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Impact of Treatment Intensity on Survival, Quality of Life, and Resource Utilization in Medically Less Fit Adults with Acute Myeloid Leukemia and Analogous Myeloid Neoplasms: A Randomized Pilot Study

Principal Investigator:

- Anna B. Halpern, MD, Assistant Professor, FHCRC; Assistant Professor, UW (206-606-1978)

Sub-Investigators at FHCRC/UW:

- Roland B. Walter, MD PhD MS, Professor, FHCRC; Professor, UW (206-667-3599)
- Mary-Beth Percival, MD, MS; Associate Professor, FHCRC; Associate Professor, UW (206-606-1320)
- Paul Hendrie, MD, PhD; Associate Medical Director, SCCA; Clinical Professor, UW (206-606-1000)

Biostatistician:

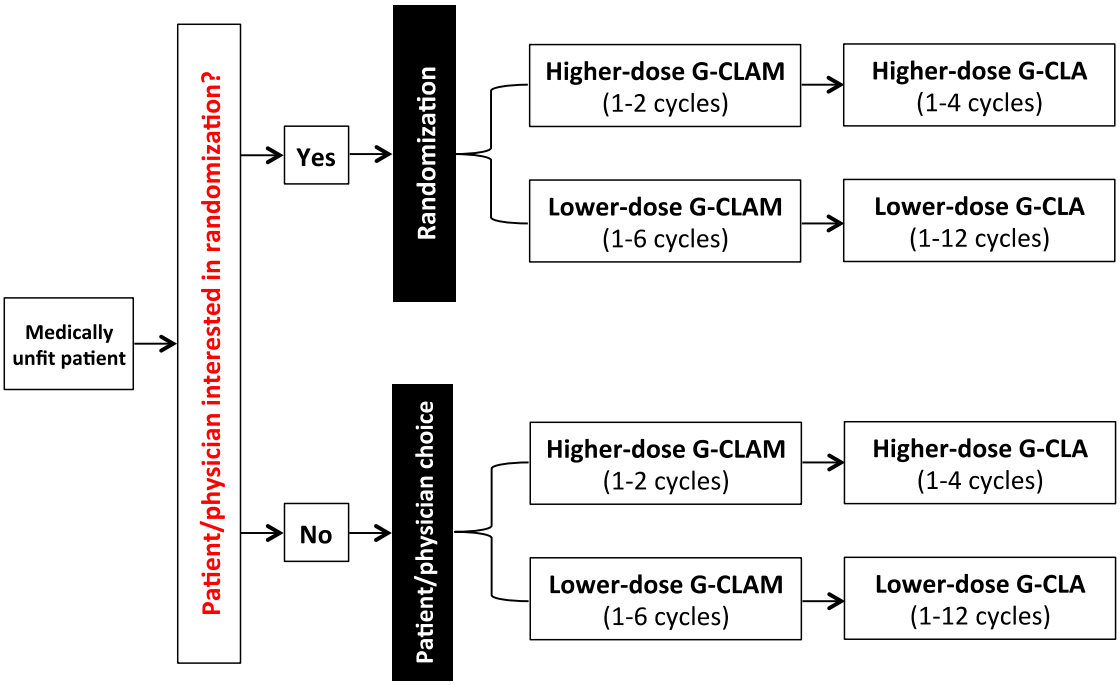
- Megan Othus, PhD, Professor, FHCRC (206-667-5749)

Study Coordinator FHCRC:

- Anna B. Halpern, MD, Assistant Professor, FHCRC; Assistant Professor, UW (206-606-1978)

Emergency Phone (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.

OVERVIEW OF TREATMENT PLAN AND DOSING SCHEME



Treatment arm	G-CSF (SC, D0-D5)	Cladribine (IV 2h, D1-D5)	Cytarabine (IV, D1-D5)	Mitoxantrone (IV, D1-D3)
Higher-dose G-CLAM	300 or 480 µg*	5 mg/m^2	2,000 mg/m^2**	18 mg/m^2
Lower-dose G-CLAM	300 or 480 µg*	2 mg/m^2	100 mg/m^2***	6 mg/m^2

*Dosing based on patient weight: <76kg vs. ≥76 kg; **over 2 hours; ***over 1 hour

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1.0 BACKGROUND AND RATIONALE

In 2016, an estimated 19,950 individuals will develop AML in the U.S.[1] With current 5-year relative survival rates of 55-60% for patients <45 years of age but only ~5% for adults >age 65 (the median age at diagnosis),[2] many patients will ultimately die from either treatment-related toxicities or therapeutic resistance.[3-5] The need for improved therapeutic approaches is therefore unquestioned. This is particularly true for individuals presenting with medical co-morbidities that may limit their ability to tolerate intensive treatments; such patients are generally, but not invariably, older. Many of these subjects never receive any AML-directed therapy.[6,7] Among those who do, the optimal treatment strategy is unknown but typically revolves around the choice of non-intensive therapy (e.g. azacitidine/decitabine or low-dose cytarabine) or intensive therapy (e.g. "7+3").[8]

U.S. and European population-based registry data support the use of intensive chemotherapy rather than low-intensity therapy (or no therapy) in most AML patients up to age 80.[6,9] Likewise, a recent retrospective analysis of 1,079 adults who received chemotherapy at 5 U.S. institutions from 2008-2012 suggested that, after adjustment for age, co-morbidity index, and cytogenetic/molecular risk, intensive therapy leads to better long-term survival even in older patients (age 70-79 years) with significant co-morbidities without increase in early mortality.[10] However, these observations must be interpreted cautiously since information on exact regimens is not available and differences in supportive care and selection bias may confound the apparent benefit of intensive therapy. This possibility highlights the need for a randomized clinical trial to define the optimal treatment intensity for medically less fit AML patients with varying co-morbidity burden.

One barrier to improving care for medically less fit adults with AML has been the lack of explicit definition of "less fit". In the AZA-001 trial, which randomized older adults with newly diagnosed AML with >30% blasts to either azacitidine or "conventional care regimens" (CCRs), i.e. best supportive care (BSC), low-dose cytarabine, or "7+3", the investigators determined which protocol-designated CCR was most appropriate for each patient on the basis of age, performance status, and institutional practice before randomization.[11] Survival with azacitidine was best in those (presumably the most fit) in whom the alternative was "7+3", and worst in those (presumably the least fit) in whom the alternative was BSC. This suggests that physicians are adept at distinguishing fit from less fit individuals. However, it seems doubtful that they are as adept as a quantitative model. To develop such a model, we recently analyzed data from 3,365 adults with newly diagnosed AML given intensive chemotherapy in SWOG trials or at M.D. Anderson Cancer Center (MDA) and found that the weekly risk of death falls sharply once 4 weeks elapse from start of intensive induction chemotherapy. This observation suggested that patients who die during this time comprise a qualitatively distinct group and allowed an empiric definition of treatment-related mortality (TRM) as deaths occurring within these 4 weeks.[12] We then used areas under the receiver operating characteristic curve (AUC) to quantify the ability of individual covariates to predict TRM in 2,238 patients treated at MDA between 1995 and 2008. Performance status (PS) and age were the most important single covariates in predicting TRM (AUC of 0.75 and 0.65 for models with PS or age alone, respectively). However, a "simplified" multicomponent model, which was validated by bootstrapping and comprised the 7 most relevant individual covariates (PS, age, platelet count, serum albumin, type of AML [secondary vs. *de novo*], white blood cell count [WBC], peripheral blood blast percentage, and serum creatinine)

led to a model with an AUC of 0.82, demonstrating an advantage of multicomponent predictive models over the use of single factors to identify the subset of patients at high risk of TRM.[12] Importantly, removal of age from this model had only a minimal effect on the AUC, suggesting that age is largely a surrogate for the other covariates contained in the model.

The TRM score, computationally derived from the "simplified" TRM model, is now in routine use at Fred Hutch, where research protocols now primarily assign patients based on predicted likelihood of TRM (e.g. NCT01342887, NCT01567059, NCT01607645, NCT01729845, NCT01804101, NCT02044796, NCT02121418, NCT02728050). Because the early death rates following intensive chemotherapy in adults with AML have declined substantially over the last 2 decades,[13,14] we very recently re-examined the value of the "simplified" TRM model to predict early deaths in patients treated at Fred Hutch.[15] Among 285 patients with newly diagnosed AML treated with intensive induction chemotherapy from 2008-2014, 17 (6.0%) died within 28 days, with the AUC of the TRM score being 0.76,[15] indicating the continued value of multicomponent modeling to predict early deaths after AML therapy. So far, the comparative abilities of a model such as the one that underlies the TRM score and "physician intuition" ("I know it when I see it") to predict TRM are uncertain. Moreover, an AUC of 0.75-0.80 approximately intermediate between certainty (AUC=1.0) and a coin flip (AUC=0.5). Therefore, although the TRM score will be the principal eligibility criterion for the pilot randomized trial, an important part of this application will be examining (a) whether incorporation of other covariates (e.g. HCT-CI, ELN risk group) will improve the ability to forecast TRM and (b) the concordance between our models and simple physician judgment. While we have developed online means to rapidly compute TRM scores (https://cstaging.fhcrc-research.org/TRM/Default.aspx), it is perhaps naïve to expect widespread use barring a quantitative demonstration of the value of predictive models.

Recognizing the current limitations in our knowledge regarding treatment approach to adults with AML who are medically less fit, the goal of our research, is to conduct a controlled clinical trial to improve outcomes in these patients. Because of the possibility of significant selection bias in non-randomized assessments, the preferred trial is based on a randomized assignment to higher-intensity vs. lower-intensity chemotherapy. However, such a trial may prove impractical. Therefore, this pilot study will explicitly test the feasibility of randomization in this situation, and explore reasons why patients and/or physicians might be reluctant to randomization in this situation. For this purpose, we will use preference surveys to examine patient and physician attitudes towards medical decision-making and treatment allocation. In addition to focusing on feasibility and estimates of anti-leukemia activity (e.g. response rates) and survival, we will also assess complementary dimensions of treatment benefit, in particular quality of life (QOL) as well as resource utilization and care cost.

Contemporary clinical trials often utilize DNA methyltransferase inhibitors (e.g. azacitidine or decitabine) or low doses of cytarabine as non-intensive therapy, whereas multi-agent chemotherapy, most typically in the classic 7+3 combination between cytarabine and an anthracycline as intensive therapy. However, treatment outcomes with standard therapeutics in medically less fit individuals with AML are relatively poor. This is exemplified by the AZA-001 trial, in which median overall survival times of approximately 6-7 months for low-dose cytarabine and 10-12 months for azacitine or 7+3 were estimated. This observation highlights the need for better therapies. In a recent phase 1/2 trial in medically fit adults with newly diagnosed AML, we found that combination therapy with G-CSF, cladribine, high-dose cytarabine, and escalated doses of mitoxantrone (G-CLAM) is well tolerated and appears to produce higher rates

of CR, CR without MRD, and possibly longer survival than 7+3, after accounting for prognostic covariates. Given these data, G-CLAM will be used as intensive therapy in our pilot trial ("higher-dose G-CLAM"). As comparator non-intensive therapy, we will use G-CLAM with reduced doses of cladribine, cytarabine, and mitoxantrone ("lower-dose G-CLAM"). Rather than selecting different classes for the non-intensive and intensive treatment arm in our trial – which may have different modes of action and therefore confound the question of treatment intensity – we purposefully chose G-CLAM as backbone for both arms.

Development of G-CLAM as highly active, intensive chemotherapy for newly diagnosed AML
Since 2012, we have used G-CLAM extensively in adults with newly diagnosed AML and high-grade MDS, primarily as part of a large, ongoing institutional phase 1/2 trial (FHCRC #2734.00). Our interest in this regimen stems from data indicating improved anti-leukemic activity with regimens containing cladribine, high-dose cytarabine, and escalated doses of mitoxantrone compared to standard 7+3 chemotherapy. Data from this trial, which was presented at the 2016 annual meeting of the American Society of Hematology, have established the safety of a G-CLAM regimen with escalated doses of mitoxantrone, which will form the basis for the backbone used in this proposal. Specifically, the phase 1 portion on 33 patients established the highest dose tested (mitoxantrone at 18 mg/m^2/day) as the maximally tolerated dose. A total of 62 patients, including 6 treated in phase 1, received G-CLAM at MTD. Patient characteristics were as follows: median age 58 (21-81) years, median TRM score 2.85 (0.06-6.73), with AML (n=52) or high-risk MDS (n=10). Cytogenetics were favorable in 6, intermediate in 44, and adverse in 12 (MRC criteria); 11 patients had NPM1 and 6 had FLT3 mutations. Fifty-two patients (83.9%, 95% confidence interval: 72.3-92.0%) achieved a CR (n=48 [77.4%: 65.0-87.1%]), or CRp/i (n=4 [6.5%: 1.8-15.7%]) with 1-2 cycles of therapy. Only 3 patients required 2 cycles to best response. Among the 48 CR patients, 43 (89.6%) were negative for measurable residual disease (MRD^{neg}) by flow cytometry. Four patients had morphologic leukemia free state, 1 patient with myeloid sarcoma had a partial remission, 4 had resistant disease, and 1 died from indeterminate cause. One patient died within 28 days of treatment initiation (septic shock). Median times to an absolute neutrophil count ≥500/μL and a platelet count of ≥50,000/μL were 26 and 23 days. Besides infections and neutropenic fever, maculopapular rash, and hypoxia (fluid overload/infection-related) were the most common grade ≥3 adverse events. In addition to the phase 1/2 MTD cohort, there were 15 patients treated in an expansion cohort and 3 eligible patients treated off protocol with mitoxantrone at 18 mg/m^2. For these 80 patients combined treated at MTD, the CR and CR/CRp/i rates were 76.3% and 81.2%. After multivariable adjustment, compared to 300 patients treated with 7+3 on the SWOG S0106 trial, G-CLAM with mitoxantrone 18mg/ m^2 was associated with an increased probability of CR (odds ratio [OR]= 3.08, p=.02), CR/CRp/i (OR=2.96, p=.03), a trend towards improved MRD^{neg} CR (OR= 3.70, p=.06), and a trend towards improved overall survival ([OS]; hazard ratio=0.34, p=.07). For the entire study cohort, the 6 and 12-month relapse-free survival were 73% (64-83%) and 62% (42-74%) and the 6 and 12-month OS were 89% (82- 96%) and 77% (67-88%). Together, our study found G-CLAM with mitoxantrone up to 18 mg/m^2/day to be well tolerated and to have potent anti-leukemia activity.

In this pilot study, patients meeting the in/exclusion criteria and primary oncologists are asked whether or not they would agree to participate in the randomized treatment assignment. Patients agreeable to randomization will be assigned in a 1:1 ratio to the higher-intensity arm and given G-CLAM or the lower-intensity arm that is built on G-CLAM but utilizes lower doses of

cladribine, cytarabine, and mitoxantrone. For the other patients, the reasons to decline randomization will be recorded, and patients will be allowed to receive the treatment intensity of their choosing. We will then follow these patient for a variety of disease specific outcomes—remission rates, overall survival—as well as examine patient and physician attitudes towards medical decision-making and treatment allocation, assess QOL, and examine resource utilization and care cost.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To evaluate the feasibility of randomizing medically less fit adults with newly diagnosed AML or analogous myeloid neoplasms to either intensive or non-intensive induction and post remission chemotherapy.

2.2 Exploratory Objectives

2.2.1 To evaluate the attitude of patients and physicians toward randomization and explore reasons for treatment preference.

2.2.2 To evaluate whether the ability to assess fitness for intensive chemotherapy can be improved by an augmented treatment-related mortality (TRM) score that includes additional (co-morbidity) factors, and to compare the ability of physicians and the prediction algorithm(s) to assess the likelihood of early death.

2.2.3 To compare, within the limits of a pilot study, response, duration of response, and survival between patients receiving intensive and those receiving non-intensive chemotherapy.

2.2.4 To describe the impact of treatment intensity on quality of life of patients undergoing chemotherapy for newly diagnosed AML.

2.2.5 To describe the impact of treatment intensity on medical resource utilization and care cost of patients undergoing chemotherapy for newly diagnosed AML.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Age ≥18 years

3.1.2 Diagnosis of untreated "high-grade" myeloid neoplasm (≥10% myeloid blasts by morphology in bone marrow and/or peripheral blood) or AML other than acute promyelocytic leukemia (APL) with t(15;17)(q22;q12) or variants according to the 2016 WHO classification.[16] Patients with acute leukemias of ambiguous lineage are eligible. Outside diagnostic material is acceptable as long as peripheral blood and/or bone marrow slides are reviewed at the study institution and cytogenetic/molecular information is available.

3.1.3 Treatment-related mortality (TRM) score ≥13.1 as calculated with simplified model (see APPENDIX A). [12]

3.1.4 The use of hydroxyurea before enrollment is permitted; hydroxyurea should be discontinued prior to start of study treatment. Patients with symptoms/signs of leukostasis, WBC >100,000/μL, or acute symptoms felt related to their high-grade myeloid neoplasm can be treated with leukapheresis or may receive up to 1 dose of cytarabine (up to 500 mg/m^2) anytime prior to study day 1.

3.1.5 Patients may have received treatment (e.g. azacitidine/decitabine, lenalidomide, growth factors) for antecedent low-grade myeloid neoplasm.

3.1.6 Left ventricular ejection fraction (LVEF) ≥45%, assessed within 3 months prior to registration, e.g. by MUGA scan or echocardiography, or other appropriate diagnostic modality.

3.1.7 Women of childbearing potential and men must agree to use adequate contraception beginning at the signing of the consent until at least 4 weeks after the last dose of study drug.

3.1.8 Ability to understand and the willingness to sign a written informed consent document

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. Patients with fever thought to be likely secondary to leukemia are eligible. Known hypersensitivity to any study drug.

3.2.4 Known hypersensitivity to any study drug used in this trial.

3.2.5 Pregnancy or lactation.

3.2.6 Concurrent treatment with any other anti-leukemia 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 SUBJECT REGISTRATION

To register, the attending physician involved in the care of the potential study participant must contact the Study Coordinator, and a copy of the signed consent form, a signed HIPAA authorization must be available and faxed to the study team (Fax Cover Sheet in APPENDIX E; FAX: +1-206-667-6519). To complete the registration process, the PI, Fred Hutch/UW Study Coordinator or designee will assign a patient study number, register the patient on the study, and enter the patient into the Clinical Trials Management System (CTMS), OnCore. A complete, signed, study consent and HIPAA consent are required for registration.

6.0 TREATMENT PLAN

This study is a single-center, open-label randomized pilot study of lower-dose vs higher-dose G-CLAM for medically less fit adults with newly diagnosed AML or analogous myeloid neoplasms at the Fred Hutchinson Cancer Research Center/University of Washington/Seattle Cancer Care Alliance.

Study Overview
In this pilot study, patients meeting the inclusion/exclusion criteria and their primary oncologists are asked whether or not they would agree to participate in the randomized treatment assignment (APPENDIX D). Patients agreeable to randomization will be assigned in a 1:1 ratio to the higher-dose G-CLAM arm or the lower-dose G-CLAM arm that utilizes lower doses of cladribine, cytarabine, and mitoxantrone. For those who wish to not be randomized, the reasons to decline randomization will be recorded, and patients will be allowed to receive the treatment intensity of their choosing. Patients will receive higher-dose or lower-dose G-CLAM as follows:

Treatment arm	G-CSF (SC, D0-D5)	Cladribine (IV 2h, D1-D5)	Cytarabine (IV, D1-D5)	Mitoxantrone (IV, D1-D3)
Higher-dose G-CLAM	300 or 480 µg*	5 mg/m^2	2,000 mg/m^2**	18 mg/m^2
Lower-dose G-CLAM	300 or 480 µg*	2 mg/m^2	100 mg/m^2***	6 mg/m^2

*Dosing based on patient weight: <76kg vs. ≥76 kg; **over 2 hours; ***over 1 hour

After study enrollment, patients will receive a first cycle of G-CLAM on one of the designated treatment arms. Post-induction bone marrows will be reassessed upon blood count recovery or between day Days +28 to +35 after start of chemotherapy, whichever occurs first. If a response other than a measurable ("minimal") residual disease-negative (MRDneg) CR is achieved, the patient will receive re-induction with G-CLAM at the same dosing. Patients who achieve a morphologic CR or CR with incomplete count recovery (CRi) with up to 2 courses of higher-dose G-CLAM or up to 6 courses of lower-dose G-CLAM can receive consolidation therapy with G-CLA (i.e. mitoxantrone omitted; up to 4 cycles with high-dose G-CLA and up to 12 cycles of low-dose G-CLA).

6.1 Baseline/Pre-Treatment Assessment

The following procedures should be obtained at baseline before initiation of study therapy to establish trial eligibility and allow patient characterization and disease prognostication. Results of tests and/or procedures conducted as per standard of care may be used to determine study eligibility if conducted within an appropriate window prior to screening. Outside testing and previously collected clinical data may be used if within the appropriate time frame.

6.1.1 History and physical examination (assessed within 14 days prior to study day 0).

6.1.2 Bone marrow examination (or peripheral blood assessment if ≥10% blasts are present) with morphologic and flow cytometric assessment. Routine cytogenetic analysis and molecular testing should be obtained. A bone marrow biopsy should be obtained if spicules are absent from the aspirate sample (aspirate and biopsy to be assessed within 2 months prior to study day 0).

6.1.2 Complete blood counts with differential blood count and platelet count (assessed within 14 days prior to study day 0).

6.1.3 Metabolic panel, including 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 for clinical management only, 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 if clinically indicated. All patients should be adequately hydrated and receive anti-emetics as necessary.

6.3 Administration of G-CSF, Cladribine, and Cytarabine Mitoxantrone on the Higher-Dose Arm: INDUCTION

6.3.1 For induction: The doses of the elements of G-CLAM chemotherapy will be as follows G-CSF 300 or 480 µcg/ (based on weight <76 kg vs. ≥76kg) daily subcutaneously daily on Days 0-5, Cladribine 5 mg/m^2 IV daily over 2 hours on Days 1-5, Cytarabine 2,000 mg/m^2 IV daily over 2 hours on Days 1-5, and Mitoxantrone 18 mg/m^2 IV daily over 60 minutes on Days 1-3.

6.3.2 The doses of all medications are calculated using the patient's actual weight.

6.3.3 Days 0 and 1 G-CSF may be omitted at physician discretion for WBC >20,000/µL, signs/symptoms of leukostasis, or acute symptoms felt related to their high-grade myeloid neoplasm.

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.

6.3.6 If the patient has significant organ-specific dysfunction at baseline (e.g. abnormal liver or kidney function), dose reduction can be considered as described in section 6.8 at the physician discretion in conjunction with the oncology pharmacist.

Outline Treatment Schedule: Higher Dose G-CLAM	
Day	**Treatment**
0	G-CSF 300/480 µcg
1	G-CSF, Cladribine 5 mg/m^2, Cytarabine 2,000 mg/m^2, Mitoxantrone 18 mg/m^2
2	G-CSF, Cladribine 5 mg/m^2, Cytarabine 2,000 mg/m^2, Mitoxantrone 18 mg/m^2
3	G-CSF, Cladribine 5 mg/m^2, Cytarabine 2,000 mg/m^2, Mitoxantrone 18 mg/m^2
4	G-CSF, Cladribine 5 mg/m^2, Cytarabine 2,000 mg/m^2
5	G-CSF, Cladribine 5 mg/m^2, Cytarabine 2,000 mg/m^2
28-35 OR blood count recovery	Bone marrow assessment

6.4 Administration of G-CSF, Cladribine, and Cytarabine Mitoxantrone on the Lower-Dose Arm: INDUCTION

6.4.1 For induction: The doses of the elements of G-CLAM chemotherapy will be as follows G-CSF 300 or 480 µcg/ (based on weight <76 kg vs. ≥76kg) daily subcutaneously daily on Days 0-5, Cladribine 2 mg/m^2 IV daily over 2 hours on Days 1-5, Cytarabine 100 mg/m^2 IV daily over 1 hour on Days 1-5, and Mitoxantrone 6 mg/m^2 IV daily over 60 minutes on Days 1-3.

6.4.2 The doses of all medications are calculated using the patient's actual weight.

6.4.3 Days 0 and 1 G-CSF may be omitted at physician discretion for WBC >20,000/µL, signs/symptoms of leukostasis or acute symptoms felt related to their high-grade myeloid neoplasm.

6.4.4 All treatment is given as intent-to-treat; missed doses will not be made up.

6.4.5 No investigational or commercial agents or therapies other than those described herein may be administered with the intent to treat the patient's malignancy.

Outline Treatment Schedule: Low-Dose G-CLAM	
Day	**Treatment**
0	G-CSF 300/480 µcg
1	G-CSF, Cladribine 2 mg/m^2, Cytarabine 100 mg/m^2, Mitoxantrone 6 mg/m^2
2	G-CSF, Cladribine 2 mg/m^2, Cytarabine 100 mg/m^2, Mitoxantrone 6 mg/m^2
3	G-CSF, Cladribine 2 mg/m^2, Cytarabine 100 mg/m^2, Mitoxantrone 6 mg/m^2

4	G-CSF, Cladribine 2 mg/m^2, Cytarabine 100 mg/m^2
5	G-CSF, Cladribine 2 mg/m^2, Cytarabine 100 mg/m^2
28-35 OR blood count recovery	Bone marrow assessment

6.5 Assessment for Response after First Induction Course

A bone marrow aspirate should be obtained upon blood count recovery (i.e. ANC >1,000/μL and platelet count >100,000/μL) or between Days +28 to +35 after start of G-CLAM chemotherapy, whichever occurs first; a bone marrow biopsy need only be obtained during this procedure if spicules are absent from the aspirate sample.

6.5.1 Patients achieving an MRDneg CR: Patients are eligible to receive consolidation therapy with G-CLA (dosing as per section 6.6): up to 4 cycles on the high-dose arm and up to 12 cycles on the low-dose arm

6.5.2 Patients achieving a MRDpos CR or CRi: Patients are eligible for a second cycle of induction therapy using the same dosing guidelines as cycle 1 or may proceed to consolidation therapy with G-CLA as per 6.6, per discretion of treating attending.

6.5.3 Patients with persistent disease: Patients with persistent disease (≥5% blasts) are eligible for a second course of induction chemotherapy at the same dosing used in cycle 1 provided all non-hematologic toxicities have resolved to Grade <2. If they are not in CR or CRi after the 2nd induction course, they will be removed from the study.

6.5.4 Patients with persistent aplasia without evidence of disease after Day +49: patients will be removed from protocol.

6.6 Consolidation Therapy

After achievement of a CR/CRi (irrespective of MRD) with 1-2 courses of G-CLAM therapy, patients are eligible for post-remission therapy with G-CLA.

6.6.1 The treatment is identical to the induction course but without mitoxantrone (i.e. G-CSF, cladribine, and cytarabine, or "G-CLA" at same dose level as induction). If a patient had excessive toxicities (grade ≥3 non-hematologic toxicity excluding neutropenic fever and infections) during induction, a dose reduction can be considered as described in sections 6.8 and 6.9, as well as APPENDIX B.

6.6.2 Post-remission courses should start within 6 weeks of achieving CR/CRi once patients have recovered to ≤Grade 2 toxicities from the previous course of therapy.

6.6.3 Patients on the higher-dose arm can receive up to 4 courses of consolidation therapy.

6.6.4 Patients on the lower-dose arm can receive up to 12 cycles of consolidation therapy.

6.6.5 Patients can proceed to transplantation barring contraindications and if a suitable donor is available.

6.7 Monitoring during/after Induction and Consolidation Therapy

For patient monitoring, the following studies and study intervals are suggested and will be performed at the physician's discretion:

6.7.1 Complete blood counts with differential blood count, including immature cells/blasts, and platelet count at least 2 times weekly until ANC >500/μL and then at least weekly until platelet count >100,000/μL.

6.7.2 Metabolic panel, including bilirubin, ALT/AST, and creatinine at least weekly until ANC >1,000/μL and platelet count >100,000/μL.

6.7.3 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).

6.8 Dose Modifications of Chemotherapeutic Drugs for Induction or Subsequent Treatment Cycles for Higher-Dose Arm

For patients who have organ dysfunction at baseline—defined as a serum creatinine > 2.0 mg/dL or a bilirubin concentration is ≥3 x IULN-- or those who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction, a dose reduction can be considered as follows (see also APPENDIX B]:

6.8.1 If a patient develops Grade ≥3 non-hematologic toxicity other than Grade 3 infections within 28 days from the last dose of G-CLAM, the next course of G-CLAM will be given once toxicity is ≤ grade 2; doses for this course will be cladribine 4 mg/m^2 days 1-5, cytarabine 1,500mg/m^2 days 1-5, mitoxantrone 14 mg/m^2 days 1-3, and G-CSF dose unchanged. Assuming these doses are well-tolerated the first course of G-CLA will be administered at these doses, omitting mitoxantrone. If Grade ≥3 non-hematologic toxicity occurs again, there will be a further reduction in doses of cladribine to 3 mg/m2 daily days 1-5 and cytarabine to 1,000mg/m2 daily days 1-5 for the first cycle of G-CLA. Doses for subsequent courses of G-CLA will be discussed with the Principal Investigator.

6.8.2 Mitoxantrone: If the bilirubin concentration is ≥3 x IULN, consider a dose reduction of mitoxantrone by 25-50% in consultation with the Oncology Pharmacist

6.8.3 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.

6.8.4 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.

6.9 Dose Modifications of Chemotherapeutic Drugs for Subsequent Treatment Cycles for Low-Dose Arm

Given the doses of the chemotherapy in this arm are already low, there will be no further dose reduction for toxicity. Also, doses do not need to be adjusted based on liver or kidney function. Decisions whether to proceed with further cycles of chemotherapy if ≥ Grade 3 toxicity in cycle 1 will be made by the PI in conjunction with the treating physician.

6.10 Supportive Therapy

6.10.1 All patients will be adequately hydrated and receive appropriate anti-emetics based upon institutional guidelines.

6.10.2 Additional growth factors may be used according to institutional practice guidelines or the preference of the attending physician.

6.10.3 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.

6.10.4 Transfusional support should be carried out according to institutional practice guidelines.

6.11 Treatment of CNS Disease

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

6.12 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.

7.0 INFORMATION ON STUDY DRUGS

G-CSF, cladribine, cytarabine, and mitoxantrone will be obtained commercially.

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.

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'-deoxyadenosnie, 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.

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, quadriparesis, 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 0.22μm 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 G_1 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 methylpredinsone.

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, hypcalcemia, 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/m^2; Appendix B 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/m^2 prior doxorubicin and 60 mg/m^2 mitoxantrone, rising to a 15% risk at 120 mg/m^2 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 CR/CRi) 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) will be determine by peripheral blood count and bone marrow evaluation as per Section 6.5 and categorized according to criteria recommended by International Working Groups.[17,18] Patients are routinely assessed for the presence of minimal residual disease (MRD) as detected by multi-parameter flow cytometry and cytogenetic assessment, as per institutional practice.

8.2 Monitoring of Exploratory Endpoints

8.2.1 Quality of life (QOL) assessment

In order to measure QOL, we will use the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), a validated 30-item instrument that includes 5 functional scales, 3 symptom scales, a global health scale, and 6 single items (APPENDIX C). Standardized scores for each scale range from 0 to 100 (higher scores representing better domain-specific QOL),[19] with a minimally clinically important difference of 10 points.[20] We will request survey completion upon study enrollment as well as after each on-study treatment cycle.Given that patients do not always fill out questionnaires due to illness, time or other constraints, we will measure percentage of returned surveys as one of our feasibility outcomes.

8.2.2 Evaluation of medical complications and use of medical resources

Information on medical complications (e.g. need for intensive care unit (ICU)-level care, length of ICU stay, neutropenic fever, documented infections, bleeding, reasons for hospitalization, etc.) and use of medical resources (e.g. red blood cells and platelet transfusions; days of IV antimicrobial therapy, total hospital length of stay) will be collected from the medical records from the UWMC and SCCA as done previously.[21,22]

8.2.3 Assessment of cost

The costs associated with inpatient and outpatient management will be calculated using electronic billing information from the UWMC and SCCA. Costs will be converted from charges using departmental cost-to-charge ratios. We anticipate reporting descriptive information identifying major cost drivers and total/subset costs per phase of treatment (i.e. induction, outpatient management, and readmission), similar to our approach used previously.[21,22]

8.2.4 Examination of patient and physician attitudes towards medical decision-making and treatment allocation

8.2.4.1 We will explore patient-reported factors influencing medical decision-making though a Patient Preference Survey (APPENDIX D) distributed on study enrollment. This survey will include a question on whether they agree to be randomized or prefer to choose their treatment arm, and explores the reasons underlying this decision. As above, given that patients do not always fill out questionnaires, we will measure percentage of returned responses regarding reasons for treatment decision-making as one of our feasibility outcomes. Surveys not returned will not be considered a protocol deviation.

8.2.4.1 We will also explore physician preferences towards treatment-intensity randomization through a Physician Preference Survey (APPENDIX E) also distributed on study enrollment. This survey includes questions about whether the physician was agreeable to randomization (even if the patient was not) and explores reasons the physician might have not wanted to randomize the patient. As physicians are extremely busy, we will measure percentage of returned responses regarding reasons for treatment decision-making as one of our feasibility outcomes. Surveys not returned will not be considered a protocol deviation.

8.3 Correlative Studies

Due to the lack of translational science 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 Fred Hutch's AML sample repository (FHCRC #1690.00; PI: Derek Stirewalt, MD).

9.0 TOXICITY MONITORING

Both acute and chronic toxicities will be recorded and reported to the PI, and will be reviewed by the independent DMC at scheduled meetings. Monitoring for acute toxicity takes place during and following the administration of the medications. Subjects are observed for the development of an immediate localized allergic reaction or anaphylactic reaction during this time.

Toxicity Criteria

This study will use the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE v5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

10.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

10.1 Criteria for Removal from Treatment

All reasons for discontinuation of treatment must be documented:

10.1.1 Completion of protocol treatment.

10.1.2 Arrival to the transplant service for planned HCT.

10.1.3 Initiation of any leukemia-directed therapy other than protocol therapy

10.1.4 Failure to achieve a CR or CRi after 2 courses of therapy with higher-dose G-CLAM or 6 courses of therapy with lower-dose G-CLAM.

10.1.5 Persistent aplasia (ANC <500/μL or platelets <50,000/ μL) without evidence of leukemia after Day +49.

10.1.6 Relapse after achievement of CR/CRi during treatment.

10.1.7 Adverse toxicities that prevent continuation with study treatment.

10.1.8 Withdrawal of consent; the patient may withdraw from the study at any time for any reason.

10.2 Duration of Follow-up

Patients will be followed after completion of study treatment to determine event free survival (EFS) and relapse-free survival ([RFS] (for patients achieving CR), 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.

11.0 ADVERSE EVENTS

11.1 Expedited Reporting Requirements

In accordance with Fred Hutch/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator (PI) 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.

11.2 Definitions:

11.2.1 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.

11.2.2 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.

11.2.3 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.

11.2.4 Unexpected AE: An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

11.3 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (http://ctep.cancer.gov). If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

11.4 Monitoring, Recordings, and Standard Reporting of Adverse Events

Only grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate per 11.1. AEs will be collected for the duration that the patient remains on protocol. If a subject decides to terminate the study early their medical record will continue to be followed for AEs for up to 4 weeks after the treatment was given or they start a new anti-leukemia therapy, whichever occurs first. 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 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.

11.5 Adverse Event Recording Period

AEs will be monitored and recorded in the study database from the time of first exposure to the therapy in this study (i.e., the start of the first dosimetry infusion). AEs with an onset date prior to the first exposure to an investigational product will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

12.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch 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 per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch /University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

Research data will be recorded in a study-specific, password protected database using a unique study ID for each patient to assure patient confidentiality. Data from source documents will be transcribed into this database. 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 files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. There will be no case reports forms (CRFs) used for this trial.

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart

documents. Patient research files will be maintained under control of the Principal Investigator and/or study team and kept in a locked office or file room within a secure building. Access to the study database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

14.0 STATISTICAL CONSIDERATIONS

This is a pilot study of medically less fit adults with newly diagnosed AML or analogous myeloid neoplasm to evaluate the feasibility of randomized assignment to either lower-intensity or higher-intensity chemotherapy in a 1:1 fashion.

14.1 Treatment allocation

Treatment will be allocated based on patient preference. If agreeable to randomization, participants will be allocated to either lower-intensity G-CLAM or higher-intensity G-CLAM in a 1:1 ratio using a computer-generated random list of numbers. Randomization will occur in blocks of 4. Participants not agreeable to randomization will be allocated to lower-intensity G-CLAM or higher-intensity G-CLAM as per subject's preference.

14.2 Sample Size and Power

This study will enroll up to 50 subjects.

14.3 Primary/Exploratory Endpoints/Hypotheses and Analytical Methods

14.3.1 Primary endpoint

The primary objective of this study is to evaluate the feasibility of randomizing patients to either intensive or non-intensive induction and post remission chemotherapy. We will consider randomization feasible (i.e. a subsequent, larger study would be designed as a randomized trial) if the true proportion of patients willing to be randomized is 60% or higher. With 50 patients in a feasibility study and accounting for the sample variation associated with 50 patients, we will consider randomization feasible if at least 52% of the patients agree to be randomized (i.e. 26 or more of 50 patients agree to be randomized). If the true proportion willing to be randomized is 60%, the probability of observing 52% of more willing to be randomized is 90%. The probability of having 26 or more of the 50 patients agree to be randomized is only 6% if the true randomization agreement rate is 40%, and <1% if the true randomization agreement rate is 30% or lower, providing good operating characteristics not only to avoid a false negative result but also a false positive result. If one treatment arm closes prematurely (see section on monitoring below), we will conclude that randomization is not feasible, and the remaining patients will be treated on the remaining arm. Continuation of enrollment into that remaining arm will allow us to gain additional experience and provide more precise estimates of treatment efficacy and treatment-related toxicities.

14.3.2 Exploratory endpoints

This pilot study will use exploratory, descriptive, and observational methods to

1) Evaluate the attitude of patients and physicians toward randomization and explore reasons for treatment preference

2) Evaluate whether the ability to assess fitness for intensive chemotherapy can be improved by an augmented treatment-related mortality (TRM) score that includes additional (co-

morbidity) factors, and to compare the ability of physicians of the prediction algorithm(s) and physician to assess the likelihood of early death
3) Estimate differences between patients treated with lower-intensity G-CLAM and those treated with higher-intensity G-CLAM with regard to anti-leukemic efficacy (response, duration of response) and survival, QOL, and medical resource utilization as well as care cost

Importantly, this trial is not powered to detect statistically significant differences between the study arms for these clinically important endpoints. Rather, the primary goal is to estimate outcomes with both treatment intensities to inform a subsequent larger study, should follow-up investigation appear warranted.

14.4 Monitoring for efficacy and early mortality

This study will evaluate each regimen separately, and also compare regimens among patients who are randomized. Details for both sets of analyses are provided below.

Within-arm monitoring for efficacy and early mortality
We will enroll patients in 2 stages in order to allow for early stopping for unacceptable differences in early mortality or inefficacy. Early mortality will be defined as death for any reason on or before day 28 after starting therapy. Inefficacy will be evaluated using MRD^{neg} CR.

We will use our ongoing clinical trial using a CPX-351 in medically less fit adults with AML or high-grade MDS will provide "historical" control data for both inefficacy and early mortality. In this trial (FHCRC #2642.00), which used essentially identically inclusion/exclusion criteria, we have so far treated 37 subjects at a CPX-351 dose of 32 units/m^2. Among these, 8 patients achieved an MRD^{neg} CR (22%). Ten patients (27%) died within 28 days of treatment initiation; at least 4 of these subjects experienced early disease progression as main cause of death, highlighting the balance between treatment efficacy and potential toxicity.

In the first stage, 10 patients will be accrued to each arm, either in a randomized or non-randomized fashion. Each arm will be evaluated separately for early death and inefficacy stopping rules. Accrual may temporarily be held while outcome data on these patients matures.. As some patients may choose to not be randomized, the 2 treatment arms may be evaluated at a different time point for early stopping.

1) Lower-dose Arm: After 10 patients have been accrued to the lower-dose arm, we will evaluate for early death and inefficacy.

> **Early death:** If the number of early deaths is 5 or higher, accrual will stop with the conclusion that the arm is too toxic for further randomization. If the true early mortality rate is 30% or less, the probability of observing 5 or more early mortality events is 15%.
>
> **Inefficacy:** If there are 0 patients with MRD^{neg} CR, accrual will stop with the conclusion that the arm is not efficacious enough for further randomization. If the true MRD^{neg} CR rate is 22%, the probability of observing 0 MRD^{neg} CRs in 10 patients is 8%.

2) Higher-dose Arm: After 10 patients have been accrued to the higher dose arm, we will evaluate for early death and inefficacy.

Early death: If the number of early deaths is 5 or higher, accrual will stop with the conclusion that the arm is too toxic for further randomization. If the true early mortality rate is 30% or less, the probability of observing 5 or more early mortality events is 15%.

Inefficacy: If there are 0 patients with MRD^{neg} CR, accrual will stop with the conclusion that the arm is not efficacious enough for further randomization. If the true MRD^{neg} CR rate is 22%, the probability of observing 0 MRD^{neg} CRs in 10 patients is 8%.

Between-arm monitoring for efficacy and early mortality

After enrollment of at least 10 patients in each arm (at which point one arm may have more than 10 patients accrued due to slower accrual in one arm), we will compare the two arms for relative mortality and efficacy. If, based on Fisher's exact test, the early mortality rate is significantly higher in one arm at the alpha =10% level (this criterion will be met if, for example, both arms have accrued 10 patients one arm has 0 early mortality events and the other arm has 4), accrual will stop in that arm with the conclusion that the arm with the higher early mortality rate is too toxic for further randomization. In addition, if based on Fisher's exact test, the MRD^{neg} CR rate is significantly higher in one arm compared to the other at the alpha = 10% level (for example, this criterion will be met if both arms have accrued 10 patients and one arm has 2 MRD^{neg} CRs and the other has 7), the accrual will stop in that arm with the conclusion that the arm with the lower MRD^{neg} CR rate is not efficacious enough for further randomization.

If accrual does not stop in both arms, up to a total of 50 patients will be accrued.

14.5 Ethnic and Gender Distribution Chart

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 50 patients with newly diagnosed AML or analogous high-grade neoplasms will be enrolled in this study.

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	20	28	48
Ethnic Category Total of All Subjects*	21	29	50
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	1	1	2

Native Hawaiian or Other Pacific	0	0	0
Black or African American	1	1	2
White	19	27	46
More Than One Race	0	0	0
Racial Categories: Total of All	21	29	50

15.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures.

16.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

16.1 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval.

16.2 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

16.3 Informed Consent

The PI and qualified designees assume the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies

available, any known previously experienced adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate. Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents. If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

16.4 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

17.0 STOPPING THE STUDY

The study will terminate as described in section 10.0. The Principal Investigator and the IRB reserve the right to terminate this study at any time.

18.0 REFERENCES

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19.0 APPENDICES

APPENDIX A: 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 B: DOSE MODFICATION TABLE

For patients who experienced ≥Grade 3 non-hematologic toxicities excluding neutropenic fever and infections during the first induction, the following dose reduction can be considered for the next course

High-Dose Arm

Drug	Dose Reduction #1	Dose Reduction #2
G-CSF	No change	No change
Cladribine	Cladribine 4 mg/m^2	Cladribine 3 mg/m^2
Cytarabine	Cytarabine 1,500 mg/m^2	Cytarabine 1,000 mg/m^2
Mitoxantrone	Mitoxantrone 14 mg/m^2	NA

Low-Dose Arm

No dose reductions required.

APPENDIX C: EUROPEAN ORGANIZATION FOR RESEACH AND TREATMENT OF CANCER QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

APPENDIX D: PATIENT PREFERENCE FOR TREATMENT ASSIGNMENT SURVEY

We would like to understand whether patients and their doctors are comfortable letting a "coin flip" decide whether lower- or higher-intensity chemotherapy is used. We also want to understand how you made this decision, and why. Please answer the following questions:

1) Preference for treatment assignment

After thinking about this study and discussing it with your doctor(s), how do you prefer to be treated?

☐ I am willing to let a coin flip (i.e. computer program) decide whether I receive lower- or higher intensity chemotherapy

☐ I would like to make the decision whether I receive lower- or higher-intensity chemotherapy myself

- ☐ My preference is to receive **lower**-intensity chemotherapy
- ☐ My preference is to receive **higher**-intensity chemotherapy

2) How did you make this decision?

☐ I made the final decision about which treatment I would receive

☐ I made the final decision of my treatment after seriously considering my doctor's opinion

☐ My doctor and I decided together which treatment is best for me

☐ My doctor made the decision after seriously considering my opinion

☐ My doctor made the final decision about which treatment I would receive

3) Which factors were most important for you in making this decision?

Patient name/signature: _____ Date: _____

APPENDIX E: PHYSICIAN PREFERENCE FOR TREATMENT ASSIGNMENT SURVEY

We are conducting a study to better understand whether patients and their doctors are comfortable letting a "coin flip" decide whether lower- or higher-intensity chemotherapy is used. We would like to ask you two questions about your preference for treatment assignment and which factors are important for making this decision. It should take about 5 minutes. There are no foreseeable risks to your participation. There is no payment for taking part in this research and your participation is voluntary. Choosing not to participate will not incur a loss of benefits to which you are otherwise entitled. You will not directly benefit from taking this survey, but we hope we can better understand how decisions about treatment intensity are made. We will ask you to provide your name and we will link your responses to similar questions we are also asking the patient you are treating. However, your name will remain confidential and if results of this study are published we will not use your name. If you have questions about this study, please contact Anna Halpern MD at 206-667-6233. If you have questions about your rights as a research participate, you can contact Karen Hansen, Director of the Institutional Review Office, Fred Hutchinson Cancer Research Center, at 206-667-4867.

1) Preference for treatment assignment

After thinking about this study and discussing it with the patient, how do you prefer for the patient to be treated.

☐ I am willing to randomize the patient to lower- or higher intensity chemotherapy and they agree

☐ I am willing to randomize the patient to lower- or higher intensity chemotherapy but the patient would prefer to choose treatment themselves and they chose:

- ☐ L**ower**-intensity chemotherapy
- ☐ H**igher**-intensity chemotherapy

☐ Neither I nor the patient want to proceed with randomization and the following person chose the treatment arm:

- ☐ Myself
- ☐ The patient

2) Which factors were most important for you in making this decision?

☐ The patient did not want to be randomized (did not like the idea of a "coin flip")

☐ The patient thought one treatment arm was better than another

☐ I thought one treatment arm was better than another

☐ I thought the patient was too frail/unfit for the higher intensity treatment and that this arm would be too toxic

☐ I was concerned the lower intensity arm would not be efficacious enough

☐ Other, please explain:

Physician name: _____ Date: _____

APPENDIX F: FAX COVER SHEET

FAX COVER SHEET

DATE:_____

_

TO: Anna Halpern

FAX (206) 667-6519

RE: RESEARCH SUBJECT CONSENT/HIPAA FORM PROTOCOL 9759

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.

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