for patients with possible CSF involvement.

CLLDAC Regimen Description (Cycle = 30 days)

Study Drug	Premedication; precautions	Dose	Route	Schedule
Cladribine*	Monitor for and report infection	5 mg/m^2	Intravenous over 2 hours	Days 1–5
Cytarabine*	None	20 mg/m^2	Subcutaneous	Days 1–10

* Treatment given per institutional guidelines. Deviations from suggested infusion times above will not result in protocol deviations.

Patients who fail to achieve a CR/CRi after the first 30-day cycle may receive a second cycle of CLLDAC, per the discretion of the treating physician. Patients who receive this second cycle should begin cycle 2 no later than 49 days after cycle 1.

8 DOSING DELAYS/DOSE MODIFICATIONS

Patients must meet eligibility criteria on Day 1 to be treated. Typically, the treatment is given for only one cycle. Hence, dose adjustments generally do not apply as subsequent cycles are not given in the protocol. In the event that a dose gets delayed, the same dose could be restarted within 1-2 days of the missed dose and subsequent doses will be timed accordingly. Dose modifications are allowed for safety per treating physician discretion.

Please see dose modification suggestions for each drug in section 9 for treatment days (after day 1). Dose modifications are suggestions only. Please follow institutional guidelines. Failure to follow dose modification suggestions will not result in a protocol deviation.

8.1 Dietary Restrictions

No dietary restrictions are applicable

8.2 Prohibited Medications

See appendix 2 for prohibited medications

9 PHARMACEUTICAL INFORMATION

9.1 CLADRIBINE

Product Description [45,47]
Cladribine is available in one strength and form: Cladribine 1 mg per mL in 10-mL single-use

vials.

Black Box Warning: Acute nephrotoxicity has been observed with high doses of LEUSTATIN (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies. Avoid nephrotoxic agents.

Classification
Cladribine is an antineoplastic; antimetabolite and purine antagonist.

Mechanism of Action
Cladribine is structurally related to fludarabine and pentostatin but has a different mechanism of action. Although the exact mechanism of action has not been fully determined, evidence shows that cladribine is phosphorylated by deoxycytidine kinase to the nucleotide cladribine triphosphate (CdATP; 2-chloro-2′-deoxyadenosine 5′-triphosphate), which accumulates and is incorporated into DNA in cells such as lymphocytes that contain high levels of deoxycytidine kinase and low levels of deoxynucleotidase, resulting in DNA strand breakage and inhibition of DNA synthesis and repair. High levels of CdATP also appear to inhibit ribonucleotide reductase, which leads to an imbalance in triphosphorylated deoxynucleotide (dNTP) pools and subsequent DNA strand breaks, inhibition of DNA synthesis and repair, nicotinamide adenine dinucleotide (NAD) and ATP depletion, and cell death. Unlike other antimetabolite drugs, cladribine has cytotoxic effects on resting as well as proliferating lymphocytes. However, it does cause cells to accumulate at the G1/S phase junction, suggesting that cytotoxicity is associated with events critical to cell entry into S phase. It also binds purine nucleoside phosphorylase (PNP), however no relationship between this binding and a mechanism of action has been established.

Metabolism
Metabolized in all cells with deoxycytidine kinase activity to 2-chloro-2'-deoxyadenosine-5'-triphosphate.

Contraindications
Hypersensitivity to cladribine; pregnancy.

Side Effects
See Section 11 (Known Risk List.) Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Solution Preparation
IV Infusion (single daily dose): Prepare per institutional standards in a 500 mL IV Normal Saline Bag. Filter with a 0.22 micron hydrophilic syringe filter prior to adding to infusion bag.

Drug product does not contain anti-microbial preservative or bacteriostatic agent, MUST use aseptic technique and take environmental precautions when dispensing.

Dextrose 5% is NOT recommended as a diluent due to the increased degradation of cladribine.

Agent Administration
IV Infusion (single daily dose): Distribute evenly over ordered time (i.e., 2 h or 24 h).

Storage Requirements
Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

Stability
When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of cladribine injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. Do not heat or microwave. Once thawed, the vial of cladribine injection is stable until expiry if refrigerated. Do not refreeze. Once diluted, solutions containing cladribine injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than eight hours prior to administration.

Nursing Implications Guidelines
Lab tests: frequent hematologic studies; periodic serum creatinine and liver function tests. Closely monitor hematologic status; myelosuppression is common during the first month after starting therapy. Monitor for and report signs and symptoms of infection. Note that within the first month, fever may occur in the absence of infection. With high doses of cladribine, monitor for neurologic toxicity (paraparesis/quadriparesis) and acute nephrotoxicity.

- Hepatic
  - No dosage adjustment [51]
- Renal
  - CrCl 10-50 mL/minute: Administer 75% of dose [51]

Handling
Use disposable gloves and protective clothing when handling the drug. Wash immediately if skin contact occurs.

Availability
This drug is commercially available.

Agent Ordering
Commercially available.

Agent Accountability
Commercial Supply

Agent Destruction and Return
At the conclusion of the study, any unused Cladribine will be destroyed according to institutional policies.

9.2 CYTARABINE

Product Description [45,48]
Cytarabine is available in vials of 100, 500, 1000 and 2000 mg (20 mg/mL) for intravenous or intrathecal infusion generically and under the brand name Cytosar-U.

Classification

Cytarabine is an antimetabolite antineoplastic agent.

Mechanism of Action
Cytarabine acts through direct DNA damage and incorporation into DNA. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported.

Metabolism
Cytarabine is rapidly metabolised, mainly in the liver, to the inactive metabolite 1-β-D-arabinofuranosyluracil. About 70 to 80% of a dose is excreted in the urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged cytarabine.

Contraindications
Cytarabine is contraindicated in patients with a history of drug-induced myelosuppression; immunization procedures; pregnancy (particularly during first trimester), lactation.

Side Effects
See Section 11 (Known Risk List). Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Product Description
Cytarabine for injection USP is available in vials containing 100 mg, 500 mg, 1 g and 2 g cytarabine.

Solution Preparation
Direct: Reconstitute with bacteriostatic water for injection as follows: add 5 mL to the 100-mg vial to yield 20 mg/mL; add 10 mL to the 500 mg vial to yield 50 mg/mL. IV Infusion: May be further diluted with 100 mL or more of D5W or NS.

Agent Administration
Direct: Give at a rate of 100 mg or a fraction thereof over three min. IV Infusion: Give over 4 hours or longer depending on the total volume of IV solution to be infused.

Storage Requirements
Store at 15°C - 25°C. Keep container in outer carton. Cytarabine should not be stored at refrigerated temperatures (2-8°C).

Stability
Although stability of cytarabine is well retained for 24 hours in intravenous vehicles noted above, it is recommended that, as with all intravenous admixtures, dilution should be made just prior to administration and the resulting solution used within 24 hours.

Nursing Implications Guidelines for cytarabine (in CLAG-M arm only)
Inspect patient's mouth before the administration of each dose. Toxicity necessitating dosage alterations almost always occurs. Report adverse reactions immediately.

Hyperuricemia due to rapid destruction of neoplastic cells may accompany cytarabine therapy. A regimen that includes a uricosuric agent such as allopurinol, urine alkalinization, and adequate hydration may be started, if the physician orders it. To reduce potential for urate stone formation, fluids may be forced in excess of 2 L, if tolerated. Management is at the discretion of the physician.

Monitor intake and output ratio and pattern.

Monitor body temperature. Be alert to the most subtle signs of infection, especially low-grade fever, and report promptly.

When platelet count falls below 50,000/mm^3 and polymorphonuclear leukocytes to below 1000/mm^3, the physician may decide to halt therapy. White blood count nadir is usually reached in five to seven days after the therapy has been stopped. Therapy is restarted with appearance of bone marrow recovery and when preceding cell counts are reached. Again, this is at the discretion of the physician.

Provide good oral hygiene to diminish adverse effects and chance of super infection. Stomatitis and cheilosis usually appear five to 10 days into the therapy.

- Hepatic
  - AST/ALT > 3 x ULN
  - Administer 50% of dose; may increase subsequent doses in the absence of toxicities (Floyd, 2006)
  - Bilirubin >2 mg/dL: Administer 50% of dose; may increase subsequent doses in the absence of toxicities
    - Administer 50% of dose; may increase subsequent doses in the absence of toxicities (Koren, 1992)
- Renal
  - Kintzel [52], 1995 (high-dose cytarabine 1 to 3 g/m^2):
    - CrCl 46 to 60 mL/minute: Administer 60% of dose
    - CrCl 31 to 45 mL/minute: Administer 50% of dose
    - CrCl <30 mL/minute: Consider use of alternative drug
  - Smith [53], 1997 (high-dose cytarabine; ≥2 g/m^2/dose):
    - Serum creatinine 1.5 to 1.9 mg/dL or increase (from baseline) of 0.5 to 1.2 mg/dL:
      - Reduce dose to 1 g/m^2/dose
    - Serum creatinine ≥2 mg/dL or increase (from baseline) of >1.2 mg/dL:
      - Reduce dose to 0.1 g/m^2/day as a continuous infusion

Patients should have a daily creatinine and total bilirubin. The dose of cytarabine will be adjusted. The dose of cytarabine should be adjusted if there is a change in the serum creatinine or bilirubin during that cycle after the start of therapy.

Serum Creatinine (mg/dL)	Serum Total Bilirubin	Dose (mg/m2)
< 2	< 3	1500
> 2 (or an increase of > 0.5 mg/dL from baseline)	< 3	750
> 3	< 3	500
Any	> 3	500

Handling
Use disposable gloves and protective clothing when handling the drug. Wash immediately if skin contact occurs.

Availability
This drug is commercially available.

Agent Ordering
Commercially available

Agent Accountability
Commercial supply

Agent Destruction and Return
At the conclusion of the study, any unused Cytarabine will be destroyed according to institutional policies.

9.3 MITOXANTRONE Product Description [45,50]

Mitoxantrone is available in several generic formulations as a solution for injection (usually 2 mg/mL).

Black Box Warning: Cardiotoxic drug, extravasation, and secondary malignancy

- Obtain baseline left ventricular ejection fraction (LVEF)

Classification
Mitoxantrone is an anthracenedione-derived antineoplastic agent.

Mechanism of Action
Mitoxantrone, a DNA-reactive agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and nonproliferating cultured human cells, suggesting lack of cell cycle phase specificity.

Metabolism
Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites. In human studies, 11% and 25% of the dose were recovered in urine and feces, respectively, as either parent drug or metabolite during the 5-day period following drug administration. Of the

material recovered in urine, 65% was unchanged drug. The remaining 35% was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates. The pathways leading to the metabolism of Mitoxantrone have not been elucidated.

Weak inducer of CYP450 2E1

Contraindications
Mitoxantrone Injection, USP is contraindicated in patients who have hypersensitivity to mitoxantrone; myelosuppression; are pregnant or lactating.

Cardiotoxic drug consider the benefit-to-risk ratio before starting Mitoxantrone in patients who were previously treated with daunorubicin or doxorubicin

Patients with low LVEF are at risk of cardiotoxicity with mitoxantrone. Of note, the LVEF threshold for mitoxantrone has only been studied in patients with multiple sclerosis and not cancer patients. In accordance with the current ongoing clinical trials in US using mitoxantrone (NCT02044796), we have used a LVEF cut-off ≥45% to eligible to receive mitoxantrone.

Side Effects
See Section 11 (Known Risk List.) Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Solution Preparation
IV Infusion: Withdraw contents of vial and add to at least 50 mL of D5W or NS. Mitoxantrone will precipitate if in the same infusion as heparin

Agent Administration
IV Infusion: Give into the tubing of a freely running IV of D5W or NS and infused over at least 3 min or longer (i.e., 30–60 min) depending on the total volume of IV solution. If extravasation occurs, stop infusion and immediately restart in another vein.

Storage Requirements
Mitoxantrone Injection, USP should be stored between 15 and 25º Celsius. Like the original solutions, the dilutions should also not be frozen.

Stability
Following preparation of the infusion, the diluted solution should be stored at room temperature and used within 24 hours. Any original solution which remains in the vial should be discarded.

Nursing Implications Guidelines
Monitor IV insertion site. Transient blue skin discoloration may occur at site if extravasation has occurred.

The physician may wish to monitor cardiac functioning throughout course of therapy. If so, report signs and symptoms of CHF or cardiac arrhythmias.

They physician may choose to order laboratory tests prior to and during the course of treatment. If so, monitor levels.

- Hepatic

- Bilirubin greater than 3.4
  - Patients were found to have an AUC three times greater than patients with normal hepatic function receiving the same dose.
- Renal
  - Pharmacokinetics unknown

Extravastation and phlebitis can occur at the infusion site. If it has occurred stop infusion and start in another vein. Place ice packs over the area of extravasation and elevate for 15 to 20 minutes at least 4 times daily for the first 24 hours. If skin is accidentally exposed to mitoxantrone rinse with warm water. No antidote

Handling
Avoid ingestion, inhalation, skin contact, and eye contact. Precautions may include the use of a containment cabinet during the weighing, reconstitution and/or solubilization of this antineoplastic agent. The use of disposable gloves and respiratory protection is recommended. Proper disposal of contaminated vials, syringes, or other materials is required when working with this product. If mitoxantrone touches skin, wash immediately with copious amounts of warm water.

Availability
This drug is commercially available.

Agent Ordering
Commercially available

Agent Accountability
Commercial supply

Agent Destruction and Return
At the conclusion of the study, any unused mitoxantrone, will be destroyed according to institutional policies.

9.4 GRANULOCYTE-COLONY STIMULATING FACTOR (FILGRASTIM)

Product Description [45,49]
Filgrastim is available in ready-to-use syringes or in a small container (vial) of liquid. The doses are either 300 mcg (micrograms) or 480 mcg.

Classification
Filgrastim is a recombinant, non-glycosylated form of the 175 amino acid protein, granulocyte colony stimulating factor (G-CSF) that induces the proliferation and maturation of neutrophils.

Mechanism of Action
Filgrastim binds to the G-CSF receptor and stimulates the production of neutrophils in the bone marrow. As a G-CSF analog, it controls proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturation time. Filgrastim acts to increase the phagocytic activity of mature neutrophils. In patients receiving cytotoxic chemotherapy, Filgrastim can accelerate neutrophil recovery, leading to a reduction in duration

of the neutropenic phase.

Metabolism
The metabolic fate of filgrastim has not been fully determined and it is not known whether the drug is metabolized or how it is eliminated from the body.

Contraindications
Filgrastim is contraindicated in patients with hypersensitivity to Escherichia coli–derived proteins.

Side Effects
See Section 11 (Known Risk List.) Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

Solution Preparation
Intermittent/Continuous: May dilute with 10–50 mL D5W to yield 15 mcg/mL or greater. If more diluent is used to yield concentrations of 5–15 mcg/mL, 2 mL of 5% human albumin must be added for each 50 mL D5W (prior to adding filgrastim) to prevent adsorption to plastic IV infusion materials.

Do not dilute with saline at any time because the product may precipitate.

Agent Administration

- Intermittent: Give a single dose over 15–30 min. Continuous: Give a single dose over 4– 24 h.
- Subcutaneous

Storage Requirements
Store filgrastim in the refrigerator, between 36 and 46 degrees F (2 and 8 degrees C). Do not freeze. If accidentally frozen, allow the medicine to thaw in the refrigerator. If frozen more than once, the medicine should be thrown away. If filgrastim is left at room temperature for more than 24 hours, it should be discarded. Keep filgrastim out of the reach of children and away from pets.

Stability
Prior to injection, NEUPOGEN may be allowed to reach room temperature for a maximum of 24 hours.

Nursing Implications Guidelines
Monitor patients with preexisting cardiac conditions closely. Myocardial infarction and arrhythmias have been associated with a small percent of patients receiving filgrastim.

Monitor temperature every four hours. Incidence of infection should be reduced after administration of filgrastim.

Assess degree of bone pain if present. Consult physician if nonnarcotic analgesics do not provide relief.

- Consider antibiotic, fungal, PCP prophylaxis during neutropenia. Patients should receive an oral Quinolone, Fluconazole, and Acyclovir to prevent infection once the ANC drops

below 1000.

- Hepatic
  - No dosage adjustments provided
- Renal
  - No dosage adjustment provided

Handling
Filgrastim should not be vigorously shaken.

Availability
This drug is commercially available.

Agent Ordering
Commercially available

Agent Accountability
Commercial supply

Agent Destruction and Return
At the conclusion of the study, any unused filgrastim will be destroyed according to institutional policies.

10 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Overall recommendations

1. Antibiotic Prophylaxis [44]
   a. Fungal Prophylaxis
      Consider prophlaxis during neutropenia and continue until resolution of neutropenia per institutional guidelines
   b. Bacterial prophylaxis per institutional guidelines
      i. Consider fluoroquinolone prophylaxis
   c. Pneumocytis jirovecii (PCP)
      i. Prophylaxis until CD4 count is greater than 200 cells/mcL
      ii. SMX/TMP (Bactrim) preferred
         1. SMX/TMP 400mg/ 80mg once daily or
         2. SMX/TMP 800mg/ 160mg 3 times per week
         3. SMX/TMP 15 mg/kg IV daily in divided doses
      iii. Atovaquone, dapsone, and pentamidine may be used if intolerant to Bactrim
   d. Herpes simplex virus (HSV)
      i. Provide prophylaxis during treatment and including times with and without neutropenia
         1. Acyclovir 400-800 mg PO BID
2. Tumor lysis prophylaxis:

a. Hydration with diuresis
b. Allopurinol or rasburicase.
    i. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence, or impaired renal function.

3. Nausea [43], [46]
    a. Moderate emetic risk: 5-HT3 antagonist + steroid
        i. Day 1-5 15 minutes prior to chemotherapy
            1. Ondansetron 16 mg IV
            2. Dexamethasone 12 mg IV
            3. Ondansetron 8 mg PO BID Day 5 @ 2100 for 5 doses
4. Eye Toxicity
    a. Corticosteroid 2 drops in each eye, 4 times a day for 10 days. The eye drops should be applied within one hour of the administration of high dose cytarabine.

Cladribine

Fever was a frequently observed side effect, especially in neutropenic patients in the first month of therapy. Initiate antibiotics as clinically indicated.

Even though it is a rare side effect, patients may experience tumor lysis syndrome. [38]

Cytarabine

Possible decrease in steady-state digoxin levels
Decrease therapeutic response of gentamycin and fluorocytosine
Cytarabine (Ara-C) Syndrome – 6 to 12 hours after administration of drug, Corticosteroids can prevent and treat this condition. [39]

Mitxantrone

Weak inducer of CYP450 2E1 [40]

Usage of Concurrent/Concomitant Medications

- Inactivated Vaccines [42]
    - Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation.
    - *Risk D: Consider therapy modification*
- Live Vaccines [42]
    - Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live- attenuated vaccines should not be given for at least 3 months after immunosuppressants.
    - *Risk X: Avoid combination*

11 CHEMOTHERAPY KNOWN RISKS

Cladribine [38]

> 10%	1% to 10%	< 1%, post-marketing and/or case reports
Central Nervous System • fatigue • headache **Dermatologic:** • rash **Gastrointestinal:** • nausea • decreased appetite • vomiting **Hematologic and Oncologic:** • neutropenia (grade 4: 70%; recovery by week5) • febrile neutropenia • anemia (1% to 37%; recovery by week 8) • bone marrow depression • thrombocytopenia (grade 4: 12%; recovery by day 12) **Infection:** • Month 1 of treatment **Local:** • injection site reaction **Respiratory:** • abnormal breath sounds **Miscellaneous:** • fever ≥ 100 or ≥ 104	**Cardiovascular:** • edema • tachycardia • phlebitis • thrombosis **CNS:** • dizziness ▪ chills • malaise • insomnia ▪ pain • anxiety • myasthenia **Dermatologic:** • diaphoresis • erythema • pruitius • hyperhidrosis **Gastrointestinal:** • diarrhea • constipation • abdominal pain • flatulence **Neuromuscular and skeletal:** • weakness • myalgia • arthralgia **Respiratory:** • cough • dyspnea • epistaxis • rales	• aplastic anemia • bacteremia • cellulitis • cerebrovascular accident • confusion • conjunctivitis • decreased CD-4 cell count (nadir: 4 to 6 months) • hemolytic anemia • hypereosinophilia • hypersensitivity reaction • impaired consciousness • increased serum bilirubin • increased serum transaminases • lower extremity weakness • myelodysplastic syndrome • opportunistic infection (cytomegalovirus disease, fungal infection, herpes virus infection, listeriosis, *Pneumocystis jirovecii*), pancytopenia (prolonged), pneumonia, polyneuropathy (with high doses), progressive multifocal leukoencephalopathy, pulmonary infiltrates (interstitial), quadriparesis (reported at high doses) • reactivated tuberculosis • renal failure • renal insufficiency (with high doses) • septic shock • Stevens-Johnson • syndrome • toxic epidermal • necrolysis • tumor lysis syndrome • urticaria

Cytarabine [39]

Adverse Events with high dose cytarabine	Frequent	Less Frequent	Infrequent/Case Reports
Cardiovascular • cardiomegaly • cardiomyopathy (in combination with cyclophosphamide) **CNS** • cerebellar toxicity • coma • neurotoxicity (up to 55% in patients with renal impairment) • personality change • somnolence **Dermatologic** • alopecia • desquamation • rash **Gastrointestinal** • ulcer • pancreatitis • peritonitis • pneumatosis • cystoides intestinalis **Hepatic** • hyperbilirubinemia • liver abscess • liver damage • necrotizing colitis **Neuromuscular and Skeletal** • Peripheral neuropathy (motor and sensory) **Respiratory** • pulmonary edema • syndrome of sudden respiratory distress	**CNS** • fever **Dermatologic** • rash **Gastrointestinal** • anal inflammation • anal ulceration • anorexia • diarrhea • mucositis • nausea • vomiting **Hematologic** • myelosuppression • neutropenia • thrombocytopenia • anemia • bleeding • leukopenia • megaloblastosis • reticulocytes decreased **Hepatic** • hepatic dysfunction • transaminases increased **Local** • thrombophlebitis	**Cardiovascular** • chest pain • pericarditis **CNS** • dizziness • headache • neural toxicity • neuritis **Dermatologic** • alopecia • pruritus • skin freckling • skin ulceration • urticaria **Gastrointestinal** • abdominal pain • bowel necrosis • esophageal ulceration • esophagitis • pancreatitis • sore throat **Genitourinary** • urinary retention **Hepatic** • jaundice **Local** • injection site cellulitis **Ocular** • conjunctivitis **Renal** • renal dysfunction **Respiratory** • dyspnea	• Acute respiratory distress syndrome • amylase increased • angina • aseptic meningitis • cardiopulmonary arrest (acute) • cerebral dysfunction • cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia) • exanthematous pustulosis • hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease) • hyperuricemia • injection site inflammation (SubQ injection) • injection site pain (SubQ injection) • interstitial pneumonitis • lipase increased • paralysis (intrathecal and IV combination therapy) • reversible posterior leukoencephalopathy syndrome (RPLS) • rhabdomyolysis • toxic megacolon

Miscellaneous • sepsis		**Miscellaneous** • allergic edema • anaphylaxis • sepsis	

Mitoxantrone [40]

> 10%	1% to 10%	< 1%, postmarketing and/or case reports
Cardiovascular • edema • arrhythmia • cardiac function changes • ECG **CNS** • fever • pain • fatigue • headache **Dermatologic** • alopecia • nail bed changes • petechiae/bruising **Endocrine & Metabolic** • menstrual disorder • amenorrhea • hyperglycemia **Gastrointestinal** • nausea • vomiting • diarrhea • mucositis • stomatitis • anorexia • weight gain/loss • constipation • GI bleeding • abdominal pain dyspepsia	**Cardiovascular** • CHF • ischemia • LVEF decreased • hypertension **CNS** • chills • anxiety • depression • seizure **Dermatologic** • cutaneous mycosis • skin infection **Endocrine/metabolic** • hypocalcemia • hypokalemia • hyponatremia • menorrhagia **Gastrointestinal** • aphthosis **Genitourinary** • impotence **Hematologic** • granulocytopenia • hemorrhage • secondary acute leukemias **Hepatic** • Jaundice	• allergic reaction • anaphylactoid reactions • anaphylaxis • chest pain • dehydration • extravasation at injection site (may result in burning, erythema, pain, skin discoloration, swelling, or tissue necrosis) • interstitial pneumonitis (with combination chemotherapy) • hyperuricemia • hypotension • phlebitis at the infusion site • rash • sclera discoloration (blue) • tachycardia • urine discoloration (blue-green) • urticaria

Genitourinary • urinary tract infection • abnormal urine **Hematologic** • neutropenia • leukopenia • lymphopenia • anemia/hemoglobin decreased • thrombocytopenia • neutropenic fever **Hepatic** • alkaline phosphatase increased • transaminases increased • GGT increased **Neuromuscular/skeletal** • weakness **Renal** • BUN increased • creatinine increased • hematuria **Respiratory** • upper respiratory tract infection • pharyngitis • dyspnea • cough **Miscellaneous** • infection • sepsis • fungal infection	**Neuromuscular/skeletal** • back pain • myalgia • arthralgia **Ocular** • conjunctivitis • blurred vision **Renal** • renal failure • proteinuria **Respiratory** • rhinitis • pneumonia • sinusitis **Miscellaneous** • systemic infection • diaphoresis	

Granulocyte-Colony Stimulating Factor (Filgrastim) [41]

> 10%	1% to 10%	< 1%, postmarketing and/or case reports
Cardiovascular • chest pain **CNS** • fatigue • dizziness • pain **Dermatologic** • skin rash **Endocrine/metabolic** • increased lactate dehydrogenase • increased uric acid **Gastrointestinal** nausea **Hematologic/oncologic** • thrombocytopenia • splenomegaly • petechial **Hepatic** • increased serum alkaline phosphatase **Neuromuscular/skeletal** • ostealgia • back pain **Respiratory** • epistaxis • cough • dyspnea **Miscellaneous** • fever	**Cardiovascular** • peripheral edema • hypertension • cardiac arrhythmia • myocardial infarction **CNS** • headache • hypoesthesia • insomnia • malaise • mouth pain **Dermatologic** • alopecia • erythema • maculopapular rash **Gastrointestinal** • vomiting • constipation • diarrhea **Genitourinary** • decreased appetite • urinary tract infection **Hematologic/oncologic** • anemia • leukocytosis **Hypersensitivity** • transfusion reaction • hypersensitivity reaction **Immunologic** • antibody development **Infection** • sepsis	• acute calcium pyrophosphate • deposition disease (in patients treated for cancer) • anaphylaxis • calcium pyrophosphate deposition disease (in patients treated for cancer) • capillary leak syndrome • cerebral hemorrhage • decreased bone mineral density • decreased hemoglobin • euthymia nodosum • exacerbation of • psoriasis • facial edema • glomerulonephritis • hematuria • hemoptysis • hepatomegaly • hypersensitivity angiitis • hypotension • injection site reaction • osteoporosis • proteinuria • pulmonary alveolar hemorrhage • pulmonary infiltrates • renal insufficiency • respiratory distress syndrome • severe sickle cell crisis • splenic rupture • Sweet syndrome • Tachycardia • Urticarial • Wheezing

	Neuromuscular/skeletal • arthralgia • limb pain • muscle spasm • musculoskeletal pain • weakness **Respiratory** • bronchitis • upper respiratory tract infection	

12 ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENTS (SAE)

12.1 Defining and reporting an Adverse Event

Definition. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

Prior to the trial. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

Reporting source. AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

For non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Signs or symptoms reported as adverse events will be graded and recorded by the investigator, according to the CTCAE version 4. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management from the date the patient signs informed consent until 30 days following the last dose of treatment.

The investigator and his or her team will follow the Medical College of Wisconsin policies related to adverse event reporting.

12.2 Defining and reporting a Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that at any dose:

- **Death.** Results in death.

- **Life threatening**. Is life threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (excluding initial CLAG-M hospitalization and planned hospitalization).

- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Reporting SAEs

Serious AEs must be reported from the date the participant signs Informed consent through 30 days post last dose or until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Since this is an investigator-initiated study, the principal investigator, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor-investigator's IRB when required.

AEs which are serious must be reported to the Data Safety Monitoring Committee (DSMC) from the date the participant signs informed consent through 30 days post last dose on the study.

Reporting to the Data and Safety Monitoring Committee

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to the DSMC as soon as possible, but no later than five calendar days of the sponsor-investigator's observation or awareness of the event.

Report Method: The investigator will use email to report SAEs to the DSMC. The SAE report must include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4 as a guideline whenever possible.

The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

12.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

12.4 Procedure for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant, or suspects that she is pregnant, while participating in this study, she must inform the investigator immediately and permanently discontinue the study drug. The sponsor-investigator must notify the DSMC by email. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately notify the DSMC. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (a sample is provided in Appendix 4)

13 REPORTING AND DOCUMENTING RESULTS

13.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first study drug treatment.

13.2 Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received the planned cladribine based salvage therapy and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according

to the definitions stated below.

13.3 Clinical assessment

Patients will be followed per institutional guidelines for safety assessments. Bone marrow (BM) study obtained at the time of diagnosis of relapsed/refractory AML/high risk MDS will be used as baseline. Repeat BM study will be obtained after the completion of cladribine based salvage therapy when absolute neutrophil count (ANC) recovers to > 1000 cells/cu.mm or at day 30,or when the treating physician determines that it is clinically indicated. If peripheral blasts are present, a bone marrow aspiration/biopsy is not required and should be performed at the discretion of the treating physician. Response to therapy will be assessed according to the standard definitions developed by the international working group [34, 35].. Patients responding to cladribine based salvage therapy may be subsequently considered for allogeneic stem cell transplantation or further consolidation chemotherapy based on the discretion of the treating clinician. Those with PR or no response could be given additional chemotherapy at the treating physician's discretion and patient's tolerability. Hematological toxicity will be assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. MRD assessment and pharmacogenomic assessment is described below in section 15.1 and 15.2.

14 RESPONSE CRITERIA

RESPONSE IN AML

Category	Definition
Complete remission (CR)	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/μL); platelet count >100 x 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 x 10^9/L (1000/μL)) or thrombocytopenia (<100 x 10^9/L (100,000/μL))
Morphologic leukemia-free state	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Cytogenetic CR	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

RESPONSE IN MDS

Complete remission	• Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines
	• Persistent dysplasia will be noted
	• Peripheral blood
	  ○ Hgb ≥ 11 g/dL
	  ○ Platelets ≥ 100 × 10^9/L
	  ○ Neutrophils ≥ 1.0 × 10^9/L†
	  ○ Blasts 0%

Partial remission	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% • Cellularity and morphology not relevant
Marrow CR	• Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† • Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment

14.1 Duration of Response Duration of overall response

The overall response duration is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. The overall CR duration is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Progression-Free Survival
Progression-free survival (PFS) is defined as the time duration from treatment start to progression time.

14.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.0 for reporting of adverse events.

15 CORRELATIVE STUDIES

15.1 Correlative #1

MRD assessment: MRD assessment by flow cytometry will be done on patients achieving CR or CR with incomplete count recovery or marrow CR, at the Wisconsin Diagnostic Laboratory. The

first pulled specimen of the bone marrow aspirate will be used for MRD testing. The test is performed using 8-color flow cytometry (FC). Briefly, EDTA-anticoagulated bone marrow aspirates are lysed and cell suspensions are prepared for incubation with 8 different, fluorochrome-labeled antibodies per tube. Antibodies analyzed across multiple tubes include: CD7, CD11b, CD13, CD14, CD15, CD22, CD33, CD34, CD36, CD38, CD45, CD56, CD64, CD117, and HLA-DR. At least 200,000 events are collected per tube on a FACS CANTO cytometer (BD Biosciences) and analyzed with Paint-A-Gate software (BD Biosciences). Blasts are identified using cluster analysis, based on reproducible forward and light scatter properties and CD45 staining across tubes, along with identification of other cell populations. Aberrant blast immunophenotypes are identified based on comparison with reproducible, known blast antigen expression patterns. Comparisons are also made to previous leukemic blast immunophenotypes, when available. MRD is defined as at least a 0.01% population of aberrant myeloblasts in the absence of morphologic evidence of disease. Contact Dr. Harrington at aharrington@mcw.edu with any MRD collection questions. This sample is collected per standard of care at Froedtert & Medical College of Wisconsin.

15.2 Correlative #2

Pharmacogenomic assessment: Genotyping with the DMET Plus array (Drug Metabolizing Enzymes and Transporters) will be performed using the DNA extracted from blood through Qiagen Blood and Cell Culture DNA extraction kit. This is a high-throughput platform capable of analyzing multiple pharmacogenomic variants (1,931variants in 225 genes) and interrogates biallelic and triallelic single nucleotide polymorphism (SNPs), copy number variations, and insertion/deletions. It uses molecular inversion probes (MIPs) technology and a single-sample genotype calling method that compares each marker to an expected signal distribution defined by large training sets at Affymetrix. It has been validated as a method of studying pharmacogenomics in clinical samples [28, 29]. This analysis will be done at Dr. Ulrich Broeckel's lab in MCW. Genes to be analyzed include those previously described in the pharmacogenomics of cladribine (RRM1, RRM2, RRM2B), mitoxantrone (ABCB1, GALNT14) and cytarabine (ABCB1, ABCC3, SLCO1B1, CDA, SLC 22A12, SLC29A1, RRM1, RRM2, RRM2B, NOS3, ADH1A, DCK, SULT2B1, DCK, GSTM1).

16 STUDY ENDPOINTS

16.1 Primary Endpoint

To determine the rate of MRD negative CR in patients with relapsed/refractory AML/high risk MDS treated with Cladribine based salvage chemotherapy.

16.2 Secondary Endpoints

1. Determination of the overall survival (OS) and progression free survival (PFS) in patients with relapsed/refractory or secondary AML/high risk MDS treated with Cladribine based salvage therapy
2. Determination of disease- or patient-related factors that predict MRD negativity and survival with Cladribine based salvage therapy, including pharmacogenomics.
3. Determination of the role of pharmacogenomics in predicting the development of treatment related toxicities with Cladribine based salvage therapy.

17 STUDY DESIGN

This is a single center non-randomized, single arm prospective study. After obtaining informed consent and enrollment in the clinical trial, patients will be treated with cladribine based salvage chemotherapy. Patients may either be inpatient or outpatient for CLLDAC salvage therapy. Baseline characteristics such as age, gender, race, disease subtype, date of initial diagnosis, date of relapse, interval between diagnosis and relapse, cytogenetics and molecular mutations at diagnosis, prior chemotherapy or HSCT, baseline laboratory tests on admission, percentage of blasts in peripheral blood and bone marrow at diagnosis and relapse will be obtained. Peripheral blood for pharmacogenomics assay will be collected once from consent to day 5. CLAG-M and CLLDAC chemotherapy regimens will be administered as described earlier in the protocol. Patients will be assessed subsequently as mentioned below

17.1 Clinical assessment

Patients will be followed per institutional guidelines for safety assessments. Bone marrow (BM) study obtained at the time of diagnosis of relapsed/refractory AML/high risk MDS will be used as baseline. Repeat BM study will be obtained after the completion of therapy when absolute neutrophil count (ANC) recovers to > 1000 cells/cu.mm or at day 30, or when the treating physician determines that it is clinically indicated. If peripheral blasts are present, a bone marrow aspiration/biopsy is not required and should be performed at the discretion of the treating physician. Response to therapy will be assessed according to the standard definitions developed by the international working group [34, 35].. Patients responding to therapy may be subsequently considered for allogeneic stem cell transplantation or further consolidation chemotherapy based on the discretion of the treating clinician. Those with PR or no response could be given additional chemotherapy at the treating physician's discretion and patient's tolerability. Hematological and extra hematological toxicity will be assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

17.2 MRD assessment

MRD assessment by flow cytometry will be done on patients achieving CR or CR with incomplete count recovery or marrow CR. It is performed using 8-color flow cytometry (FC). Briefly, EDTA-anticoagulated bone marrow aspirates are lysed and cell suspensions are prepared for incubation with 8 different, fluorochrome-labeled antibodies per tube. Antibodies analyzed across multiple tubes include: CD7, CD11b, CD13, CD14, CD15, CD22, CD33, CD34, CD36, CD38, CD45, CD56, CD64, CD117, and HLA-DR. At least 200,000 events are collected per tube on a FACS CANTO cytometer (BD Biosciences) and analyzed with Paint-A-Gate software (BD Biosciences). Blasts are identified using cluster analysis, based on reproducible forward and light scatter properties and CD45 staining across tubes, along with identification of other cell populations. Aberrant blast immunophenotypes are identified based on comparison with reproducible, known blast antigen expression patterns. Comparisons are also made to previous leukemic blast immunophenotypes, when available. MRD is defined as at least a 0.01% population of aberrant myeloblasts in the absence of morphologic evidence of disease. This analysis will be done by pathology at MCW.

17.3 Pharmacogenomic assessment

Genotyping with the DMET Plus array (Drug Metabolizing Enzymes and Transporters) will be performed using the DNA extracted from blood through Qiagen Blood and Cell Culture DNA extraction kit. This is a high-throughput platform capable of analyzing multiple pharmacogenomic variants (1,931variants in 225 genes) and interrogates biallelic and triallelic single nucleotide polymorphism (SNPs), copy number variations, and insertion/deletions. It uses molecular inversion probes (MIPs) technology and a single-sample genotype calling method that compares each marker to an expected signal distribution defined by large training sets at Affymetrix. It has been validated as a method of studying pharmacogenomics in clinical samples [15, 16]. This analysis will be done at Dr Ulrich Broeckel's lab in MCW. Genes to be analyzed include those previously described in the pharmacogenomics of cladribine (RRM1, RRM2, RRM2B), mitoxantrone (ABCB1, GALNT14) and cytarabine (ABCB1, ABCC3, SLCO1B1, CDA, SLC 22A12, SLC29A1, RRM1, RRM2, RRM2B, NOS3, ADH1A, DCK, SULT2B1, DCK, GSTM1). Any leftover blood will be stored for 6 months at Dr. Ulrich Broeckel's Lab.

17.4 Randomization

There is no randomization planned for this study as this is single arm.

17.5 Stratification Factors

There is no preplanned stratification for the institution of treatment or subsequent monitoring. However, during final analysis, patients will be stratified into those who achieve MRD negative CR, MRD positive CR and did not achieve CR.

18 DETERMINATION OF SAMPLE SIZE AND ACCRUAL RATE

Sample size of 90 patients was arrived using binomial proportion estimates of the number of patients needed to achieve an anticipated MRD negativity of 60% of the total patient population who would achieve CR with Cladribine based salvage. Accrual rate of 10 patients per year is determined by the Investigator's personal experience of the number of patients with relapsed/refractory AML/high risk MDS at our Institution.

18.1 Accrual Estimates

With an expected accrual rate of 10 patients per year, and an accrual time of 9 years, we anticipate an eventual accrual of 90 patients. If accrual falls short of expectations within the study period, the study duration will be extended in order to achieve a target sample size of 90 patients.

18.2 Sample Size and Power Estimate

With a projected CR rate of 60% after Cladribine based salvage and a further anticipated MRD-negative rate of 60%, 36% of the study population is anticipated to be in MRD-negative CR. Based on binomial proportions, there will be between 23 and 41 MRD-negative patients with a 95.3% confidence, and an expected 22 MRD-positive CR patients for comparison.

18.3 Interim Analyses and Stopping Rules

There is no interim analysis planned for this trial. The study will complete enrollment once the target number of patients is recruited and received therapy with Cladribine based salvage.

Stopping Rule

Number of Patients, *n*	2	3	7	12	18	25	32	40	48	56	64	73	81	90
Boundary, b_n	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Example: 5 deaths with 13 enrolled would halt the study, 5 deaths with 20 enrolled would continue. 6 deaths with 21 enrolled would halt the study. Stopping Rule applies only to those patient deaths that occur while patient is actively receiving study treatment or patient deaths believed to be, in the treating physician's opinion, related to study treatment.

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.08, using a one-sided level 0.011536 test.

Methods: Sequential boundaries will be used to monitor on-study death rate. The accrual will be halted if excessive numbers of deaths are seen, that is, if the number of deaths is equal to or exceeds bn out of n patients within 30 days of treatment. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most [probability of early stopping] when the rate of deaths is equal to 8%.

This stopping rule has the following characteristics for actual stopping probability, expected accrual and mortality, given these true mortality rates.

True Mortality Rate	Actual probability of stopping	Expected Mortality (SD)	Expected Accrual (SD)
0.08	0.049	6.97 (2.44)	87.03 (14.23)
0.1	0.135	8.29 (2.58)	82.95 (20.37)
0.2	0.911	7.66 (3.30)	38.33 (27.20)

18.4 Analyses Plans

Baseline characteristics will be analyzed using descriptive statistics. The primary objective of the rate of MRD negative CR achieved with Cladribine based salvage will be described using binomial proportion and confidence intervals. Progression-free survival (PFS) will be calculated from the first day of remission after Cladribine based salvage until documentation of another relapse. Overall survival (OS) will be calculated from the first day of salvage therapy until death. PFS and OS estimates will be done by Kaplan-Meier method. For secondary objectives, the log rank test will be used examine the potential significance of patient-related factors. Multivariate analysis using Cox proportional hazard regression method will be used to analyze the

determinants of MRD negative CR, OS, and PFS. All analyses will be done at a significance level of 0.05. Statistical analysis will be supervised by the division of biostatistics at MCW.

18.5 Analysis Population

All patients who meet the study criteria and enrolled in this trial will be included in the final analysis except those who are lost to follow-up or who did not get the planned treatment with Cladribine based salvage therapy.

18.6 Primary Analysis (or Analysis of Primary Endpoints)

Primary end point of the study is to determine the rate of MRD negative CR in patients with relapsed/refractory AML/high risk MDS treated with Cladribine based salvage. This will be done by identifying the number of patients who attained MRD negative CR amongst all those patients who were treated with Cladribine based salvage in this clinical trial.

18.7 Secondary Analysis (or Analysis of Secondary Endpoints)

1. Determination of the overall survival (OS) and progression free survival (PFS) in patients with relapsed/refractory AML/high risk MDS treated with Cladribine based salvage therapy will be done using Kaplan-Meier method
2. Determination of disease- or patient-related factors that predict MRD negativity and survival will be done using multivariate analysis.
3. Pharmacogenomics profile obtained at baseline will be used in predicting MRD negativity, and survival.

18.8 Other Analyses/Assessments

Pharmacogenomics profile obtained at baseline will be used in predicting treatment related toxicities

Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

Study Results

Results of the study will describe the number of patients achieving MRD negative CR with Cladribine based salvage and their OS and PFS. Determinants of MRD negativity, survival and toxicity will be reported as multivariate analysis using hazard ratio, 95% confidence interval.

19 DATA AND SAFETY MONITORING PLAN (DSMP)

19.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee(DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local,

investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with regular safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

19.2 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist and the study biostatistician. While subjects are on treatment, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance are documented.

19.3 Quality Assurance

The MCWCC Clinical Trials Office provides ongoing quality assurance audits.

- Intermediate risk trials are reviewed every year.
- 20% of subject files will be selected randomly for review (a maximum of 10 subjects at each monitoring time point). Consent/eligibility and objective-based data will be reviewed for those files selected.
- One file will be selected randomly for a comprehensive review at each monitoring time point.
- Regulatory documents (IRB submissions, reportable events, etc.) will be reviewed at each monitoring time point.

19.4 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

19.5 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) Grade 4 hematological events are expected and only need routine reporting.
- Review all DSM reports

- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

20 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

20.1 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

20.2 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

20.3 Informed Consent Process

Informed consent is a process that is 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 this therapy will be provided to the subjects and their families.

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

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the

investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

20.4 Protection of Human Subjects Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

20.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

20.6 Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

21 DATA HANDLING AND RECORD KEEPING

21.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

21.2 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

21.3 Study Record Retention

The principal investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects, as well as written records of the disposition of the drug when the study ends.

In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

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APPENDIX 1. *PERFORMANCE STATUS CRITERIA*

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. *PROHIBITED MEDICATIONS*

Other concomitant AML therapy including but not limited to FLT3 inhibitors, IDH1 or IDH2 inhibitors except agents to reduce leukocytosis such as hydroxyurea

APPENDIX 3. *SPECIMEN COLLECTION*

Specimen Collection & Handling

Pharmacogenomic collection:
Collect approximately 10ml of whole blood in an EDTA vacutainer (lavender top) No pre-processing is required

Specimen Labeling:
All tubes must be labeled with the patient's initials, patient study ID#, patient's date of birth, and date/time of specimen collection

Transporting and Storage Requirements:
For all transportations, a requisition should accompany all samples. A copy of the requisition will be retained at the site. Only transport samples Monday thru Friday. Samples can be transported at room temperature. Samples should be packed and transported according to IATA regulations.

Sample Drop Off Procedure:
Location: Children's Hospital-Pediatric TRU

1. All samples must be in a biohazard sample bag.
2. Locate a TRU staff member to unlock the door to the sample room for you.
3. Locate the blue DNL Sample Binder.
    a. On the **DNLSample Pickup Log**,
        i. In the "Sample IN" column, write the sample ID/ attach a sample ID sticker, date, and initial.
        ii. Fill in one line per sample.
        iii. Sample IDs on the blood tubes and sample IDs on the **DNL Sample Pickup Log**must match**.**
    b. Replace DNL SampleBinder to the original location.
4. Place the biohazard bag with samples into the **red** bin marked "**DNL Lab**" in refrigerator.
5. The "**DNL Lab"** bin is checked and any samples are picked up daily from the TRU.

Specimen Requisition Form

A Phase II Study of the Efficacy and Pharmacogenomics of Cladribine based Salvage Chemotherapy in Patients with Relapse/Refractory Acute Myeloid Leukemia (AML)

Patient Information:

Patient initials: _____

Birth Date: _____

Study ID #: _____

Pharmacogenomic Sample Information:

Date of Collection_____Time of Sample Collection _____

Physician_____Email _____

Person Completing Requisition_____Phone Number _____

APPENDIX 4. *PREGNANCY FORM*

Pregnancy occurring in participant in a Clinical Trial of Investigational Medicinal Product, while not considered an adverse event or serious adverse event, requires monitoring and follow up.

The investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects. This includes subjects who become pregnant while participating in a clinical trial or during a stage where the fetus could have been exposed to the investigational medicinal product (e.g., if the active substance or one of its metabolites has a long half-life).

Any pregnancy should be reported by the PI to the sponsor using either a study specific or generic pregnancy reporting form (see below).

The pregnancy should be followed up by the investigator until delivery. It may be necessary to monitor the development of the newborn for an appropriate period post-delivery. Any occurrences that result in a Serious Adverse Event should be reported as per the SAE reporting procedure.

The below form will be used.

Study Drug: Study/Protocol Nº:	PATIENT ID Patient's Initials 1. 2. fam. If applicable Centre No. Patient No	REPORT TYPE Initial ☐ Follow-Up ☐

STUDY PREGNANCY FORM **Page 1 of 3**

1. Country:	2. LOCAL CASE ID:

I. MATERNAL INFORMATION

3. DATE OF BIRTH day monthyear	4. AGE yrs./mo.	5. RACE Caucasian ☐ Oriental ☐ Black ☐ Other ☐	6. HEIGHT cm	7. WEIGHT kg

8. Date of Last Menstrual Period day month year

9. Expected Date of Delivery day month year

10. Method of Contraception	***11. Contraception used as instructed***	**yes**	**no**	**uncertain**
		☐	☐	☐

II. HISTORY

12. PATIENT'S PAST MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy e.g. alcohol, smoking, other substance consumption, hypertension, eclampsia, diabetes including gestational, infections during pregnancy, environmental or occupational exposure that may pose a risk factor).

13. PREVIOUS OBSTETRIC HISTORY – provide details on all previous pregnancies below, including abortion or stillbirth (use page 3 if needed)

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		
5		

14. DRUG INFORMATION – please list the drug(s) first and all other therapies taken prior to or during pregnancy

Drug Names	Daily Dose	Route	Treatment Dates Start	Treatment Dates Stop	Indication	(specify week of pregnancy) Start	(specify week of pregnancy) Stop

2. LOCAL CASE ID:

III. PREGNANCY INFORMATION

18. PRENATAL
Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?

☐ **No** ☐ **Yes** ☐ **Not known**

If yes, please specify test date and results:

19. PREGNANCY OUTCOME

Delivery

☐ **Normal** ☐ **Forceps/Ventouse** ☐ **Caesarean section**

Maternal complications or problems related to birth: _____

Abortion

☐ **Therapeutic** ☐ **Planned** ☐ **Spontaneous** **Please, specify reason and any abnormalities (if known)**

_____

☐ **Unspecified** _____

Date of abortion/delivery day month year
at week _____

20. **MATERNAL PREGNANCY ASSOCIATED EVENTS:**

If the mother experiences a serious adverse drug reaction (ADR) during a pregnancy, please complete a SAE form and submit as requested.

IV. CHILD INFORMATION

21. **Neonate**

☐ **Normal** ☐ **Abnormal** ☐ **Stillbirth** **please specify any abnormalities:** _____

Sex	Height	Weight	Apgar Scores	Head circumference
☐ **Male** ☐ **Female**	**inches**	**pounds**	**1 min.** **5 mins.** **10 mins.**	**inches**

For additional information, please use page 3 (please provide copies of relevant documentation)

V. ASSESSMENT OF PREGNANCY OUTCOME

22. SERIOUSNESS CRITERIA

☐ **Non Serious**

☐ **Mother** died day month year ☐ died **Stillbirth** / Neonate day month year

☐ Involved or prolonged inpatient hospitalization ☐ Life-threatening

☐ Results in persistent or significant disability/incapacity

Other Seriousness Criteria: ☐ Congenital anomaly/birth defect ☐ Other significant medical events

23. ASSESSMENT OF CAUSALITY
Please indicate the relationship between pregnancy outcome and Novartis study drug

☐ Not suspected ☐ Suspected

INFORMATION SOURCE

24. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR	25. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT
Signature:	daymonthyear

2. LOCAL CASE ID:

FOR ADDITIONAL INFORMATION:

INFORMATION SOURCE

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature:	33. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING daymonthyear

PLEASE SEND FORM TO: DSMC

APPENDIX 5. *WHO CLASSIFICATION OF ACUTE MYELOID LEUKEMIA*

AML with certain genetic abnormalities [54]

- AML with a translocation between chromosomes 8 and 21
- AML with a translocation or inversion in chromosome 16
- AML with a translocation between chromosomes 9 and 11
- APL (M3) with a translocation between chromosomes 15 and 17
- AML with a translocation between chromosomes 6 and 9
- AML with a translocation or inversion in chromosome 3
- AML (megakaryoblastic) with a translocation between chromosomes 1 and 22

AML with myelodysplasia-related changes

AML related to previous chemotherapy or radiation

AML not otherwise specified (This includes cases of AML that don't fall into one of the above groups, and is similar to the FAB classification.)

- AML with minimal differentiation (M0)
- AML without maturation (M1)
- AML with maturation (M2)
- Acute myelomonocytic leukemia (M4)
- Acute monocytic leukemia (M5)
- Acute erythroid leukemia (M6)
- Acute megakaryoblastic leukemia (M7)
- Acute basophilic leukemia
- Acute panmyelosis with fibrosis

Myeloid sarcoma (also known as granulocytic sarcoma or chloroma)

Myeloid proliferations related to Down syndrome

Undifferentiated and biphenotypic acute leukemias (leukemias that have both lymphocytic and myeloid features). Sometimes called ALL with myeloid markers, AML with lymphoid markers, or mixed phenotype acute leukemias.