

**FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE**

Current version: 04/17/2017
Previous version: 03/28/2017

A Phase 1/2 Trial of G-CSF, Cladribine, Cytarabine, and Dose-Escalated Mitoxantrone (G-CLAM) in Adults with Newly Diagnosed or Relapsed/Refractory Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndromes (MDS)

Principal Investigator:

- Roland B. Walter, MD PhD, Associate Member, FHCRC; Associate Professor, UW (206-667-3599)

Co-Investigators at FHCRC/UW:

- Anna B. Halpern, MD, Research Associate, FHCRC; Acting Instructor in Medicine, UW (206-314-5944)
- Sarah A. Buckley, MD, Senior Hematology/Oncology Fellow, UW (206-416-5066)
- Elihu H. Estey, MD, Member, FHCRC; Professor, UW (206-288-7176)
- Mary-Beth Percival, MD, Assistant Member, FHCRC; Assistant Professor, UW (206-288-1320)
- Tara L. Chen, PharmD, BCOP, Affiliate Investigator, UW/SCCA

Biostatistician:

- Megan Othus, PhD, Associate Member, FHCRC (206-667-5749)

Study Coordinator FHCRC:

- Anna B. Halpern, MD, Research Associate, FHCRC; Acting Instructor in Medicine, UW (206-314-5944)

Emergency Phone (24 hours):

For non-transplant patients: Call the paging operator at the University of Washington Medical Center at 206-598-6190, and ask for the Fellow on call for Hematology/Oncology.

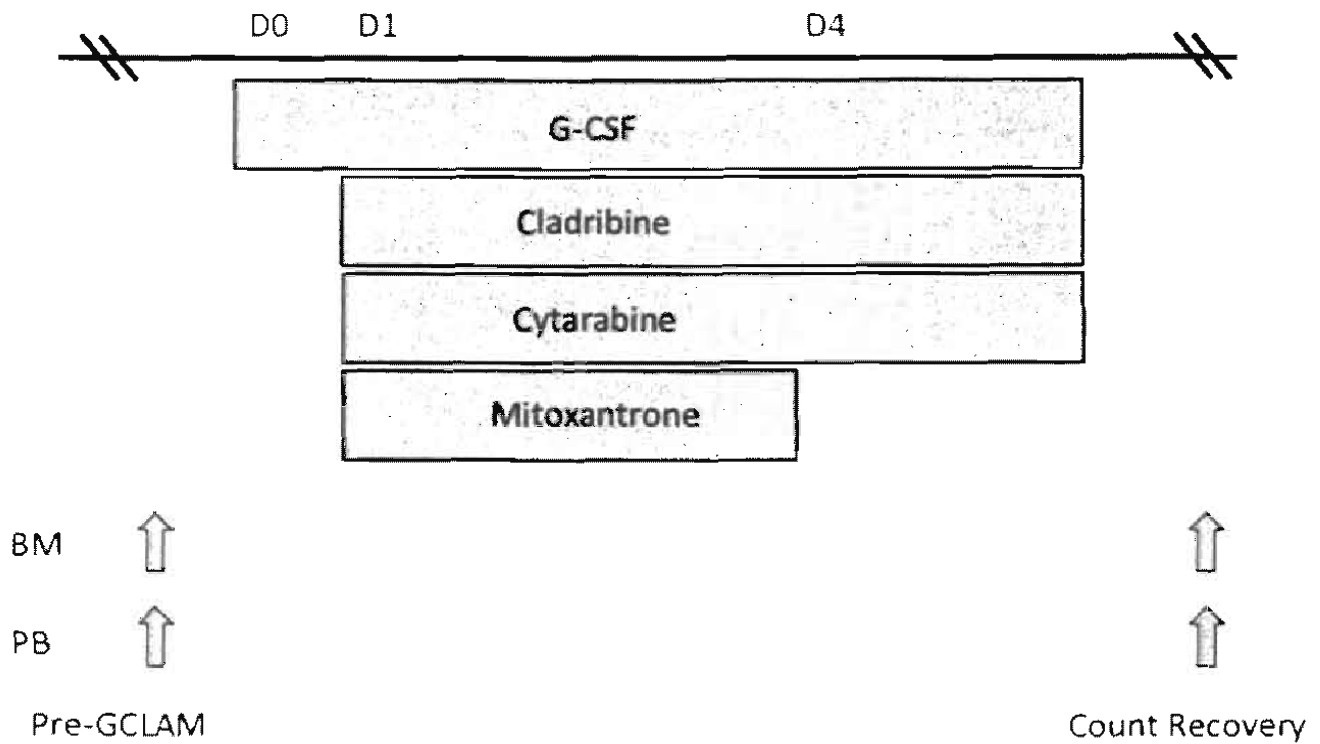
For transplant patients: Call the 8NE front desk at the University of Washington Medical Center at 206-598-8902, and ask for the triaging provider covering the transplant service.

FHCRC IRB Approval

DEC 29 2017

Document Released Date

OVERVIEW OF THE TREATMENT PLAN



DOSE ESCALATION SCHEME

Level	G-CSF (SQ, D0 to D5) ¹	Cladribine (IV, D1 to D5) ²	Cytarabine (IV, D1 to D5) ^{2,3}	Mitoxantrone (IV, D1 to D3) ²
1	300 or 480 µg	5 mg/m ²	2 g/m ²	12 mg/m ²
2	300 or 480 µg	5 mg/m ²	2 g/m ²	14 mg/m ²
3	300 or 480 µg	5 mg/m ²	2 g/m ²	16 mg/m ²
4	300 or 480 µg	5 mg/m ²	2 g/m ²	18 mg/m ²

¹Dosing based on patient weight: <76 kg vs. ≥76 kg; D0 and D1 dose may be omitted if WBC >20,000/µL. ²Dosing based on actual patient weight. ³Started 2h after completion of cladribine

TABLE OF CONTENTS

OVERVIEW OF TREATMENT PLAN	2
DOSE-ESCALATION SCHEME	2
1.0 Background and Rationale	4
2.0 Objectives	6
3.0 Patient Eligibility	6
4.0 Evaluation and Counseling of Patient	8
5.0 Protocol Registration	8
6.0 Treatment Plan	8
7.0 Information on Study Drugs	13
8.0 Evaluations and Endpoint Definitions	17
9.0 Records	18
10.0 Correlative Studies	18
11.0 Protocol Enrollment and Special Considerations	19
12.0 Guidelines for Serious Adverse Event Reporting	19
13.0 Data and Safety Monitoring Plan	21
14.0 Ethical and Regulatory Considerations	21
15.0 Statistical Considerations for Patients with Newly Diagnosed Disease	22
16.0 Statistical Considerations for Patients with Relapsed/Refractory Disease	25
17.0 Study Termination	26
18.0 References	27
Appendix A: WHO Classification and Criteria for MDS	29
Appendix B: WHO Classification of Acute Myeloid Leukemia	30
Appendix C: Treatment-Related Mortality (TRM) Score	31
Appendix D: Cardiotoxicity Index of Anthracyclines	32
Appendix E: Research Subject Registration Form	33

1.0 BACKGROUND AND RATIONALE

Despite some recent improvements in treatment, adult acute myeloid leukemia (AML) remains a difficult-to-treat malignancy, with only gradual improvements over the last 3-4 decades.^{1,2} Although many patients will achieve a complete remission (CR) with 1 or 2 courses of curative-intent, intensive induction chemotherapy, the majority will ultimately relapse, and few patients will be alive 2-5 years after diagnosis.^{1,2} Patients have particularly poor outcomes if relapses occur early after initial remission or if the disease proved primary refractory to initial induction therapy; the outlook is similarly bleak for patients receiving second, third, and fourth salvage regimens, with CR rates of 11%, 10%, and 6% respectively.³ Therefore, the need for better first-line as well as salvage therapies for relapsed or refractory AML is unquestioned.

While the chemotherapeutic regimens have changed little over the last 4 decades, incremental improvements have been made over the last several years. Specifically, well-controlled studies have indicated that escalated doses of anthracyclines given during initial induction chemotherapy can improve response rates and survival.^{4,5} In addition, a single phase 3 randomized study has suggested that the addition of cladribine to a standard cytarabine/anthracycline-containing backbone may improve responses and survival.⁶ Furthermore, a very recent study has demonstrated that the combination of fludarabine, high-dose cytarabine, granulocyte colony stimulating factor (G-CSF), and idarubicin (“FLAG-Ida”) may be superior to a regimen containing standard-dose cytarabine and an anthracycline.⁷ Together, these data suggest benefits of escalated doses of an anthracycline, cladribine, and high-dose cytarabine during induction chemotherapy.

In 2008, Polish investigators reported their experience with the use of G-CSF, cladribine (5 mg/m² on days 1-5), high-dose cytarabine (2,000 mg/m² on days 1-5), and mitoxantrone (10 mg/m² on days 1-3; “G-CLAM”) for the treatment of primary refractory AML or early relapsed disease, with encouraging activity – among 118 treated patients, a complete remission (CR) rate of 58% was obtained – and acceptable tolerability.⁸ While this regimen has not yet been directly compared with other salvage regimens in a controlled fashion, a recent retrospective analyses from consecutive patients treated at a single institution indicated that a relatively similar regimen (cladribine, cytarabine, and G-CSF; i.e. without inclusion of mitoxantrone) may be superior than the standard salvage regimen, MEC (mitoxantrone, etoposide, cytarabine) for relapsed/refractory AML.⁹

Since 2012, we have used G-CLAM in 26 adults with AML, primarily those with relapsed/refractory disease. Among 23 currently evaluable patients (as of August 11, 2013), we observed 13 CRs (57%; unpublished data). While many tolerated the treatment well with reversible side effects, 6 patients required intensive care unit (ICU)-level care and 3 of these died early after administration of chemotherapy. Infectious complications were common, with 20 patients (87%) developing febrile neutropenia, 15 (65%) developing a documented infection, and 11 (48%) developing a bloodstream infection. Importantly, stratification by treatment related mortality (TRM) score¹⁰ allowed the separation of patients into those with lower and others with higher risk for treatment-related morbidity and mortality. Specifically, using a TRM score cut-off of 6.9, which corresponded to a predicted 28-day mortality of 3% for those scores below this cut-off and a mortality of 20% or greater in those with scores above this cut-off in a cohort of >2,200 patients with newly diagnosed AML receiving standard induction therapy,¹⁰ those with higher

scores appeared to have a higher likelihood of death (2/8 [25%] vs. 1/14 [7%] for those patients with available TRM score data) and requirement for ICU-level care (4/8 [50%] vs. 2/14 [14%] than those with lower scores. Likewise, they were more likely to experience fever ($P=0.048$) and infection ($P=0.041$), as well as Grade 3-4 adverse events (62.5% vs. 28.6%; CTCAE vs. 4.03), although the latter difference did not reach statistical significance ($P=0.19$).

Based on the tolerability and efficacy of G-CLAM in low-risk patients, as well as the above mentioned data suggesting benefit of escalated doses of anthracyclines in adult AML,^{4,5} our goal is to determine whether a G-CLAM based regimen that includes escalated doses of mitoxantrone (an anthracenedione, a drug structurally related to anthracyclines) provides an improved treatment option for adult patients with either newly diagnosed or relapsed/refractory AML with lower-risk TRM scores in a phase 1/2 trial. Our dose escalation protocol is based on prior studies evaluating toxicities of higher doses of mitoxantrone in acute leukemia. Compared to the standard total dose in the G-CLAM regimen of 30 mg/m² (delivered as 10 mg/m² daily for 3 doses), doses up to 100 mg/m² (delivered as 20 mg/m² daily for 5 doses) have been used in a single agent dose escalation trial with dose-limiting toxicities (DLTs) occurring in only a minority of patients (most common was oral mucositis).¹¹ Furthermore, doses of 60 mg/m² (delivered as 15 mg/m² for 4 daily doses) have been described without DLT in a trial of dose escalation as part of the FLAM regimen (flavopiridol, cytarabine, and mitoxantrone).¹² Given these observations, we will conduct a phase 1/2 study to determine the maximum tolerated dose (MTD) of mitoxantrone when used as part of the G-CLAM regimen separately for patients with newly diagnosed AML and those with relapsed/refractory AML requiring salvage therapy. Our study will explore step-wise higher doses of mitoxantrone starting with 12 mg/m² and increasing by 2 mg/m² for each dose level up to 18 mg/m² (resulting in a total dose of 54 mg/m² over 3 days). For dose escalation in phase 1, we will determine the maximum tolerated dose (MTD) as the highest dose studied in which the incidence of DLTs is <33%, loosely based on the rules from the classic “3+3” phase 1 design where 1 DLT observed among 6 participants is acceptable, whereas 2 DLTs among 6 participants are not. Since many of our potential study participants have received chemotherapy regimens containing anthracyclines – and anthracycline use is associated with cumulative, dose-dependent risk of cardiotoxicity¹³ – the adequacy of baseline cardiac function will be ascertained as part of the pre-treatment evaluation.

1.1 Interim Data Update on Newly Diagnosed Arm

As of January 20, 2016, we have data available for response assessment from 66 patients enrolled in the study arm for newly diagnosed AML or high-risk MDS (including 47 patients treated at the MTD), and have compared the observed responses with those from 300 patients with newly diagnosed AML treated on the SWOG S0106 trial with standard induction chemotherapy (“3+7”). On average, patients in the G-CLAM study were significantly older than the S0106 patients (mean age 58 vs. 49 years, $p<0.001$) and had less favorable disease (favorable risk: 6% vs. 14%, $p=0.025$; unfavorable risk: 23% vs 18%, $p=0.025$). Despite these differences, patients receiving G-CLAM more likely achieved a CR/CRi with incomplete count recovery (CRi) than patients treated on S0106 trial (88% vs. 70%, $p=0.0021$). In multivariable analysis, the odds ratio (OR) for achieving CR/CRi in the G-CLAM vs. S0106 study was 2.99 (95% CI: 1.26-7.06, $p=0.013$) after adjustment for a variety of factors including age, gender, risk group, and mutational status. The depth of the responses appeared deeper with G-CLAM, as indicated by fact that the proportion of CR patients achieving a minimal residual disease-negative

(MRD^{neg}) remission was higher with G-CLAM than “3+7” (86% vs. 77%, p=0.19; adjusted OR=1.93 [0.68-5.44], p=0.21. Among the 47 patients treated at the MTD, the adjusted OR for CR/CRi for G-CLAM vs. “3+7” was similar to the entire cohort (2.02 [0.83-4.92], p=0.12, as was the adjusted OR for MRD^{neg} CR (2.7 [0.78-9.32], p=0.12). The relatively small number of patients receiving G-CLAM provides estimates with wide confidence intervals, limiting the conclusions that so far can be drawn.

1.2 Update on Relapsed/Refractory Arm: Now Closed to Accrual

As of 4/11/17, the last patient has enrolled on the relapsed/refractory arm on this trial. Per the statistical section 16.2, the plan for phase 2 of this arm was based on a two-stage design. In the first stage, 20 eligible patients were to be accrued, including those treated at the maximum tolerate dose (MTD) in phase 1 which was mitoxantrone at 16mg/m². In these first 20 patients, 7 achieved either a CR or CRps; therefore, 20 additional patients were accrued for a total of 40 patients treated at the MTD. Thus far, 38 of these 40 patients are evaluable for response: with 20 achieving either a CR or CRp (another 2 have a CR with incomplete neutrophil recovery [CRi]), our study exceeded the threshold to be considered worthy of further investigation.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 Estimate the maximum tolerated dose (MTD) of dose-intensified mitoxantrone as part of the G-CLAM regimen separately for adults with newly diagnosed AML and those with relapsed/refractory AML receiving first or greater salvage therapy.

2.2 Secondary Objectives

2.2.1 To determine, within the limits of a Phase 1/2 study, disease response and duration of remission separately for patients with newly diagnosed and relapsed/refractory AML.

2.2.2 To describe, within the limits of a Phase 1/2 study, the toxicity profile of the study regimen separately for patients with newly diagnosed and relapsed/refractory AML.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Age \geq 18 years

3.1.2 For patients with newly diagnosed disease: diagnosis of “high-risk” MDS (\geq 10% blasts) or AML other than acute promyelocytic leukemia (APL) with t(15;17)(q22;q12) or variants according to the 2008 WHO classification (see Appendices A and B). For patients with relapsed/refractory disease: prior diagnosis of “high-risk” MDS or non-APL AML, with relapsed/refractory disease according to standard criteria^{2,14} requiring first or subsequent salvage therapy. Patients with biphenotypic AML are eligible.

- 3.1.3 Outside diagnostic material is acceptable as long as peripheral blood and/or bone marrow slides are reviewed at the study institution. Flow cytometric analysis of peripheral blood and/or bone marrow should be performed according to institutional practice guidelines.
- 3.1.4 For patients with relapsed/refractory disease: patients with prior autologous or allogeneic hematopoietic cell transplantation (HCT) for MDS/AML are eligible if relapse occurs provided symptoms of graft-versus host disease are well controlled with stable use of immunosuppressive agents.
- 3.1.5 Treatment-related mortality (TRM) score ≤ 6.9 as calculated with simplified model¹⁰ (see Appendix C).
- 3.1.6 The use of hydroxyurea prior to study registration is allowed. Patients with symptoms/signs of hyperleukocytosis or WBC $>100,000/\mu\text{L}$ can be treated with leukapheresis or may receive up to 2 doses of cytarabine (up to $500 \text{ mg}/\text{m}^2/\text{dose}$) prior to enrollment.
- 3.1.7 For patients with relapsed/refractory disease: patients may have previously received chemotherapy with a mitoxantrone- or cladribine-based regimen for MDS or AML. If the patient has received G-CLAM before and has been sensitive to this regimen, eligibility will be determined on a case-by-case basis by the Study PI.
- 3.1.8 Should be off any active systemic therapy for AML with the exception of hydroxyurea for at least 14 days prior to study registration unless patient has rapidly progressive disease, and all Grade 2-4 non-hematologic toxicities should have resolved.
- 3.1.9 Adequate organ function.
 - 3.1.9.1 Bilirubin ≤ 2.5 x Institutional Upper Limit of Normal (IULN) unless elevation is thought to be due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis (assessed within 14 days prior to study day 0).
 - 3.1.9.2 Serum creatinine $\leq 2.0 \text{ mg}/\text{dL}$ (assessed within 14 days prior to study day 0).
 - 3.1.9.3 Left ventricular ejection fraction $\geq 45\%$, assessed within 3 months prior to study day 0, e.g. by MUGA scan or echocardiography, or other appropriate diagnostic modality and no clinical evidence of congestive heart failure. If the patient had anthracycline-based therapy since the most recent cardiac assessment, cardiac evaluation should be repeated if there is clinical or radiographic suspicion of cardiac dysfunction, or if the previous cardiac assessment was abnormal.
- 3.1.10 Women of childbearing potential and men must agree to use adequate contraception.
- 3.1.11 Provide written informed consent.

3.2 Exclusion Criteria

- 3.2.1 Myeloid blast crisis of chronic myeloid leukemia (CML), unless patient is not considered candidate for tyrosine kinase inhibitor treatment.

- 3.2.2 Concomitant illness associated with a likely survival of <1 year.
- 3.2.3 Active systemic fungal, bacterial, viral, or other infection, unless disease is under treatment with anti-microbials and/or controlled or stable (e.g. if specific, effective therapy is not available/feasible or desired [e.g. chronic viral hepatitis, HIV]). Patient needs to be clinically stable as defined as being afebrile and hemodynamically stable for 24 hours. Patients with fever thought to be likely secondary to leukemia are eligible.
- 3.2.4 Known hypersensitivity to any study drug.
- 3.2.5 Pregnancy or lactation.
- 3.2.6 Treatment with any other investigational agent.

4.0 EVALUATION AND COUNSELING OF PATIENT

The patient will be completely evaluated with a history, physical examination, diagnostic testing if necessary, and review of outside slides and records if available. The protocol will be discussed thoroughly with the patient and family (if present), with description of all known risks to the patient. Alternative forms of treatment will be presented as objectively as possible, and the risks and hazards of the study explained to the patient. Consent will be obtained using forms approved by the local Institutional Review Board (IRB).

5.0 PROTOCOL REGISTRATION

To register, the attending physician involved in the care of the potential study participant must contact either the Principal Investigator or the Study Coordinator and fax the Research Subject Registration Form (Appendix E) to the study team (FAX: +1-206-667-6519). For registration, a completed Research Subject Registration Form including completed eligibility checklist (Appendix E), a copy of the signed consent form, and a signed HIPAA authorization must be available, and all eligibility requirements according to section 3.0 must be met. To complete the registration process, the Principal Investigator or his designee will assign a patient study number, and register the patient on the study.

6.0 TREATMENT PLAN

This study is an open-label, Phase 1/2 dose escalation trial designed to estimate the maximum tolerated dose (MTD) of mitoxantrone as part of G-CLAM chemotherapy separately in adults with newly diagnosed AML/high-risk MDS and those with relapsed/refractory disease requiring first or greater salvage therapy. Bone marrows will be reassessed upon blood count recovery or between day Days +25 to +31 after start of chemotherapy, whichever occurs first. Patients who achieve a CR or CR with incomplete platelet count recovery (CRp) are eligible for consolidation chemotherapy with G-CSF, cladribine, and cytarabine (i.e. "G-CLA"). Patients with CRi, partial remission, or persistent disease are eligible for a second course of induction chemotherapy provided all non-hematologic toxicities have resolved to Grade <2, and become eligible for consolidation chemotherapy with G-CLA if a CR, CRp, or CRi is obtained with the 2nd cycle of induction therapy.

Update: the relapsed/refractory arm is now closed to accrual.

6.1 Baseline/Pre-Treatment Assessment

The following studies should be obtained at baseline before initiation of study therapy to establish trial eligibility and allow patient characterization and disease prognostication:

- 6.1.1** History and physical examination (assessed within 14 days prior to study day 0).
- 6.1.2** Bone marrow examination with morphologic and flow cytometric assessment, routine cytogenetic analysis, and molecular testing (FLT3/ITD, NPM1, CEBPA); a bone marrow biopsy should be obtained if spicules are absent from the aspirate sample. Bone marrow examination is not required if >20% blasts are present in the peripheral blood as per International Working Group recommendations^{2,14} (either assessed up to 2 months prior to study day 0 as long as no anti-AML therapy has been given in the interim).
- 6.1.2** Complete blood counts with differential blood count, including immature cells/blasts; platelet count (assessed within 14 days prior to study day 0).
- 6.1.3** Metabolic panel, including electrolytes (Na, K), bilirubin, albumin, and creatinine (assessed within 14 days prior to study day 0).
- 6.1.4** MUGA scan or echocardiography, or other appropriate diagnostic modality, to assess left ventricular ejection fraction (LVEF; assessed within 3 months prior to study day 0).

6.2 Pre-Treatment

At the discretion of the treating physician, allopurinol 300 mg po daily (or equivalent dose adjusted for renal function) may be considered in all patients without known allergies to allopurinol to reduce the risk of tumor lysis. Higher doses of allopurinol are permitted if patients develop tumor lysis syndrome. Patients may receive rasburicase, a recombinant uric acid oxidase, for the prevention and/or treatment of tumor lysis syndrome at the discretion of the treating physician. All patients should be adequately hydrated and receive anti-emetics as necessary.

6.3 Administration of Mitoxantrone

- 6.3.1** Patients will receive mitoxantrone at 1 of 4 total dose levels as allocated: Level 1, 12 mg/m²/day on Days 1 through 3; Level 2, 14 mg/m²/day on Days 1 through 3; Level 3, 16 mg/m²/day on Days 1 through 3; and Level 4, 18 mg/m²/day on Days 1 through 3. If dose Level 1 is found to be too toxic, dose escalation of G-CLAM will be considered not feasible, and the study will be terminated.
- 6.3.2** The dose of mitoxantrone is calculated using the patient's actual weight.
- 6.3.3** Mitoxantrone will be administered IV over 60 minutes.
- 6.3.4** All treatment is given as intent-to-treat; missed doses will not be made up.
- 6.3.5** No investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

6.4 Administration of G-CSF, Cladribine, and Cytarabine

- 6.4.1** The dose of the other elements of G-CLAM chemotherapy will be as follows: G-CSF 300 or 480 μg (based on actual weight: <76 kg vs. ≥ 76 kg) subcutaneously daily on Days 0-5, cladribine 5 mg/m^2 daily IV over 2 hours on Days 1-5, and cytarabine 2 g/m^2 daily IV over 2 hours on Days 1-5. Note that we refer to the first day of G-CLAM induction as Day +1 for all cohorts.
- 6.4.2** The doses of G-CSF, cladribine, and cytarabine are calculated using the patient's actual weight.
- 6.4.3** If WBC $>20,000/\mu\text{L}$, Day 0 and Day 1 G-CSF may be omitted at provider discretion.
- 6.4.4** Administration in the outpatient clinic can be considered but should be discussed with the study investigators.
- 6.4.5** All treatment is given as intent-to-treat; missed doses will not be made up.
- 6.4.6** No investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

6.5 Monitoring during/after Induction Therapy

For patient monitoring, the following studies and study intervals are suggested:

- 6.5.1** Complete blood counts with differential blood count, including immature cells/blasts, and platelet count at least 3 times weekly until ANC $>1,000/\mu\text{L}$ and then at least weekly until platelet count $>100,000/\mu\text{L}$.
- 6.5.2** Metabolic panel, including electrolytes (Na, K), bilirubin, ALT/AST, and creatinine at least weekly until ANC $>1,000/\mu\text{L}$ and platelet count $>100,000/\mu\text{L}$.
- 6.5.3** If patients develop signs or symptoms suggestive of cardiac dysfunction, LVEF should be assessed using the same method to evaluate baseline LVEF status (MUGA scan or echocardiography, or other appropriate diagnostic modality).

6.6 Assessment for Response after First Induction Course

A bone marrow aspirate should be obtained upon blood count recovery (i.e. ANC $>1,000/\mu\text{L}$ and platelet count $>100,000/\mu\text{L}$) or between Days +25 to +31 after start of G-CLAM chemotherapy, whichever occurs first; a bone marrow biopsy should be obtained if spicules are absent from the aspirate sample. In patients with unclear response status, the bone marrow examination should be repeated every 7-10 days until the response can be assessed or until Day +45. Responses are defined in section 8.1.

- 6.6.1 Patients achieving CR or CRp:** Patients are eligible for consolidation chemotherapy, as described in section 6.8.
- 6.6.2 Patients with CRi, partial remission, or persistent disease:** patients are eligible for a second course of induction chemotherapy provided all non-hematologic toxicities have resolved to Grade <2 . For patients who experienced \geq Grade 3 non-hematologic toxicities during the first induction, a dose reduction is recommended as described in section 6.7.

- 6.6.3** Patients with persistent aplasia without evidence of disease after Day +45: patients will be removed from protocol.

6.7 **Dose Modifications of Chemotherapeutic Drugs for Subsequent Treatment Cycles**

The following dose modifications are suggested both for subsequent treatment cycles:

- 6.7.1** If a patient develops Grade ≥ 3 non-hematologic toxicity other than Grade 3 infections within 21 days from the last dose of G-CLAM, subsequent doses of cladribine and cytarabine will be reduced by 25% and dose of mitoxantrone will drop by one level (2 mg/m^2). The patient may receive future cycles using this dose-reduced regimen if he/she demonstrated potential response and once the non-hematologic toxicity has resolved to a level of \leq Grade 2. If a patient develops Grade ≥ 3 non-hematologic toxicity other than Grade 3 infection within 21 days from the last dose of the dose-reduced regimen, the dose of the cladribine and cytarabine for subsequent cycles will be reduced by 50% and the dose of mitoxantrone will drop by two levels (4 mg/m^2). The patient may receive future cycles using the new dose-reduced regimen, if the patient demonstrated potential response and once the non-hematologic toxicity has resolved to a level of $<$ Grade 2, unless, at any time, a patient displays Grade ≥ 3 non-hematologic toxicity other than Grade 3 infections while receiving the new dose-reduced regimen, at which point the patient will not be eligible for additional therapy as part of the protocol. Furthermore, if patients require treatment interruption of > 21 days from the planned start of the next cycle, the patient will be not be eligible for additional therapy as part of the protocol.
- 6.7.2** Mitoxantrone: Consider dose reduction of mitoxantrone by 50% if the bilirubin concentration is $1.5\text{-}4.5 \times \text{IULN}$. The dose of mitoxantrone will be reduced to 25% if the bilirubin concentration is $>4.5 \times \text{IULN}$.
- 6.7.3** Cladribine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases to less than 50 mL/min during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.
- 6.7.4** Cytarabine: If the serum creatinine exceeds 2.0 mg/dL and/or estimated creatinine clearance (calculated by Cockcroft-Gault) decreases significantly during therapy, we will consider dose reduction in discussion with the Oncology Pharmacist.

6.8 **Consolidation Therapy**

After a maximum of 2 cycles of induction therapy, patients are eligible for consolidation therapy if CR/CRp/CRi is achieved by the end of induction.

- 6.8.1** The treatment is similar to the induction course but without mitoxantrone (i.e. G-CSF, cladribine, and cytarabine, "G-CLA"), provided the patient had $<$ Grade 3-4 non-hematologic toxicity during induction. If there was such toxicity, doses should be reduced as described in section 6.7.
- 6.8.2** Consolidation courses should start within 6 weeks of achieving CR/CRp/CRi once patients have recovered to \leq Grade 2 toxicities from the previous course of therapy.

- 6.8.3 Patients can receive up to 4 courses of consolidation therapy.
- 6.8.4 Patients can proceed to transplantation barring contraindications and if a suitable donor is available.

6.9 Supportive Therapy

- 6.9.1 All patients will be adequately hydrated and receive appropriate anti-emetics based upon institutional guidelines.
- 6.9.1 Additional growth factors may be used according to institutional practice guidelines or the preference of the attending physician.
- 6.9.2 Antimicrobial prophylaxis should be used according to institutional practice guidelines. In case of neutropenic fever, standard diagnostic testing will be performed, and empiric antibiotic coverage will be utilized as per usual care and standard institutional practices.
- 6.9.3 Transfusional support should be carried out according to institutional practice guidelines.

6.10 Treatment of CNS Disease

Treatment of CNS disease is done according to institutional practice guidelines or the preference of the attending physician.

6.11 Recommended Follow-up Care

After completion of protocol treatment, patients should be evaluated by treating physicians according to institutional and/or national guidelines or the discretion of the attending physician. These evaluations may include peripheral blood studies and/or bone marrow examinations, as clinically indicated.

6.12 Criteria for Removal from Treatment

All reasons for discontinuation of treatment must be documented:

- 6.12.1 Completion of protocol treatment.
- 6.12.2 Consolidation with HCT after achievement of CR, CRp, or CRi.
- 6.12.3 Failure to achieve CR, CRp, or CRi after up to 2 cycles of G-CLAM induction therapy.
- 6.12.4 Persistent aplasia without evidence of leukemia after Day +45.
- 6.12.5 Relapse after achievement of CR, CRp, or CRi during treatment.
- 6.12.6 Adverse toxicities that prevent continuation with study treatment.
- 6.12.7 Withdrawal of consent; the patient may withdraw from the study at any time for any reason.

7.0 INFORMATION ON STUDY DRUGS

7.1 Drug Information on G-CSF (Granulocyte colony-stimulating factor)

- 7.1.1 Mechanism of Action: G-CSF is a growth factor that stimulates the production, maturation, and activation of neutrophils. Further, it promotes premature release of neutrophils from the bone marrow and enhances their phagocytic capacity.
- 7.1.2 Pharmacokinetics: Peak G-CSF concentrations after sub-cutaneous dosing occur in 2 to 8 hours, though the onset of action is approximately 24 hours, with plateau concentrations in 3-5 days, and elimination over an 11-20 day period. G-CSF is cleared by systemic degradation. Notably, as G-CSF binds neutrophils, plasma levels are controlled in large part by the absolute neutrophil count.¹⁵
- 7.1.3 Adverse Effects (AEs): *Common drug-related AEs (occurring in >10% of patients)* include fever, petechiae, elevated uric acid, splenomegaly, bone pain, and epistaxis. *Less common drug-related AEs (occurring in 1% -10% of patients)* include hyper- or hypotension, arrhythmias, headache, nausea, vomiting, leukocytosis, and transfusion reaction. *Infrequent drug-related AEs (occurring in <1% of patients)* include acute respiratory distress syndrome, allergic reactions, alopecia, alveolar hemorrhage, arthralgia, bone density decrease, capillary leak syndrome, cerebral hemorrhage, vasculitis, dyspnea, edema, erythema nodosum, hematuria, hemoptysis, hepatomegaly, hypersensitivity, injection site reaction, pericarditis, proteinuria, psoriasis exacerbation, pulmonary infiltrates, renal insufficiency, sickle cell crisis, splenic rupture, Sweet's syndrome, tachycardia, and thrombophlebitis.
- 7.1.4 Recommended dose adjustments for organ dysfunction: There is limited or no data examining the toxicity of G-CSF in patients with renal or liver dysfunction. Therefore, administration of G-CSF to patients with liver or kidney disease must be done with caution.

7.2 Drug Information on Cladribine (2-chloro-2'-deoxyadenosine, 2-CdA)

- 7.2.1 Mechanism of Action: Cladribine is a prodrug that is converted to an adenosine deaminase-resistant triphosphate derivative (2-CdATP). This molecule is then activated by deoxycytidine kinase to a 5'-triphosphate derivative (2-CdAMP), which is incorporated into DNA where it acts as a transcription regulator. In addition to its cytotoxic properties in dividing cells, cladribine induces death in quiescent cells of lymphoid origin through an unknown mechanism.¹⁶
- 7.2.2 Pharmacokinetics: Cladribine is renally excreted, with 18-35% as unchanged drug. It is able to penetrate the CSF, where it achieves 25% of plasma concentrations. It is 20% protein-bound. The half-life for elimination after a 2-hour infusion is 6.7±2.5 hours in patients with normal renal function.
- 7.2.3 Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include fever, fatigue, headache, rash, nausea, anorexia, vomiting, myelosuppression (including grade 3/4 neutropenia/thrombocytopenia), injection site reaction, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include edema, tachycardia, thrombosis, chills, dizziness, insomnia, malaise,

diarrhea or constipation, weakness, myalgias and arthralgias, cough, dyspnea, epistaxis, and diaphoresis. *Rare adverse effects (occurring in <1% of patients)* include aplastic anemia, bacteremia, opportunistic infections, lymphocytopenia, altered mental status, hemolytic anemia, hypersensitivity, myelodysplastic syndrome, quadriplegia, and renal dysfunction/failure.

- 7.2.4** Reconstitution: Cladribine is supplied as a sterile, preservative-free, isotonic solution containing 10 mg of cladribine (1 mg/mL) in 10 mL single-use vials. Cladribine should be passed through a sterile 0.22 μ m filter prior to introduction into the infusion bag containing 0.9% Sodium Chloride Injection, USP.
- 7.2.5** Administration and Compatibility: The use of 5% dextrose is not recommended as a diluent because of increased degradation of cladribine. The infusion solution is stable for 24 hours at room temperature.
- 7.2.6** Storage and Stability: Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.
- 7.2.7** Recommended Dose Adjustments for Organ Dysfunction: Specific guidelines for cladribine dosing in patients with hepatic/renal dysfunction or hypoalbuminemia are not clearly defined. Because of the potential for compensatory elimination of cladribine in patients with hepatic and/or renal dysfunction, specific guidelines for dosing are difficult to define. Thus, when deciding whether to adjust cladribine doses for renal dysfunction, the risks for potential toxicities (e.g., myelosuppression, neurotoxicity) against the benefits and goals of treatment must be considered.

7.3 Drug Information on Cytarabine (Cytosine arabinoside)

- 7.3.1** Mechanism of Action: Cytarabine is a synthetic pyrimidine analog, in which the sugar moiety (normally a ribose or deoxyribose) has been replaced with arabinose. Although its mechanism of action is not completely understood, the active form of cytarabine is probably incorporated into the DNA and interferes with DNA synthesis. As such, cytarabine has been found to primarily effect dividing cells, blocking their progression from G₁ to S phase.
- 7.3.2** Pharmacokinetics: Cytarabine is metabolized by deoxycytidine kinase and other kinases into its most active form (aracytidine triphosphate). Aracytidine triphosphate is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. This balance between the levels of kinases and deaminases is critical for regulating the sensitivity/resistance of cells to the drug. The plasma clearance of cytarabine is biphasic, with an initial rapid phase and more prolonged second clearance phase. The rapid clearance phase has a relatively short half-life ($t_{1/2\alpha}$ = 10 minutes), while the half-life of the second clearance phase is slightly longer ($t_{1/2\beta}$ = 1 – 3 hours). The nontoxic metabolites from the drug are excreted in the urine, and within 24 hours after the infusion, approximately 80% of these nontoxic metabolites can be recovered from the urine.
- 7.3.3** Adverse Effects: The dose-limiting toxicity for cytarabine is myelosuppression. *Adverse Events Associated with Standard Dose Cytarabine: Frequent AEs (not definitely quantified)* include the following: myelosuppression (leucopenia,

anemia, neutropenia, thrombocytopenia), pyrexia, rash, anorexia, diarrhea, nausea, vomiting, mucositis, anal inflammation or ulceration, hepatic dysfunction or increased liver enzymes, and local thrombophlebitis. *Less frequent AEs (not definitely quantified)* include chest pain, pericarditis, dyspnea dizziness, headache, neural toxicity, neuritis, alopecia, pruritis, skin freckling, skin ulceration, urticaria, abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat, urinary retention, jaundice/hyperbilirubinemia, local site cellulites, renal dysfunction, allergic edema or anaphylaxis, sepsis, and sudden respiratory distress syndrome. *Infrequent AEs (not definitely quantified)* include aseptic meningitis, cardiopulmonary arrest, cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia), exanthematous pustulosis, hyperuricemia, intestinal pneumonitis, increased lipase, paralysis with intrathecal and IV combination therapy, rhabdomyolysis, veno-occlusive disorder, and death. *Adverse Events Associated with High Dose Cytarabine* include cardiomegaly and cardiomyopathy, coma, severe neurotoxicity, personality change, somnolence, total body alopecia, severe rash or skin desquamation, gastrointestinal ulceration, peritonitis, intestinal pneumatosis, necrotizing colitis, liver abscess or damage, peripheral neuropathy, corneal toxicity, hemorrhagic conjunctivitis, pulmonary edema, sudden respiratory distress syndrome, and sepsis.

- 7.3.4** Reconstitution: Cytarabine should be reconstituted in sterile water and can be further diluted using either 5% dextrose or sodium chloride solutions into appropriate concentrations for infusion.
- 7.3.5** Administration and Compatibility: The diluted cytarabine solution should be inspected for particulate matter, discoloration, and haze prior to infusion. If there is evidence of particulate matter, discoloration, or haze the solution should not be infused. Patients should be medicated with standard anti-emetic therapy. Cytarabine is not compatible (1) during Y-site administration with allopurinol, amphotericin B, ganciclovir; (2) in syringe with metoclopropamide; or (3) admixed with fluorouracil, heparin, insulin (regular), nafcillin, oxacillin, penicillin G. Cytarabine may have variable compatibility when admixed with gentamycin, hydrocortisone, and methylprednisone.
- 7.3.6** Storage and Stability: Vials of non-reconstituted cytarabine should be stored at room temperature 15°C - 30°C (59°F - 86°F). The diluted cytarabine solution may be stable for up to 48 hours if stored at room temperature.
- 7.3.7** Drug-Drug Interaction: Reversible decreases in the plasma steady-state concentration for digoxin and cardiac glycosides may occur. Cytarabine may diminish the therapeutic effect of flucytosine. There is *ex vivo* data suggesting that cytarabine may reduce the effectiveness gentamycin for killing *K. pneumoniae*.
- 7.3.8** Warnings and Precautions: *Ex vivo* and *in vivo* studies have found that cytarabine causes extensive chromosomal damage and potential malignant transformation. Although there have been some case reports describing cytarabine use in pregnant humans, these cases reports are few. Thus, cytarabine is considered Pregnancy Category D. Women should be advised not to become pregnant while receiving

cytarabine, and men should be advised not to father a child while receiving cytarabine and for at least 3 months after completing the therapy. It is not known whether cytarabine or its metabolites are excreted in breast milk; thus, it is not recommended for lactating females who are breast-feeding. As with any highly immunosuppressive medication, cytarabine may diminish the effectiveness of dead and live vaccines and enhance the toxic/adverse effect of live vaccines. One should avoid use of live vaccines while receiving it. A small percentage of patients will have a hypersensitivity reaction to cytarabine, and these individuals should not receive the drug again.

- 7.3.9** Recommended Dose Adjustments for Organ Dysfunction: Guidelines for adjusting cytarabine dose due to renal or liver dysfunction are not standardized, but many clinicians will adjust the dose based upon the function of these organs.

7.4 Drug Information on Mitoxantrone

- 7.4.1** Mechanism of Action: Mitoxantrone (dihydroxyanthracenedione) is an anthracenedione derivative that intercalates with DNA, resulting in inhibition of nucleic acid synthesis.
- 7.4.2** Pharmacokinetics: Mitoxantrone is 78% bound to plasma proteins. A three-compartment model was described after a single intravenous dose of mitoxantrone. The mean alpha half-life is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours, and the mean terminal (gamma) or elimination half-life is 23 to 215 hours (median 75 hours). Mitoxantrone has extensive distribution into body tissues and is metabolized in the liver to two main inactive metabolites (monocarboxylic acid derivative and dicarboxylic acid derivative). The major route of excretion for mitoxantrone appears to be biliary into the feces; approximately 11% of the dose is recovered in the urine within 5 days of drug administration, with 65% of this being unchanged drug.
- 7.4.3** Adverse Effects: *Common adverse effects (occurring in >10% of patients)* include edema, fever, fatigue, headache, alopecia, nausea/vomiting, diarrhea, mucositis/stomatitis, myelosuppression, weakness, dyspnea, cough, and infection. *Less common adverse effects (occurring in 1 to 10% of patients)* include congestive heart failure, decreased left ventricular ejection fraction (LVEF), hypertension, chills, anxiety, cutaneous mycosis, hypocalcemia, hypokalemia, hyponatremia, menorrhagia, jaundice, myalgia, arthralgia, renal failure, proteinuria, rhinitis, diaphoresis, and infection.

Mitoxantrone may cause cardiac toxicity with prolonged administration and doses exceeding 80 to 100 mg/m²; Appendix D provides an overview of the cardiotoxicity index of individual anthracyclines as well as mitoxantrone. When used after doxorubicin, cardiotoxicity is more frequent; an analysis by the Southwest Oncology Group revealed a risk of 6% at 134 mg/m² prior doxorubicin and 60 mg/m² mitoxantrone, rising to a 15% risk at 120 mg/m² mitoxantrone. Cardiac events reported included arrhythmias, decreased left ventricular function, chronic heart failure, tachycardia, ECG changes, and, infrequently, myocardial infarction. Bradycardia has been rarely reported. Patients with prior treatment

with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease may have more frequent occurrences of cardiac toxicity.

- 7.4.4** Reconstitution: Mitoxantrone must be diluted prior to use. The dose of mitoxantrone should be to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). Mitoxantrone may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately.
- 7.4.5** Administration and Compatibility: Care in the administration of mitoxantrone will reduce the chance of extravasation. Mitoxantrone should be administered into the tubing of a freely running intravenous infusion of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes, or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein.
Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form.
- 7.4.6** Storage and Stability: Mitoxantrone should be stored between 15°C - 25°C (59°F - 77°F).

8.0 EVALUATION AND END POINT DEFINITIONS

8.1 Treatment Response and Outcome

Treatment response (e.g. morphologic/cytogenetic/molecular complete remission, partial remission) or treatment failure (e.g. resistant disease, aplasia, morphological or molecular/cytogenetic relapse) as well as treatment outcome (e.g. overall survival, relapse-free survival, event-free survival, and remission duration) are categorized according to criteria recommended by International Working Groups.^{2,14} Patients are routinely assessed for the presence of MRD as detected by multiparameter flow cytometry, as per institutional practice.

8.2 Toxicity Criteria

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

8.3 Definition of Dose-limiting Toxicities (DLTs)

Reported adverse events and potential risks for G-CSF, cladribine, cytarabine, and mitoxantrone, are described in section 7. Dose-limiting toxicities (DLTs) used for trial monitoring for both newly diagnosed and relapsed/refractory patients are defined as follows:

- 8.3.1** Any Grade 3 non-hematologic toxicity lasting >48 hours that results in >7 day delay of the subsequent treatment cycle, with the exception of febrile neutropenia or infection.

- 8.3.2** Any Grade ≥ 4 non-hematologic toxicity with the exception of febrile neutropenia/infection unless felt to be a direct consequence of treatment-related toxicity (e.g. intestinal infection following mucosal barrier breakdown), and with the exception of constitutional symptoms if recovery to Grade ≤ 2 within 14 days.

8.4 Duration of Follow-up

After removal from protocol, patients will be monitored for late toxicities/complications for 1 month or until additional anti-AML therapy is given. Patients will be followed after completion of study treatment to determine event-free survival and disease-free survival (for patients achieving CR, CRp, or CRi) as well as overall survival (for all patients) for a maximum of 5 years. Follow-up may include periodic (e.g. every 3 months) review of medical records, and, if absolutely necessary, direct contact of the study participant.

9.0 RECORDS

Research data will be recorded on study-specific Case Report Forms (CRFs) using a unique study ID for each patient to assure patient confidentiality. Data from source documents are used to transcribe critical protocol data on CRFs. Source documents are documents where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, quality of life assessments, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, X-rays, patient filed, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial.

Any publication or presentation will refer to patients by this number and not by name. The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files are maintained by a designated research coordinator and kept in a locked room with access restricted to personnel authorized by the Clinical Research Division. A study-specific database will also use the unique patient number and will not include patient names. Access to the database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

10.0 CORRELATIVE STUDIES

Due to the lack of additional funding, there are no pre-planned correlative studies. However, study participants will be encouraged to provide biospecimens (i.e. peripheral blood and/or bone marrow specimens) to the Center's AML sample repository (FHCRC #1690.00; PI: Derek Stirewalt, MD); thus, correlative studies (e.g. gene-specific or genome-wide expression gene expression or mutation analyses to identify prognostic biomarkers of response/outcome) could be conducted at a later time point should funding support be secured.

11.0 PROTOCOL ENROLLMENT AND SPECIAL CONSIDERATIONS

All eligible patients will be included in this study without regard to gender or ethnicity. The incidence of AML is slightly higher in men, so it is expected that the distribution of these patients will reflect a slight male predominance of the disease as well as the general demographic distribution of AML patients seen at our institution. Up to 139 patients with newly diagnosed AML/MDS and 60 patients with relapsed/refractory disease will be enrolled, respectively, for a total of 199 patients.

Projected Target Accrual ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects = 199			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	3	4	7
Not Hispanic or Latino	81	111	192
Ethnic Category Total of All Subjects*	84	115	199
Racial Categories			
American Indian / Alaska Native	1	1	2
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	5
White	79	108	187
Other/Unknown	0	0	0
Racial Categories: Total of All Subjects*	84	115	199

12.0 GUIDELINES FOR SERIOUS ADVERSE EVENT REPORTING

12.1 Expedited Reporting Requirements

In accordance with FHCRC/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the "Expedited Reporting Form for Unanticipated Problems or Noncompliance" and the "Adverse Event Reporting Form", or equivalent forms, will be completed for this reporting.

12.2 **Definitions**

12.2.1 Adverse Event (AE): Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. Mechanisms of obtaining information on AE include monthly transcripts, assessment forms obtained after each clinic visit, and hospital progress and discharge notes. Grade ≥ 3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate.

12.2.2 Related or Possibly Related AE: An AE is “related or possibly related to the research procedures” if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not “related or possibly related”. If there is any question whether or not an AE is related or possibly related, the AE should be reported.

12.2.3 Serious AE (SAE): An adverse event that results in any of the following outcomes:

- Death
 - Life-threatening adverse event (real risk of dying)
 - Prolongation of hospitalization*
 - Persistent or significant disability/incapacity/or change in psychosocial status
 - Congenital anomaly
 - Requirement of intervention to prevent permanent impairment of damage
- *Hospitalization itself will not be considered a serious adverse event if required for complications of AML or comorbid conditions. Hospitalization will be considered a SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described.

12.2.4 Unexpected AE: An AE is “unexpected” when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document, and other relevant sources of information such as product labeling and package inserts; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition or any predisposing risk factor prone for the adverse event.

AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol. Myelosuppression and associated complications are expected events during leukemia therapy; therefore, myelosuppression and associated simple

complications such as fever, infections, bleeding, and related hospitalizations will not be reported as individual AE but will be summarized in the annual report to the IRB.

13.0. DATA AND SAFETY MONITORING PLAN

The Principal Investigator, Dr. Roland B. Walter, and the Study Coordinator will carry out ongoing trial oversight. They will meet at least monthly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. All investigators on the protocol have received formal training in the ethical conduct of human research. Institutional support of trial monitoring is provided in accordance with the FHCRC Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, the FHCRC Research Trials Office coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits. In addition, the Protocol and Data Monitoring Committee (PDMC) and the IRB review protocols at least annually. The PDMC reviews accrual, adverse events, stopping rules, and adherence to the DSMP. The FHCRC IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of the IRB is necessary to continue the study. An independent Data and Safety Monitoring Board will not review the protocol. The trial will comply with the standard guidelines set forth by the regulatory committees of the FHCRC/UW (Scientific Review Committee, IRB, PDMC) and other state and federal guidelines.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Institutional Review Board

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study.

14.2 Consent

The Principal Investigator or his designee must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment. Patients must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. In accordance with federal regulations (21 CFR 50), all patients enrolled in the study must sign the IRB-approved consent form.

14.3 Confidentiality

Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Upon the patient's request and written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the patient's welfare. Data generated for this study must be available for inspection on request to representatives of the national or local health authorities, and the associated IRB/IEC. Release of research results or data that reveal patient names or other identifiers, such as photographs, audio or videotapes, must be carried out in accordance with Department of Health and Human Services Final Standards for Privacy of Individual Health Information, 45 CFR 164.508. Written authorization must be obtained from the patient and IRB/IEC prior to the release of such information. Identifiable patient data may not be used for purposes of promoting any drugs used in this trial.

14.4 Publication Statement

The results of this clinical trial may be used for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an investigator. Identifiable patient data may not be used for any of these presentations, manuscripts, or reports unless directed by law.

15.0 STATISTICAL CONSIDERATIONS FOR PATIENTS WITH NEWLY DIAGNOSED DISEASE

15.1 Phase 1

15.1.1 General Considerations: DLTs are defined in Section 8.3. Only DLTs occurring during Cycle 1 will be used to guide dose escalation. However, before the phase 2 portion is begun, all grade 3 and 4 adverse events of all patients treated in the phase 1 portion will be reviewed to assess for late and cumulative toxicities that were not captured during the phase 1 portion of the trial. The Principal Investigator reserves the right to reduce the drug doses identified in the phase 1 portion of this assessment suggests a significant risk of late/cumulative toxicities. Patients will be considered evaluable for DLT if they received at least 75% of the assigned doses of each chemotherapeutic during Cycle 1 or if they developed a DLT. If a patient does not develop a DLT but does not receive at least 75% of treatment during Cycle 1, the patient will be considered not evaluable for DLT and will be replaced. Maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of DLT is <33%.

15.1.2 Dose Escalation scheme:

Starting with dose level K=1:

- A. Evaluate 6 patients at dose level K
 - a. If 0 or 1 have DLT, increase dose to level K+1 and go to A.
 - b. If 2 or more have DLT, stop dose escalation.

The dose level below that which dose escalation was stopped is the potential MTD. If dose level 1 is found too toxic, the study will terminate.

In order to better define safety and initial evidence of anti-leukemic activity, any dose level cohort may be expanded up to 12 patients, provided that 2 or fewer of 6 patients had DLT at that dose level. If a cohort is expanded to 12 patients, the following rules will be used to determine further dose escalation:

- a. If 3 or fewer have DLT, increase dose level to K+1 (go to A).
- b. If 4 or more have DLT, stop dose escalation.

15.1.3 Phase I MRD^{neg} CR evaluation: Among 146 patients younger than age 65 who received high-dose cytarabine-based induction chemotherapy at UW/SCCA, 87 (60%) achieved a CR without flow cytometric evidence of MRD. It is assumed that this regimen will not be of further interest if the true MRD^{neg} CR rate is 60% or less (null hypothesis) and that an MRD^{neg} CR rate of 75% or more would be of considerable interest for further investigation (alternative hypothesis). At predefined analyses times, the study will be stopped if the upper boundary of the 95% confidence interval around the observed MRD^{neg} CR rate does not include 75%. The first response evaluations will be done on the first 12 patients evaluable for DLT, and early termination of this study will be considered if 5 or fewer patients achieved an MRD^{neg} CR. Further response evaluation will be done after cohorts of 6 additional evaluable patients have been accrued. Stopping rules based on response are summarized below:

N (evaluable for DLT)	Number of MRD ^{neg} remissions stopping rules	Probability of stopping for average MRD ^{neg} CR rate		
		50%	60%	75%
12	5 or fewer	39%	16%	1%
18	9 or fewer	59%	26%	2%
24	13 or fewer	73%	35%	2%
30	17 or fewer	82%	42%	2%
36	21 or fewer	88%	48%	2%

It is recognized that the response rate could be different at different dose levels. The numbers above consider an “average” response rate across all patients in a cohort for response evaluation.

15.2 Phase 2

The study will be conducted in two sequential parts. Patients enrolled in the Phase 1 portion and treated at the MTD dose will be included in the analysis of the Phase 2 portion. The primary objective of the Phase 2 portion is to evaluate the MRD^{neg} CR rate after up to 2 courses of induction chemotherapy. It is assumed that this regimen will not be of further interest if the true MRD^{neg} CR rate is 60% or less (null hypothesis) and that a response rate of 75% or more would be of considerable interest for further investigation (alternative hypothesis).

A two-stage design will be used (Simon Optimal Two-Stage). In the first stage, 21 eligible patients will be accrued. If necessary, the study may be temporarily closed while remission data is collected. If 13 or fewer MRD^{neg} CRs are observed, the study will be closed with the conclusion this regimen does not warrant further study. If 14 or more remissions are observed, an additional 41 patients will be accrued. Forty-two or more responses out of 62 patients will be considered evidence that this regimen warrants further study, provided other factors such as overall survival and adverse events also appear favorable. This design has 80% power with a one-sided alpha of 7%. If the true response rate is 60%, the probability the study is stopped after the first stage of accrual is 65%. If the true response rate is 75%, the probability the study is stopped after the first stage of accrual is 13%.

15.3 Phase 2 Expansion Cohort

Since this study was designed, analysis of SWOG leukemia trial data has indicated that CR and event-free survival (with events defined as failure to achieve CR, relapse from CR, and death from any cause) are not strongly with long-term overall survival (M. Othus et al., manuscript submitted). A poor MRD^{neg} CR rate would be a reason to not further study this regimen, but the promising MRD^{neg} CR rate shown thus far may not be convincing enough to justify Phase 3 testing of overall survival. A Phase 2 expansion cohort will provide the ability to assess whether the overall survival rates of this regimen provide evidence for Phase 3 testing of the regimen. Overall survival (OS) patterns for AML patients treated with intense regimens (such as the one studied here) do not follow an exponential distribution. As an alternative to designs that assumption exponential survival patterns, we will test the 12-month survival rate. S0106, the most recent SWOG trial in a comparable study population, had a 12-month OS of 75%. If the 12-month OS rate with this regimen is 85%, 139 patients (112 of whom treated at the MTD) will provide 90% power for a one-sided test with alpha of 5%; if 113 or more of the 139 patients are alive at 12-months, this trial will provide evidence that the regimen would warrant Phase 3 testing of OS. For patients treated at the MTD, the 112 patients will provide 84% power for a one-sided test with alpha of 5%; if 92 or more of the 112 MTD-treated patients are alive at 12-months, this trial will provide evidence that the regimen would warrant Phase 3 testing of OS. In addition to the formal test of 12-month OS, the entire survival curve will be estimated using the Kaplan-Meier method. Also, OS of this cohort will be compared to the historical SWOG cohort treated with standard of care (from S0106) using Cox regression models to control for known prognostic factors including age, performance status, and cytogenetic risk.

16.0 STATISTICAL CONSIDERATIONS FOR PATIENTS WITH RELAPSED/REFRACTORY DISEASE

16.1 Phase 1

16.1.1 General Considerations: DLTs are defined in Section 8.3. Only DLTs occurring during Cycle 1 will be used to guide dose escalation. However, before the phase 2 portion is begun, all grade 3 and 4 adverse events of all patients treated in the phase 1 portion will be reviewed to assess for late and cumulative toxicities that were not captured during the phase 1 portion of the trial. The Principal Investigator reserves the right to reduce the drug doses identified in the phase 1 portion of this assessment suggests a significant risk of late/cumulative toxicities. Patients will be considered evaluable for DLT if they received at least 75% of the assigned doses of each chemotherapeutic during Cycle 1 or if they developed a DLT. If a patient does not develop a DLT but does not receive at least 75% of treatment during Cycle 1, the patient will be considered not evaluable for DLT and will be replaced. MTD is defined as the highest dose studied in which the incidence of DLT is <33%.

16.1.2 Dose Escalation scheme:

Starting with dose level K=1:

B. Evaluate 6 patients at dose level K

- a. If 0 or 1 have DLT, increase dose to level K+1 and go to A.
- b. If 2 or more have DLT, stop dose escalation.

The dose level below that which dose escalation was stopped is the potential MTD. If dose level 1 is found too toxic, the study will terminate.

In order to better define safety and initial evidence of anti-leukemic activity, any dose level cohort may be expanded up to 12 patients, provided that 2 or fewer of 6 patients had DLT at that dose level. If a cohort is expanded to 12 patients, the following rules will be used to determine further dose escalation:

- c. If 3 or fewer have DLT, increase dose level to K+1 (go to A).
- d. If 4 or more have DLT, stop dose escalation.

16.1.3 Remission evaluation: The first response evaluations will be done on the first 12 patients evaluable for DLT. If 0 patients achieve a CR or CRp, early termination of this study will be considered. Further response evaluation will be done after cohorts of 6 additional evaluable patients have been accrued. Stopping rules based on response are summarized below:

N (evaluable for DLT)	Number of remissions stopping rules	Probability of stopping for average response rate		
		10%	20%	30%
12	0	28%	7%	1%

18	1 or fewer	45%	10%	1%
24	2 or fewer	56%	11%	1%
30	3 or fewer	65%	12%	1%
36	4 or fewer	71%	13%	1%

It is recognized that the response rate could be different at different dose levels. The numbers above consider an “average” response rate across all patients in a cohort for response evaluation.

16.2 Phase 2

The study will be conducted in two sequential parts. Patients enrolled in the Phase 1 portion and treated at the MTD dose will be included in the analysis of the Phase 2 portion. The primary objective of the Phase 2 portion is to evaluate the remission rate (RR, includes CR and CRp) of this regimen. It is assumed that this regimen will not be of further interest if the true RR is 15% or less (null hypothesis) and that a response rate of 30% or more would be of considerable interest for further investigation (alternative hypothesis).

A two-stage design will be used. In the first stage, 20 eligible patients will be accrued. If necessary, the study may be temporarily closed while remission data is collected. If 2 or fewer remissions (CR or CRp) are observed, the study will be closed with the conclusion this regimen does not warrant further study. If 3 or more remissions are observed, an additional 20 patients will be accrued. Ten or more responses out of 40 patients will be considered evidence that this regimen warrants further study, provided other factors such as overall survival and adverse events also appear favorable. This design has 80% power with a one-sided alpha of 7%. If the true response rate is 15%, the probability the study is stopped after the first stage of accrual is 41%. If the true response rate is 30%, the probability the study is stopped after the first stage of accrual is 4%.

17.0 STUDY TERMINATION

The study will terminate as described in sections 15.0 and 16.0. The Principal Investigator reserves the right to terminate this study at any time.

18.0 REFERENCES

1. Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013;381(9865):484-495.
2. Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-474.
3. Estey E, Kornblau S, Pierce S, Kantarjian H, Beran M, Keating M. A stratification system for evaluating and selecting therapies in patients with relapsed or primary refractory acute myelogenous leukemia. *Blood*. 1996;88(2):756.
4. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259.
5. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.
6. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol*. 2012;30(20):2441-2448.
7. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol*. 2013;31(27):3360-3368.
8. Wierzbowska A, Robak T, Pluta A, et al. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. *Eur J Haematol*. 2008;80(2):115-126.
9. Price SL, Lancet JE, George TJ, et al. Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens. *Leuk Res*. 2011;35(3):301-304.
10. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4423.
11. Paciucci PA, Ohnuma T, Cuttner J, Silver RT, Holland JF. Mitoxantrone in patients with acute leukemia in relapse. *Cancer Res*. 1983;43(8):3919-3922.
12. Koller CA, Kantarjian HM, Feldman EJ, et al. A phase I-II trial of escalating doses of mitoxantrone with fixed doses of cytarabine plus fludarabine as salvage therapy for patients with acute leukemia and the blastic phase of chronic myelogenous leukemia. *Cancer*. 1999;86(11):2246-2251.

13. Volkova M, Russell R, 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev.* 2011;7(4):214-220.
14. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003;21(24):4642-4649.
15. Carton E, Bellesoeur A, Mir O. Colony-stimulating factors for febrile neutropenia. *N Engl J Med.* 2013;369(3):285-286.
16. Reiss AL, Aylward E, Freund LS, Joshi PK, Bryan RN. Neuroanatomy of fragile X syndrome: the posterior fossa. *Ann Neurol.* 1991;29(1):26-32.

APPENDIX A: 2008 WHO CLASSIFICATION AND CRITERIA FOR MDS

Disease	Blood findings	Bone marrow findings
A.1 Refractory cytopenias with multilineage dysplasia (RCUD); Refractory anemia (RA), Refractory neutropenia (RN), Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia No or rare blasts	Unilineage dysplasia: $\geq 10\%$ of cells in one myeloid lineage <5% blasts <15% of erythroid precursors are ring sideroblasts
A.2 Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia <i>only</i> $\geq 15\%$ ringed sideroblasts <5% blasts
A.3 Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bi- or pancytopenia) No or rare blasts No Auer rods <1 x 10 ⁹ /L monocytes	Dysplasia in $\geq 10\%$ of cells in ≥ 2 myeloid cell lines <5% blasts in marrow No Auer rods $\neq 15\%$ ringed sideroblasts
A.4 Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods <1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia 5% to 9% blasts No Auer rods
A.5 Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5% to 19% blasts Auer rods \pm <1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts Auer rods \pm
A.6 Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias $\leq 1\%$ blasts	Unequivocal dysplasia in <10% of the cells ≥ 1 myeloid cell lines when accompanied by cytogenetic abnormality considered as presumptive evidence for MDS
A.7 MDS associated with isolated del(5q)	Anemia Platelet count usually normal or increased No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del(5q)

From: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): WHO Classification of Tumours and Haematopoietic and Lymphoid Tissues. 4th edition, IARC: Lyon 2008.

APPENDIX B: 2008 WHO Classification of Acute Myeloid Leukemia

- B.1 Acute myeloid leukemia with recurrent genetic abnormalities**
 - B.1.1** Acute myeloid leukemia with t(8;21)(q22;q22), RUNX1-RUNX1T1
 - B.1.2** Acute myeloid leukemia inv(16)(p13.1q22) or t(16;16)(p13.1;q22), CBFβ-MYH11
 - B.1.3** Acute promyelocytic leukemia with t(15;17)(q22;q12), PML/RARα
 - B.1.4** Acute myeloid leukemia with t(9;11)(p22;q23); MLLT3-MLL
 - B.1.5** Acute myeloid leukemia with t(6;9)(p23;q34); DEK-NUP214
 - B.1.6** Acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVII
 - B.1.7** Acute myeloid leukemia (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
 - B.1.8** Acute myeloid leukemia with mutated NPM1
 - B.1.9** Acute myeloid leukemia with mutated CEBPA

- B.2 Acute myeloid leukemia with myelodysplasia-related changes**

- B.3 Therapy-related myeloid neoplasms**

- B.4 Acute myeloid leukemia, not otherwise specified**
 - B.4.1** Acute myeloid leukemia with minimal differentiation
 - B.4.2** Acute myeloid leukemia without maturation
 - B.4.3** Acute myeloid leukemia with maturation
 - B.4.4** Acute myelomonocytic leukemia
 - B.4.5** Acute monoblastic/acute monocytic leukemia
 - B.4.6** Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
 - B.4.7** Acute megakaryoblastic leukemia
 - B.4.8** Acute basophilic leukemia
 - B.4.9** Acute panmyelosis with myelofibrosis
 - B.4.10** Myeloid sarcoma

- B.5 Myeloid sarcoma**

From: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds.): WHO Classification of Tumours and Haematopoietic and Lymphoid Tissues. 4th edition, IARC: Lyon 2008.

APPENDIX C: TREATMENT-RELATED MORTALITY (TRM) SCORE

Calculation of Simplified Treatment-Related Mortality (TRM) Score

Includes covariates: performance status (PS), age, platelet count, albumin, secondary AML, white blood cell count (WBC), peripheral blood blast percentage, and creatinine

Score = $100/(1+e^{(-x)})$, with $x = -4.08 + 0.89*PS + 0.03*age - 0.008*platelet\ count - 0.48*albumin + 0.47*(have\ secondary\ AML) + 0.007*WBC - 0.007*(peripheral\ blood\ blast\ percentage) + 0.34*creatinine$

Probability of TRM Above and Below Various Simplified TRM Score Cut-offs

TRM Score Interval	Patients below/within/above TRM Score Interval (%)	TRM Probability if below TRM Score Interval (%)	TRM Probability if within TRM Score Interval (%)	TRM Probability if above TRM Score Interval (%)
0 – 1.9	0/20/80	-	1	12
1.91 – 3.9	20/20/60	1	2	16
3.91 – 6.9	40/20/40	1	7	20
6.91 – 9.2	60/10/30	3	7	24
9.21 – 13.1	70/10/20	4	12	31
13.11 – 22.8	80/10/10	5	20	41
22.81 – 100	90/10/0	6	41	-

From: Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, Appelbaum FR, Kantarjian HM, Estey EH. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011;29(33):4417-4424.

APPENDIX D: CARDIOTOXICITY INDEX OF ANTHRACYCLINES

Drug	Schedule	Relative Myelosuppressive Potency¹	Approximate Relative Cardiotoxicity	Cardiotoxicity Index²
<i>Doxorubicin</i>	<i>Rapid infusion</i>	<i>1</i>	<i>1</i>	<i>1</i>
Doxorubicin	24hr infusion	1	0.62	0.62
Epirubicin	Rapid infusion	0.67	0.66	0.44
Mitoxantrone	Rapid infusion	5	0.5	2.5
Daunorubicin	Rapid infusion	0.67	0.75	0.5
Idarubicin	Rapid infusion	5	0.53	2.67

¹Of single dose compared with doxorubicin administered by standard schedule. ²The cardiotoxicity index represents a factor by which to multiply the cumulative dose of a drug administered to obtain an approximation of toxicity that might be expected had the resultant amount of doxorubicin been given by rapid infusion

Adapted from Holland J, et al. Cancer medicine, 5th ed. American Cancer Society. Hamilton and London: B.C. Decker, Inc. 2000.

APPENDIX E: RESEARCH SUBJECT REGISTRATION FORM

Protocol 2734.00 Patient Demographics and Eligibility Form
 Please fax this completed form to 206-667-6519 for patient registration.
 Questions regarding eligibility should go to Roland B. Walter, MD PhD, 206-667-3599

UPN#: _____

Patient Name: _____
 Last First MI

Date of Birth: _____
 Month / Day / Year

Planned starting day of treatment: _____
 Month / Day / Year

Ethnicity (*choose one*): instruct the patient to select one of the following:

- Hispanic or Latino** (A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race). Term "Spanish Origin" can also be used in addition to "Hispanic" or "Latino"
- Not Hispanic or Latino**
- Declined to Report**

Race (*check all that apply*): instruct the patient to select one or more of the following:

- American Indian/Alaska Native** (A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment)
- Asian** (A person having origins in any of the original peoples of the Far East, Southeast, Asia, or the Indian subcontinent including, for example, Cambodia, China, India Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam)
- Native Hawaiian/Pacific Islander** (A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands)
- Black/African American** (A person having origins in any of the black racial groups of Africa.)
- White** (A person having origins in any of the original peoples of Europe, the Middle East or North Africa)
- Research Subject does not know race**
- Declined to Report**

Gender: Male
 Female
 Unknown

ATTACH SIGNED CONSENT AND HIPAA AUTHORIZATION FORMS, AND SEND TO PRINCIPAL INVESTIGATOR FOR REGISTRATION.

APPENDIX E cont'd
Protocol 2734.00 Eligibility

D) Inclusion Criteria:

Each of the following questions (1-13) must be marked "Yes" for the patient to enroll on Protocol 2734.00

- 1) Yes No Patient signed and dated consent form
Date: _____
- 2) Yes No Patient signed and dated HIPAA authorization
- 3) Yes No Age ≥ 18 years
- 4) Yes No Diagnosis of "high-risk" MDS ($\geq 10\%$ blasts) or non-APL AML requiring induction or first/subsequent salvage therapy
- 5) Yes No Treatment-related mortality (TRM) score ≤ 6.9 as calculated by simplified model available at <https://cstaging.fhcr-research.org/TRM>
- 6) Yes No Off any systemic therapy for AML with the exception of hydroxyurea for at least 14 days prior to study registration unless patient has rapidly progressive disease, and all Grade 2-4 non-hematologic toxicities have resolved. Patients with symptoms/signs of hyperleukocytosis or $WBC > 100,000/\mu L$ can be treated with leukapheresis or may receive up to 2 doses of cytarabine (up to $500 \text{ mg}/\text{m}^2/\text{dose}$) prior to enrollment.
- 7) Yes No
N/A May have received chemotherapy with a mitoxantrone- or cladribine-based regimen for MDS or AML
- 8) Yes No
N/A If patient received prior G-CLAM therapy, study PI approved enrollment
- 9) Yes No Bilirubin $< 2.5 \times$ institutional upper limit normal, unless elevation is thought to be due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis (assessed within 14 days prior to registration)
- 10) Yes No Serum creatinine $\leq 2.0 \text{ mg}/\text{dL}$ (assessed within 14 days prior to registration)
- 11) Yes No Left ventricular ejection fraction (LVEF) $\geq 45\%$, assessed within 3 months prior to registration, e.g. by MUGA scan or echocardiography, or other appropriate diagnostic modality and no clinical evidence of congestive heart failure. If the patient had anthracycline-based therapy since the most recent cardiac assessment, cardiac evaluation should be repeated if there is clinical or radiographic suspicion of cardiac dysfunction, or if the previous cardiac assessment was abnormal.

For patients with relapsed/refractory AML/MDS only

- 13) Yes No For post-transplant patients: symptoms of graft-versus-host disease are well controlled with stable use of immunosuppressive agents
N/A

II) Exclusion Criteria:

The following question (14-20) must be marked "No" for the patient to enroll on Protocol 2734.00

- 14) Yes No Blast crisis of chronic myelogenous leukemia
- 15) Yes No Concomitant illness associated with a likely survival of <1 year
- 16) Yes No Active systemic fungal, bacterial, viral, or other infection, unless under treatment with anti-microbials and controlled/stable, as defined as being afebrile and hemodynamically stable for 24hours. Patients with fever thought to be likely secondary to leukemia are eligible.
- 17) Yes No Known hypersensitivity to any study drug
- 18) Yes No Pregnancy or lactation
- 19) Yes No Treatment with any other investigational agent

III) Treatment Assignment:

- Newly-diagnosed disease.
- Relapsed/refractory disease.

Name of person completing form: _____

Signature of 1st Study Investigator: _____ Date: _____

Signature of 2nd Study Investigator: _____ Date: _____

FAX COVER LETTER

DATE: _____

TO: Roland B. Walter

FAX (206) 667-6519

**RE: RESEARCH SUBJECT REGISTRATION FORM
PROTOCOL 2734.00**

FROM: _____

FAX: _____

PHONE: _____

THE INFORMATION CONTAINED IN THIS TRANSMISSION IS INTENDED ONLY FOR THE ADDRESSEE OR THE ADDRESSEE'S AUTHORIZED AGENT. THE FAX CONTAINS INFORMATION THAT MAY BE PRIVILEGED, CONFIDENTIAL AND EXEMPT FROM DISCLOSURE. IF THE READER OF THE MESSAGE IS NOT THE INTENDED RECIPIENT OR RECIPIENT'S AUTHORIZED AGENT THEN YOU ARE NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR COPYING OF THIS INFORMATION IS PROHIBITED.

IF YOU HAVE RECEIVED THIS INFORMATION IN ERROR, PLEASE NOTIFY THE SENDER BY TELEPHONE, AND RETURN THE ORIGINAL AND ANY COPIES OF THE MESSAGE BY MAIL TO THE SENDER AT FRED HUTCHINSON CANCER RESEARCH CENTER, 1100 FAIRVIEW AVE N. LF-229, SEATTLE, WA 98109

Fred Hutchinson Cancer Research Center
University of Washington School of Medicine

Consent to take part in a research study:

**A Phase 1/2 Trial of G-CSF, Cladribine, Cytarabine, and
Dose-Escalated Mitoxantrone (G-CLAM) in Adults with
Newly Diagnosed or Relapsed/Refractory Acute Myeloid
Leukemia (AML) or High-Risk Myelodysplastic
Syndromes (MDS)**

Consent Form for Phase 2 for Patients with Newly Diagnosed AML/MDS

Principal Investigator: Roland B. Walter, MD PhD. University of Washington; Fred
Hutchinson Cancer Research Center. Phone: 206-667-3599.

Emergency number (24 hours):

- Call the paging operator at the University of Washington Medical Center at 206-598-6190, and ask for the Fellow on call for Hematology/Oncology.

We would like you to join this research study.

Since you are a patient who has been newly diagnosed with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS), we would like to ask you to join this research study. We will enroll up to 112 people with newly diagnosed AML/MDS in the phase 2 portion of this study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in this study. You are free to say yes or no, or to drop out after joining. There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Why are we doing this study?

We are doing this study to examine dose-escalated G-CLAM, a chemotherapy regimen consisting of G-CSF (also called filgrastim), Cladribine, Cytarabine (also called Ara-C), and Mitoxantrone. Regular-dose G-CLAM has been used to treat patients who have AML that has relapsed or is refractory to standard treatment. We want to know whether G-CLAM can be safely given to patients with newly diagnosed AML/MDS if higher doses of Mitoxantrone are used.

In the phase 1 portion of this study, we identified an escalated dose of Mitoxantrone that was well tolerated among a small group of patients. In the phase 2 portion of this study, we want to learn how well this higher dose of Mitoxantrone in combination with the other drugs works against AML or high-risk MDS in a larger group of patients, and what side effects (good or bad) will occur. The doctors will watch patients carefully for any side effects.

What research tests, procedures, and treatments are part of this study?

If you decide to join this study, we will do these tests and procedures:

- **Baseline Assessment.** You will need tests, including a bone marrow and/or peripheral blood analysis, and a physical exam to see if you are eligible for the trial. Please tell your medical team of any past or current medical problems. These tests and physical exam are usually considered part of regular cancer care. If you have recently had some of these tests, they may not need to be repeated. You may also need a catheter inserted to receive chemotherapy and to simplify blood draws and transfusions.
- **Study Treatment.** While you will receive G-CSF, Cladribine, and Cytarabine at the same doses as are used in regular-dose G-CLAM, while Mitoxantrone will be given through the vein at a dose of 18 mg/m² (as compared to 10 mg/m² used in the regular-dose G-CLAM) every day for 3 days. The other drugs will be given as follows:
 - G-CSF will be given as a shot underneath the skin every day for 6 days, starting the day before the rest of the chemotherapy.
 - Cladribine will be given in your vein over 2 hours each day for a total of 5 days.
 - Cytarabine will be given in your vein over 4 hours each day for a total of 5 days.
- **Monitoring during Study.** During the trial you will need routine procedures, tests and close follow-up. This care is part of routine monitoring for patients receiving chemotherapy. Some examples of these tests, procedures, and care include the following:
 - A medical history
 - Physical examinations
 - Blood tests

- Bone marrow examinations (i.e., aspiration and/or biopsy)
- Radiology tests such as a chest x-ray if clinically indicated
- Ultrasound of your heart or other heart tests if there are any concerns about your heart function
- Red blood cell or platelet transfusions

How long will I be in this study?

We think you will be in this study for up to 6-8 months. The exact length of treatment will depend on the side effects and your response to the treatment.

If you still have your cancer after one cycle of G-CLAM with dose-escalated Mitoxantrone, you may be eligible to have this therapy repeated. If this is the case, your doctors will discuss this with you. If you fail to achieve a good response (“remission”) after 1 or 2 cycles of therapy, you will not be eligible for additional therapy as part of this clinical trial.

If you achieve a good response with G-CLAM with dose-escalated Mitoxantrone (i.e. achieve what is called a “remission”), you will be able to receive up to 2 cycles of additional chemotherapy on this study to further the amount of cancer cells that may be left in your body. This chemotherapy, also known as “consolidation” chemotherapy, will consist of the three drugs G-CSF, Cladribine, and Cytarabine without Mitoxantrone (G-CLA). The consolidation will be given after your blood counts are better and you have recovered from side effects that you may experience. Some doctors or patients may elect to use therapies other than G-CLA for your consolidation (e.g. transplantation), and your doctors will discuss these options after your initial treatment.

After you have finished the study treatment, you may return to your primary oncologist or choose to receive additional care at the Seattle Cancer Care Alliance (SCCA). As with any patient receiving such therapy, you will need monitoring. This future care will likely include visits to your doctor, physical examinations, and routine tests. These tests may include repeat bone marrow evaluations. The investigators may want to know about your health after you leave the SCCA. The investigators may contact you or your doctor to see how you are doing. The plan is to follow patients for 5 years after treatment.

The study doctor or your doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You are unable or unwilling to follow study procedures.
- The whole study is stopped.

If you are thinking about dropping out of this study, please tell the study doctor. The doctor can tell you about the effects of stopping G-CLAM. You and the doctor can talk about what follow-up care and testing would help you the most.

If you leave the study, your test results and information cannot be removed from the study records.

What are the side effects (risks)?

In this part of the consent form, we tell you the side effects we expect from the tests and treatments in this study. There may be side effects we do not know about yet. If we learn about other side effects, we will tell you.

We carefully watch everyone in the study for side effects. If you want more information about side effects and risks, ask the doctor, pharmacist, or nurse.

This form lists side effects of *individual* drugs. When we use these drugs *together*, there may be other side effects.

Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study treatment. In some cases, side effects can last a long time or never go away. There also is a risk of death.

You should talk to your doctor about any side effects that you have while you are in this study.

G-CSF

Likely side effects (>20% of patients) of G-CSF are:

- Pain or discomfort at the injection site
- Pain and/or aching in the chest, back, arms, legs, and in the bones

Less likely side effects (\leq 20% of patients) of G-CSF are:

- Nausea / vomiting
- Headache
- Diarrhea or constipation
- Some amount of hair loss
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Sores in or around the mouth
- Cough or shortness of breath
- Skin rash

- Weakness
- Sore throat
- Nose bleeds

Rare but serious side effects of G-CSF are:

- Allergic reactions (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives)
- Difficulty breathing or coughing up blood
- Bleeding in the brain
- Blood in the urine
- Blood clots
- Worsening of psoriasis if you already have psoriasis
- Kidney problems including kidney failure
- Elevated heart rate
- Blood clot
- Rupture of the spleen (when an organ in your abdomen bursts); this may be life-threatening
- Inflammation of the sac around the heart

Cladribine

Likely side effects (>20% of patients) of Cladribine are:

- Nausea and vomiting
- Tiredness or fatigue
- Rash
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Low blood counts (low WBC, RBC, platelets)

Less likely side effects (\leq 20% of patients) of Cladribine are:

- Headache
- Dizziness
- Cough or shortness of breath
- Abdominal pain, possibly with diarrhea or constipation
- Muscle or joint pain
- Pain at the place of injection
- Bruising
- Itching

Rare but serious side effects of Cladribine are:

- Stevens-Johnson syndrome
- Allergic reactions (fever, chills, shortness of breath, fast heartbeat, loss of consciousness, sweating, swelling of face or tongue, tightness of throat, wheezing)

Cytarabine

Likely side effects (>20% of patients) of Cytarabine are:

- Fatigue
- Low blood counts (low WBC, RBC, platelets)
- Diarrhea, nausea, vomiting, and loss of appetite
- Irritation, inflammation, or damage to the mouth, throat, esophagus (tube between the mouth and stomach), stomach, intestines or colon
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Rash
- Abnormal liver tests or liver function

Less likely side effects (\leq 20% of patients) of Cytarabine are:

- Chest pain
- Fluid collection around the heart
- Shortness of breath
- Headaches
- Dizziness
- Irritation or inflammation of nerves which causes pain in various parts of the body
- Itching
- Jaundice (yellow discoloration of the skin)
- Constriction of the lung airways causing shortness of breath or wheezing
- Inflammation of the pancreas (the organ in your abdomen that helps you digest food and controls your blood sugars)
- Difficulty in passing urine
- Inflammation or irritation of the eye or surface of the eyelids
- Kidney problems

Rare but serious side effects of Cytarabine are:

- Inflammation around the brain
- Heart failure
- Diffuse pain in the muscles, bones, chest, and eyes

- Severe skin rash with flat discolored areas and raised bumps
- Weakness
- Muscle damage
- Life-threatening liver damage

Mitoxantrone

Likely side effects (>20% of patients) of Mitoxantrone are:

- Fatigue
- Low white blood cell counts
- Fever during times of low blood counts (i.e., “neutropenic fever”)
- Nausea / vomiting
- Temporary discoloration of the urine and other body fluids (due to blue color of medication)

Less likely side effects (\leq 20% of patients) of Mitoxantrone are:

- Skin rash
- Fast or irregular heart beat
- Fever or chills
- Lower back or side pain
- Painful or difficult urination; decrease in urination
- Swelling of feet and lower legs
- Sore, red eyes
- Yellow eyes or skin
- Pain or inflammation at injection site
- Blue skin at place of injection

Rare but serious side effects of Mitoxantrone are:

- Allergic reactions (fever, chills, shortness of breath)
- Heart failure
- Secondary acute myeloid leukemia from drug treatment

Reproductive risks

Chemotherapy and radiation treatments may make you sterile (unable to have children).

Also, the drugs in this study may affect a baby, before or after the baby is born.

For women who can become pregnant:

- You should not become pregnant while you are in this study.
- You should not nurse a baby while you are in this study.

For women and men:

- If you are having sex that could lead to pregnancy, you should use birth control while you are in this study.
- Check with the study doctor about birth control methods and how long to use them. Some common methods might not be appropriate while you are in this study.

Non-physical risks

Non-physical risks are:

- You may not be able to work.
- Breach of confidentiality.

What are the benefits?

We do not know if this study will help patients. We are testing G-CLAM with dose-escalated Mitoxantrone to see its effects on people with AML and high-risk MDS. Patients who get this study treatment may get better, but their condition could stay the same or even get worse. We hope the information from this study will help other people with AML or high-risk MDS in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.

If you do not join this study, you have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor about them.

Your other choices may include:

- Another research treatment.
- Standard treatment.
- No treatment.
- Comfort care.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information

Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.
- US National Institutes of Health, Office for Human Research Protections, U.S. Food & Drug Administration, and other agencies as required.

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, a court may order study information to be disclosed. Such cases are rare.

We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

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

Information about your participation in this study such as the title of the study and the names of the researchers involved in the study will be made a part of your permanent medical record. If you authorize others to see your medical record, they will find out about your participation in this study.

Will you pay me to be in this study?

There is no payment for being in this study.

How much will this study cost me?

There may be some extra costs for being in this study. You or your insurer will have to pay these costs. Some insurers will not pay for research. Check with your insurer before you join this study.

The extra costs may be:

- Cost of tests that are given more often than usual.
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care you may need because of this study.

You or your insurer will have to pay for the costs of treating your cancer in this study.

What if I get sick or hurt in this study?

If you get sick or hurt in this study, tell the study doctor in person or call 206-667-3599.

Emergency medical treatment is available at the usual charge. You or your insurance company will have to pay for medical care or hospitalization. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family.

If you get sick or hurt in this study, you will get medical treatment. You or your insurer will have to pay for treatment.

Your rights

- You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.
- If you join this study, you do not have to stay in it. You may stop at any time (even before you start). There is no penalty for stopping. Your regular medical care will not change.
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we may learn new information you need to know. For example, some information may affect your health or well-being. Other information may make you change your mind about being in this study. If we learn these kinds of information, we will tell you.

For more information

If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you can talk to are listed below.

If you have questions about:	Call:
This study (including complaints and requests for information)	206-667-3599 (Dr. Roland B. Walter)
If you get sick or hurt in this study	206-667-3599 (Dr. Walter)
Your rights as a research participant	206-667-4867 (Karen Hansen, Director of Institutional Review Office, Fred Hutchinson Cancer Research Center)
Your bills and health insurance coverage	206-288-1113

Signature

If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

Participant / Printed Name, Signature, and Date

If you served as an interpreter during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

Interpreter / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature / Printed Name, Signature, and Date

Protocol: 2734.00

Current version date: 01/27/2016

Previous version date: 02/11/2015

Copies to: Patient, Medical Records, Research File