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Initial cytoreductive therapy for myelodysplastic syndrome prior to allogeneic hematopoietic cell transplantation (the ICT-HCT Study).

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1.0 INTRODUCTION

While allogeneic hematopoietic cell transplantation (HCT) is currently the only curative treatment modality for myelodysplastic syndrome (MDS), relapse remains a major cause of failure. Pre-HCT cytoreductive therapy has been utilized with regularity to reduce post-HCT relapse. – at our institution among 141 MDS patients transplanted over the past three years 130 (92%) received prior chemotherapy (unpublished data) – however, the optimum modality, and the impact on post-HCT outcome remain to be determined. Since MDS is primarily a disease of older age, often complicated by comorbidities, a major concern with induction chemotherapy (IC) as used for acute myeloid leukemia is treatment-related toxicity and mortality. Treatment-related toxicities are likely to affect patients' candidacy for and capacity to tolerate the subsequent HCT. Recently, many patients have received pre-HCT cytoreduction with hypomethylating agents (azacitidine and decitabine), rendered attractive by ease of administration and a low toxicity profile. Although there is a growing body of retrospective literature, no randomized prospective trials comparing IC with hypomethylation have been performed.

We are conducting a prospective trial randomizing patients with intermediate and high-risk MDS who are HCT candidates to receive pre-HCT therapy with IC versus hypomethylation. The primary aim is to prospectively assess the impact of IC versus hypomethylation as initial therapy on survival in the study population. We will also assess transplant frequency, relapse, and quality of life. Results from this study will provide controlled, prospective data on the impact of pre-HCT IC versus hypomethylating therapy on transplantability and transplant outcome, thereby guiding clinical practice.

2.0 BACKGROUND

2.1 Study Disease

MDS represents a group of clonal myeloid stem cell disorders with a heterogeneous spectrum of presentation, ranging from an indolent course over several years to rapid progression to acute myeloid leukemia (AML). MDS typically occurs without a preceding insult (*de novo* MDS) but can also occur after chemotherapy or radiotherapy resulting in secondary MDS. The natural history of patients with MDS is varied with a median survival ranging from 5.7 years for patients with low-risk IPSS (International Prognostic Scoring System) scores, to 0.4 years for those with high-risk scores [1]. Although some conventional therapies have been shown to prolong survival, the only treatment modality for MDS with demonstrated curative potential is allogeneic hematopoietic cell transplantation.

With a median age at the time diagnosis of 65 years, the care of patients with MDS is often complicated by medical comorbidities, and treatment considerations revolve around a balance of the benefit and tolerability of a given modality. Historically, transplantation had been reserved for the young and fit with related donors as the intensive conditioning led to high rates of transplant-related mortality. As a result of improved conditioning regimens, prevention of liver toxicity with ursodiol, and improved microbial surveillance, prevention, and treatment with reduced complications from cytomegalovirus and fungal infections HCT outcomes have improved over time [2]. Furthermore, the development of reduced intensity conditioning (RIC) regimens has extended transplantation to patients with increasing age and comorbidities. Currently, over 60% of patients undergoing HCT for MDS are conditioned with a reduced intensity regimen.

Despite the curative potential of HCT, relapse remains the primary cause of failure after transplantation [3-5]. The risk of relapse not only correlates with intrinsic disease properties such as cytogenetics, but also with the total disease burden. Although there is less non-transplant-related mortality with RIC regimens, there is an increase in relapse as compared to conventional high-dose regimens [4,5]. This result is thought to be due to the fact that little disease reduction occurs with reduced conditioning, placing more responsibility on the graft-versus-leukemia effect to clear the disease. This conclusion is supported by the fact that patients with a higher disease burden prior to

HCT, regardless of conditioning regimen, experience increased rates of relapse as compared to those in remission [4,5].

2.2 Clinical Data to Date

The strategy of using chemotherapy prior to transplantation in an attempt to reduce disease burden, therefore reducing the risk of relapse after HCT, has become commonplace. Nevertheless, in the absence of randomized prospective trials the role of pre-HCT cytoreduction remains undefined. Prior to 2004, the mainstay of cytoreduction was intensive chemotherapy regimens developed as induction therapy for AML though retrospective studies of these regimens before HCT have not pointed to a clear benefit [6-8]. Furthermore, intensive pre-HCT therapy may lead to lead to a worsening in performance status impacting patients' candidacy for and capacity to tolerate the subsequent HCT [9].

More recently, hypomethlyating agents (azacitidine and decitabine) have increasingly been used for pre-HCT cytoreduction rendered attractive by their ease of administration and a low toxicity profile in an attempt to better balance cytoreduction and treatment-related toxicity. In the absence of prospective data, several groups have published the results of retrospective analyses noting the feasibility of this approach [10-12]. We recently reported our experience in 68 patients who underwent HCT for MDS who received either induction chemotherapy or azacitidine prior to HCT [13]. The 1-year overall survival after transplant was 57% in the azacitidine group, and 36% in the group given induction chemotherapy. Although the risk of post-HCT relapse and non-relapse mortality was lower in the azacitidine group, none of the differences including overall survival were statistically significant suggesting that at a minimum azacitidine did not confer worse outcomes when compared to induction chemotherapy.

2.3 Study Agent

This study does not prescribe a specific study agent, but rather a treatment strategy with a particular class of agents as the backbone of each treatment strategy. Therefore, a description of the study agent, its make-up, chemical properties and any relevant physical properties is not applicable. If patients are subsequently enrolled on an additional study for treatment after randomization on the present study, please refer to the protocols of the other studies for information regarding the specific agents of those studies. If patients are not enrolled on other studies, the agents administered as part of the treatment plan will be at the discretion of the attending physician.

2.4 Risks/Benefits

There is a potential risk of increased toxicity and death with intensive chemotherapy over that of hypomethylating agent-based therapy. However, this risk will be mitigated by selecting patients who are deemed to have an adequate level of fitness to receive intensive chemotherapy. In the prospective AZA 001 study [14], patients selected for and who received intensive chemotherapy had comparable rates of early treatment-related mortality and grade 3/4 toxicity compared to those who received azacitidine. Based on the available data, it is reasonable to conclude that cytoreduction prior to transplant can improve the rates of post-HCT relapse, thereby improving the overall outcome for patients with MDS. The knowledge gained from the present study will help identify the optimal pre-HCT cytoreductive strategy.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective is to determine the effect of IC (intensive AML-like therapy), versus less intensive hypomethylating agents (HMA) as initial therapy, on failure-free survival. We will test the hypothesis that HMA will lead to failure-free survival that is at least as good as that with IC.

3.2 Secondary Objectives

Determine if IC (intensive AML-like therapy) in comparison to HMA as initial therapy, will affect transplantation frequency, and quality of life. Conduct exploratory analysis of post-HCT outcomes (overall survival, and relapse).

4.0 STUDY DESIGN

4.1 Description of Study

This study is a multi-center, open-label randomized study of intensive chemotherapy versus hypomethylating agent-based therapy as the initial pre-transplant cytoreductive therapy in patients with myelodysplastic syndrome.

Patients will be randomized to receive treatment with either hypomethylating agent therapy or intensive chemotherapy; they will not receive both.

4.2 Endpoints

4.2.1 Primary Endpoint

18-month failure-free survival (failure defined as death or relapse)

4.2.2 Secondary Endpoints

1. Frequency at which the patients undergo transplantation
2. Impact on quality of life
3. Post-transplant outcomes:
    a. Overall Survival
    b. Relapse

5.0 SUBJECT SELECTION

5.1 Inclusion Criteria

5.1.1 Disease Criteria

1. Diagnosis of *de novo* or secondary MDS, including chronic myelomonocytic leukemia, as defined by the 2008 World Health Organization Classification System.
2. Patients must have measurable disease requiring cytoreduction, defined as a bone marrow myeloblast count ≥ 5% and < 20% on morphologic examination or by flow cytometry in cases in which adequate morphologic examination is not possible.

5.1.2 Age Criteria

1. Age ≥ 18 years

5.1.3 Organ Function, Performance Status and Other General Criteria

1. Patients must be considered to have an acceptable risk of early mortality with intensive chemotherapy as determined by the attending physician at the time of the initial visit. Since

the specific therapy within each arm will be determined after randomization, there is no threshold of organ dysfunction or performance status for inclusion.
2. Considered a potential transplant candidate. The attending/treating physician will determine transplant candidacy at the time of consent.
3. Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent.

5.2 Exclusion Criteria

1. A diagnosis of acute promyelocytic leukemia as defined by the 2008 World Health Organization Classification System.
2. Previous treatment for MDS or AML with intensive chemotherapy regimen (induction chemotherapy) or hypomethylating agent.
3. Have any other severe concurrent disease or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or other organ system that may place the patient at undue risk to undergo treatment.
4. Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
5. Females who are pregnant or breastfeeding.
6. Fertile men and women unwilling to use contraceptive techniques during and for 12 months following treatment.
7. Any uncontrolled or significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow up, or interpretation of study results.
8. Clinical evidence suggestive of central nervous system (CNS) involvement with MDS unless a lumbar puncture confirms the absence of leukemic blasts in the cerebrospinal fluid (CSF).

6.0 SUBJECT REGISTRATION

Complete and submit the FHCRC Research Subject Registration Form (see Appendix A) with the signed informed consent to the FHCRC Research Coordinator, Fax (206) 667-2284.

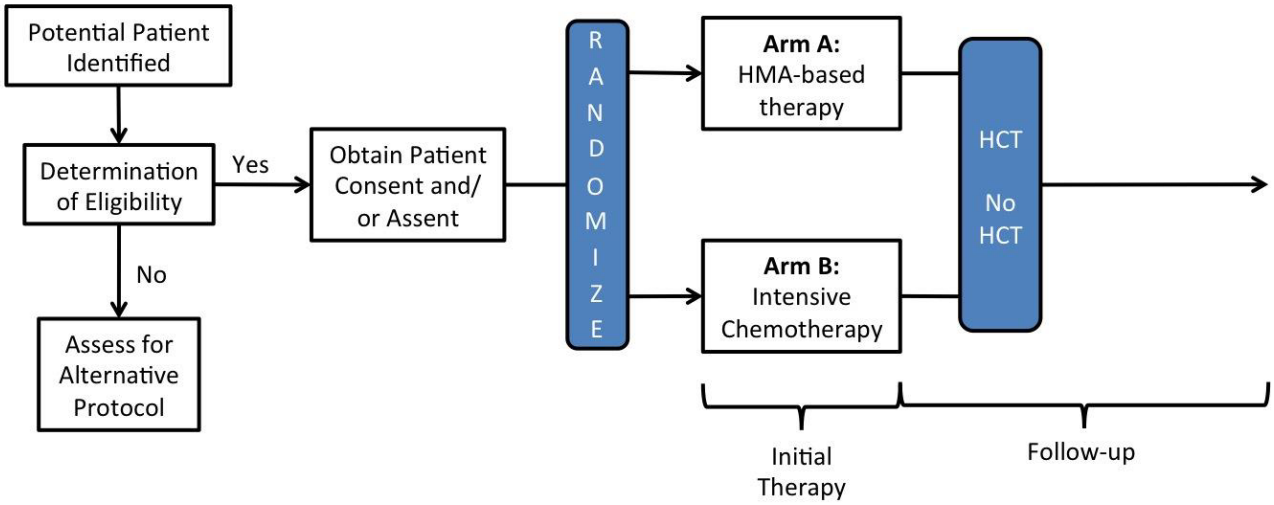
After the eligible subjects have been registered, subjects will be randomized by the FHCRC Data Management Office (DMO), Monday through Friday between 8:30 and 4pm PST/PDT. FHCRC Research Coordinator will fax the randomization assignment back to the Study Coordinator at the outside site.

7.0TREATMENT PLAN

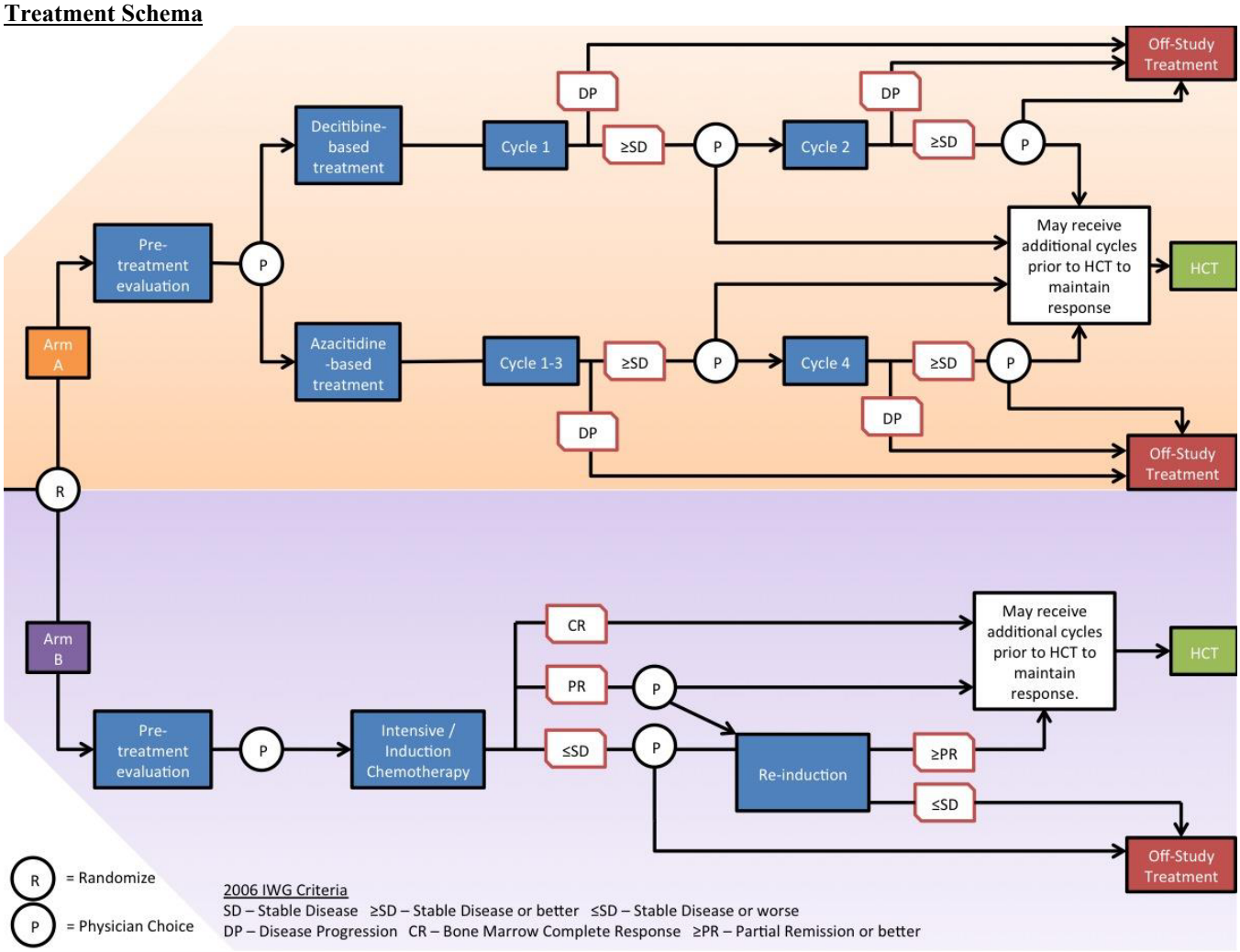
Treatment Schema

This schema is a pictorial overview only; please see narrative sections of the protocol for specifics and allowable deviations from time frames shown.

Pre-treatment Determination of Eligibility and Randomization



Treatment Schema



5.37.1 Agent Administration

For patients enrolled on subsequent treatment protocols, the treatment regimen, including treatment agents, doses and method, timing and setting of administration (inpatient or outpatient) will be determined by the specific treatment protocol.

For patients who are not enrolled on other treatment protocols, the treatment regimen, including treatment agents, doses and method, timing and setting of administration (inpatient or outpatient) will be determined by the attending physician.

Although not mandatory, a suggested treatment for patients in Arm A is azacitidine intravenous or subcutaneous at 75 mg/m^2/day for 7 days repeated every 28 (+/- 3) days [14]. For patients in Arm B, the suggested treatment is the "7+3" regimen, which combine a seven-day continuous intravenous infusion of cytarabine (100 or 200 mg/m^2 per day) with a short infusion or bolus of an anthracycline (idarubacin 10-12 mg/m^2 or daunorubicin 40-90 mg/m^2) given on days one through three [15,16]. (See Appendix B)

7.2 Concomitant Medication and Supportive Care Guidelines

Supportive care measures (e.g. antibiotic prophylaxis and treatment, transfusion support) should be carried out according to institutional practice guidelines or the preference of the attending physician.

7.3 Screening

Bone marrow biopsy or aspirate for morphology must be collected within 60 days prior to Day 1 of treatment.

Within 30 days before Day 1 of treatment, perform these assessments

- Complete medical history and physical examination,
- CBC with differential
- Serum Chemistry
- Pregnancy test for women of childbearing potential
- EORTC-QLQ-C30 questionnaire

7.4 Duration of Therapy (Treatment Phase)

Duration of study therapy will depend on response and donor availability. Please see Appendix C for definitions of response criteria. For patients enrolled on concurrent treatment protocols, assessment of response as dictated by the treatment protocol will take precedence over the following treatment response evaluation and treatment duration guidelines.

The specific treatment agents and schedule will vary per patient within both study arms (please see section 7.1 for details). These agents and schedules will be determined by treatment protocols, institutional standards, or physician preference. Follow-up prior to each cycle of therapy will also be determined by treatment protocols, institutional standards, or physician preference.
Patients randomized to either arm must receive at least one cycle of therapy. If at any point after the administration of the first cycle of therapy a donor is available, the patient may proceed to HCT. Patients may receive additional cycles of treatment to maintain response while waiting for donor availability. However, continued therapy should not be used to delay available HCT. If patients demonstrate disease progression at any point after the first cycle, they should discontinue the study treatment.

For patients who are receiving decitibine-based therapy under Arm A, it is recommended that a bone marrow biopsy or aspirate be obtained after 2 to 4 cycles to assess response. For patients who are receiving azacitidine-based therapy under Arm A, it is recommended that a bone marrow biopsy or

aspirate be obtained after 4 to 6 cycles to assess response. If at that point stable disease or better is achieved and a donor is available, the patient may proceed to HCT. If the desired degree of response or cytoreduction has not been met by 4 cycles of decitibine-based therapy, or 6 cycles of azacitidene-based therapy patients should be offered alternative treatments.

For patients randomized to Arm B, response to therapy will be determined by bone marrow biopsy or aspirate 28 (+/- 3) days after the start of therapy or at the time of count recovery. If a desired response is achieved, the patient may proceed to HCT. If a less-than desired response is achieved with the first cycle of intensive chemotherapy, it is recommended that the patient receive an additional cycle of intensive therapy (re-induction). If after re-induction a partial remission or better is achieved, the patient may proceed to HCT. However, if the patient has stable disease or disease progression, the patient should be offered alternative treatment or proceed directly to transplant if possible. .

If at any point a patient no longer desires to undergo HCT, or is no longer considered an HCT candidate, the patient will be withdrawn from the study. However, the patient may go on to receive the assigned treatment off study protocol.

The number and timing of clinic visits or scheduled inpatient admissions will be determined by either the primary treatment protocol or at the discretion of the attending physician.

Treatment phase evaluations are outlined in the study calendar (Appendix D). After initial treatment and before transplant, complete the EORTC-QLQ-C30 and EORTC-QLQ-HDC29 questionnaires.

7.5 Duration of Follow-Up

Study follow-up and evaluations are outlined in the study calendar (Appendix D). The total length of follow-up will be 18 months from the start of treatment (day 1).

Assessments required within 30 days prior to HCT will be completed as per institutional protocols and should include a physical exam, medical history, pregnancy test (women of childbearing potential), CBC, serum chemistry, and bone marrow biopsy or aspirate for morphology.

At Day 100 post-HCT (+/- 14 days), EORTC-QLQ-C30 and EORTC-QLQ-HDC29 quality-of-life measures will be collected.

7.6 Dosing Delays/Dose Modifications

For patients who are enrolled on subsequent treatment protocols, the strategy for managing situations that require dosing delays or modifications, e.g. if the subject's marrow has not recovered to acceptable levels for the next cycle of therapy will be determined by the subsequent treatment protocol.

For patients who are not enrolled on other treatment protocols, the management of situations that require dosing delays or modifications should be carried out according to institutional practice guidelines or the preference of the attending physician.

7.7 Criteria for Removal/Withdrawal

A patient must be discontinued from protocol-prescribed therapy under the following circumstances:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative;
- Any event that, in the judgment of the Investigator, poses an unacceptable safety risk to the patient;
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being;

- Significant deviation from inclusion/exclusion criteria, in the opinion of the investigator;
- A positive pregnancy test at any time during the study;
- An intercurrent illness that, in the judgment of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy, or
- Completion of the study

Once the attending physician has met and discussed the decision with the patient and/or family member, the Notice of Withdrawal from a Research Study form (see Appendix E) should be filled out. Complete this form only when the patient has withdrawn consent.

- It is the responsibility of the PI or his/her designee to complete the Notice of Withdrawal From a Research Study Form and fax it to the FHCRC Research Coordinator at (206) 667-2284.

Study treatment is defined as “any activity involving a patient or donor described in a protocol that is not part of their routine medical care”. Patients who withdraw from study treatment will be asked permission to continue to collect and record survival data up to the protocol-described end of the subject follow-up period.

Patients who are withdrawn from the protocol will not be replaced as this is intent to treat analysis.

8.0 Adverse Event Reporting

Adverse events will not be reported as all AEs and SAEs that occur are considered to be related to treatment and would be considered “expected” side effects from standard of care treatment for either study arm. If patients are enrolled on an additional treatment protocol where they will receive an investigational drug, please refer to that protocol for a list of expected adverse events and event-capture procedures.

Patients who are not enrolled on this protocol who are not enrolled on an additional protocol, will receive standard therapies with FDA-approved medications. Please refer to the package insert of those medications for a listing of specific expected adverse events.

Death will be reported at the annual continuing review if it occurs within the participant’s 18-month study participation period.

After the completion of treatment, patients will be tracked for progression and survival during the patient’s 18-month study participation.

Outside sites will be required to report all deaths to the coordinating center that occur during subjects’ 18-month participation period. Outside sites will communicate deaths to the coordinating center by email or fax. The coordinating center will maintain a death log for all protocol participants.

9.0 DATA AND SAFETY MONITORING PLAN

The principal investigator (PI) of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the FHCRC Scientific Review Committee and Institutional Review Board. The PI will ensure that the monitoring plan is followed and that all data required for oversight of monitoring are accurately reported to the FHCRC/UW Cancer Consortium Data and Safety Monitoring Committee (DSMC).,. Once per month, the PI will personally review with the Research Nurse the clinical status of all the enrolled patients.

Under the provisions of the DSMP, the Cancer Consortium Clinical Research Support (CRS) team provides monitoring for quality process and compliance by qualified monitors unaffiliated with the

conduct of the study. Monitoring visits occur at specified intervals determined by the FHCRC DSMC assessed risk level of the study and the findings of the previous visit.

An annual review of the progress of the study with respect to the monitoring plan will be performed by the DSMC. The DSMC reviews accrual, serious adverse events, stopping rules and adherence to the protocol-specific data and safety-monitoring plan.

10.0 STUDY AGENT INFORMATION

Patients enrolled in this study may receive different treatments under each of the study arms. If enrolled on a treatment protocol, please refer to that protocol for information regarding information regarding obtaining, handling and accounting for the study agent and whether the study agent is provided by the study.

If the patient is not enrolled on a treatment protocol, the agent will be obtained and handled through the pharmacy where the patient is receiving care. The study agent will not be provided by the study.

11.0 ASSESSMENT OF EFFICACY

11.1 Efficacy Parameters

The primary outcome is 18-month failure-free survival (failure defined as death or relapse).

Relapse will be as defined by the International Working Group (IWG) response criteria in myelodysplasia (Cheson, et. al., Blood 2006;108:419.). Please see Appendix B for a table defining the response criteria for this study. Response criteria are determined by a morphologic count of the myeloblast population on aspirate smear. If an aspirate cannot be obtained, myeloblast percentage should be determined by morphologic and/or immunohistochemical staining of the bone marrow biopsy or alternatively determined by flow cytometry of a decalcified bone marrow biopsy sample.

11.2 Method and Timing of disease burden assessment

The results of a bone marrow biopsy/ aspirate obtained for clinical purposes within 60 days of the start of treatment will be used to establish a baseline prior to the start of treatment. For patients enrolled on concurrent treatment protocols, timing of response assessment will be as outlined by the protocol and will take precedence over the following treatment response assessment guidelines.

If at any point a patient is suspected to have disease progression, a bone marrow biopsy or aspirate may be obtained for clinical purposes to document this progression. For patients who are receiving decitibine-based therapy under Arm A, it is recommended that a bone marrow biopsy or aspirate be obtained after 2 to 4 cycles to evaluate response. For patients who are receiving azacitidine-based therapy under Arm A, it is recommended that a bone marrow biopsy or aspirate be obtained after 4 to 6 cycles to evaluate response.

For patients randomized to Arm B, response to therapy will be determined by bone marrow biopsy or aspirate 28 (+/- 3) days after the start of therapy or at the time of count recovery.

A bone marrow biopsy/ aspirate will be obtained prior to HCT as per institutional protocol (standard practice).

11.3 Quality of Life Assessment

Quality of life will be assessed using the EORTC QLQ-C30 questionnaire and the QLQ-HDC29 module (Appendix G) at the following timepoints:

- EORTC QLQ-C30 questionnaire at the time of screening
- EORTC QLQ-C30 & QLQ-HDC29 at the completion of initial therapy prior to transplant
- EORTC QLQ-C30 & QLQ-HDC29 at 100 (± 14) days after stem cell infusion (Day +100)

The QLQ-C30 is a validated and widely used questionnaire to assess quality of life in cancer patients. The QLQ-HDC29 is treatment-specific quality of life questionnaire to QLQ-C30), that addresses treatment-specific side effects as well as emotional, social, and family issues for patients treated with high-dose regimens and HCT. The QLQ-HDC29 module is targeted to cover time during the treatment and up to 6 months post-treatment.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / quality-of-life scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
When the Quality of Life questionnaires are scored, the principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.
2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The QLQ-HDC29 module includes 29 items, consisting of 6 multi-item scales and 8 single-items. The scoring algorithms are similar to the scoring for the EORTC QLQ-C30. For the multi-item scales and single-item scales (except item 52) a high score is equivalent to worse or more symptoms/problems. For Spiritual item 52, a higher score indicates positive experience or less problems.

12.0 DATA MANAGEMENT/CONFIDENTIALITY

Study data will be stored in a locked cabinet in a building with restricted key-card access. A password protected data recording tool (e.g., excel spreadsheet) will be used to record disease progression, relapse and death for all patients (See Appendix I). Each subject is assigned a unique patient number to assure 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.

At FHCRC, local subject clinical records and transplant-related documents are scanned and stored in a secure, electronic document management platform (OWL). OWL records are maintained by the FHCRC data abstraction staff. Access is restricted to personnel authorized by the Division of Clinical Research.

13.0 STATISTICAL CONSIDERATIONS

Eligible patients will be randomized in a 1:1 fashion. The primary outcome will be analyzed on an intention-to-treat basis. It is not possible to enroll enough patients to this trial to show a statistically significant difference in overall survival between groups unless the assumed-true difference is unrealistically large. Instead, we have set a benchmark for "success" to be that the observed 18-month failure-free survival with hypomethylating agent-based treatment be at least as high as that in the intensive chemotherapy group. With 30 patients per arm, if the assumed-true survival probabilities are 50% and 30%, respectively, then the probability of observing an 18-month failure-free survival in the HMA group that is at least as high as that in the IC group is approximately 0.96. If the assumed-true probabilities are 45% and 30%, the probability of observing a success is approximately 0.91. On the other hand, if the 18-month failure-free survival in the HMA group and IC group is 50% and 60%, respectively, then the probability of observing a rate in the HMA group that is at least as high as that in the IC group is approximately 0.26.

The quality-of-life questionnaires will be scored. In addition to reporting the absolute scores, a distribution-based interpretation will be conducted using the standardized response mean to analyze changes in scores over time and differences between groups.

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	24	34	58
Ethnic Category Total of All Subjects*	25	35	60
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	24	33	57
Racial Categories: Total of All Subjects*	25	35	60

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."

14.0 TERMINATION OF THE STUDY

The principal investigator may terminate the study at any time. The IRB and FDA also have the authority to terminate the study should it be deemed necessary.

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APPENDIX A

FRED HUTCHINSON CANCER RESEARCH CENTER

Clinical Research Division
Research Subject Registration Form

Protocol Number: 2661

Research Subject Name:_____

Date of Birth: ___ ___/___ ___/ ___ ___ ___ ___
Month Day Year

Ethnicity: *(Choose one)*

☐ **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**

☐ **Refused to Report**

Race: *(check all that apply)*

☐ **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)

☐ **Unknown**

☐ **Refused to Report**

Gender:

☐ Male

☐ Female

☐ Unknown

HIPAA Authorization: (check one)

☐ Protocol covered under general HIPAA authorization

☐ Protocol specific HIPAA authorization required for this protocol.

(Attach and submit with this form)

Name of person completing form (Please Print)

_____

Name Phone Number

_____

Date Submitted Time

ATTACH SIGNED CONSENT AND SEND TO DATA MANAGEMENT WITHIN 10 HOURS OF CONSENTING.

FRED HUTCHINSON CANCER RESEARCH CENTER

Clinical Research Division

Research Subject Registration Fax Coversheet

Date: _____

TO: **MDS Protocol 2661 Research Coordinator**

FAX: **(206) 667-2284**

RE: **RESEARCH SUBJECT REGISTRATION FORM**

FROM: _____

FAX: _____

PHONE: _____

APPENDIX B

Potential Regimens for Each of the Treatment Arms

This list is intended to serve as a guide while determining if a potential regimen is appropriate for either Arm A or Arm B of this study. This list is not exhaustive as protocols over time may change, and is again to serve as a guide. The principal investigator makes the final determination if a regimen is appropriate for either arm prior to treatment.

Potential regimens for **Arm A** (HMA-based therapy):

- Azacitidine 75 mg/m^2/day IV/SQ Days 1-7 (J Clin Oncol. 2002 May 15;20(10):2429-40.)
- Azacitidine 75 mg/m^2/day IV/SQ Days 1-5 (J Clin Oncol. 2009 Apr 10;27(11):1850-6.)
- Decitabine 15 mg/m^2 q8H IV Days 1-3 (Cancer. 2006 Apr 15;106(8):1794-803.)
- Decitabine 20 mg/m^2/day Days 1-5 (Blood. 2007 Jan 1;109(1):52-7.)
- Tosedostat 120 mg/day Days 1-21, Decitabine 20 mg/m^2/day Days 1-5 (FHCRC 2566)

Potential regimens for **Arm B** (intensive chemotherapy):

- Cytarabine 100-300 mg/m^2/day CIVI Days 1-7, Daunorubicin 40-90 mg/m^2/day IV Days 1-3 (Blood. 1987 May;69(5):1441-9., N Engl J Med. 2009 Sep 24;361(13):1249-59.)
- Cytarabine 100-300 mg/m^2/day CIVI Days 1-7, Idarubicin 10-12 mg/m^2/day IV Days 1-3 (J Clin Oncol. 2013 Jan 20;31(3):321-7.)
- Fludarabine 30mg/m^2/day IV Days 1-5, Cytarabine 2000 mg/m^2/day IV Days 1-5, GCSF 400 mcg/m2/day IV Day 0 until ANC recovers (J Clin Oncol. 1994 Apr;12(4):671-8.)
- Cytarabine 200 m g/m^2/day CIVI Days 1-7, Daunorubicin 60 mg/m^2/day Days 1-3, Cladribine 5 mg/m^2/day Days 1-5 (J Clin Oncol. 2012 Jul 10;30(20):2441-8.)
- Cytarabine 3 g/m^2 q12h Day 1-4, Daunorubicin 60 mg/m^2/day IV Days 1-3 (Blood. 1996 Oct 15;88(8):2841-51.).
- PF-04449913 100-200 mg PO Days 1-18, Cytarabine 100 mg/m^2/day CIVI Days 1-7, Daunorubicin 60 mg/m^2/day IV Days 1-3 (Arm C of FHCRC 2592)

APPENDIX C

Response Criteria

Category	Response criteria (responses must last at least 4 wk)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines
Partial remission (PR)	All CR criteria if abnormal before treatment except: - Bone marrow blasts decreased by ≤ 50% over pretreatment but still > 5% - Cellularity and morphology not relevant
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression
Disease Progression (DP)	For patients with: - Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts - 5%-10% blasts: ≥ 50% increase to > 10% blasts - 10%-20% blasts: ≥ 50% increase to > 20% blasts - 20%-30% blasts: ≥ 50% increase to > 30% blasts
Relapse after CR or PR	At least 1 of the following: - Return to pretreatment bone marrow blast percentage - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets - Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence

From: Cheson, BD, et al. Blood. 2006;108:419-425.

APPENDIX D

Study Calendar

Procedure	Screening Phase	Treatment Phase**			Follow-up phase		
	Screening within 30 days	**Cycle 1** Day 1	**Cycle 2-n***** Day 1	**After Initial Treatment$^{\Delta}$**	**Prior to HCT** within 30 days	**100 Days Post HCT (+/- 14 days)**	**18 months Post C1 D1**
Physical Exam	X				X		
Medical History	X				X		
Pregnancy Test*	X				X		
CBC	X				X		
Serum Chemistries	X				X		
Bone Marrow Aspiration/ Biopsy	X±			X ∞	X		
EORTC-QLQ-30	X			X		X	
EORTC-QLQ-HDC29				X		X	
Treatment		X**	X**				
Survival							X
Relapse							X

*women of childbearing potential
**per physician determination following randomization
*** per treatment protocol and/or local institutional policy
Δ after initial treatment and before transplant
± must be collected within 60 days prior to Day 1 of treatment
∞ recommended after 6 cycles of the HMA, if the patient has not had a bone marrow procedure since screening

APPENDIX E

Notification of Withdrawal From a Research Study

This form must be completed and routed when a study participant notifies you of his/her withdrawal from a Fred Hutchinson Cancer Research Center (FHCRC) Clinical Research Division Protocol.

Research Subject Name	Hospital No. (U-number)	UPN/Study No.
2661	Bart Scott, MD	
Protocol Number or Title	Principal Investigator	Current Attending

Person(s)	Responsibility
Initial person who receives the participant's notification of withdrawal (e.g., Team Nurse, Study Nurse or Study Coordinator)	❑ Complete Notification of Withdrawal From a Research Study form. ❑ If appropriate, notify other members of participant's care team. ❑ Fax the completed form to FHCRC (667-2284).
Attending Physician	❑ Acknowledge the notice from the participant or responsible adult on behalf of a pediatric participant to withdraw from a research study if appropriate. ❑ Meet with participant/family member and discuss reasons for withdrawal and the risks and benefits of withdrawing from the study if appropriate. ❑ If a meeting occurs with the participant/family, document discussion with participant/family in the participant's medical record.
Primary Provider	❑ Review medical orders and discontinue any upcoming research study-related orders.

I ensure that the above providers and staff have been notified of their responsibilities.

Signature	Printed Name	Date

*****For FHCRC Data Management Use*****

Sent to PI on _____(date) Sent to Study Coordinator on _____(date)

Sent to SCCA HIM (SCCA patients only) on _____(date)

APPENDIX F

Adverse Event Reporting Form was deleted in Protocol Amendment dated 17 February 2015

APPENDIX G

EORTC QLQ-C30 and HDC29

ENGLISH

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

ENGLISH

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

ENGLISH

EORTC QLQ – HDC29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had soreness in your mouth?	1	2	3	4
32. Have you had a dry mouth?	1	2	3	4
33. Have you had trouble swallowing?	1	2	3	4
34. Did food and drink taste different from usual?	1	2	3	4
35. Have you had abdominal pains or cramps?	1	2	3	4
36. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
37. Have you been upset by how the treatment has affected your hair?	1	2	3	4
38. Have you worried about your weight being too low?	1	2	3	4
39. Have you had fevers or chills?	1	2	3	4
40. Did you urinate frequently?	1	2	3	4
41. Have you had aches or pain in your bones?	1	2	3	4
42. Have you found it difficult to finish things you started?	1	2	3	4
43. Did you worry about the results of examinations and tests?	1	2	3	4

Please, complete the following questions if you are currently still in hospital for your treatment. If not, please go to question 48 on next page.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
44. Have you had trouble coping with the hospital stay?	1	2	3	4
45. Has the isolation in hospital troubled you?	1	2	3	4
46. Have you worried that the blood (i.e. blood counts) may not recover?	1	2	3	4
47. How satisfied were you with the preparation for your treatment?	1	2	3	4

Please go on to the next page

During the past <u>four weeks:</u>	**Not at all**	**A little**	**Quite a bit**	**Very much**
48. Have you felt isolated from those close to you (family, friends)?	1	2	3	4
49. Have you been concerned about disruption to your family life because of your treatment?	1	2	3	4
50. How distressing, do you think, your illness or treatment has been to those close to you?	1	2	3	4
51. Have you felt a need to keep your fears/ concerns from family or friends?	1	2	3	4
52. Has your experience helped you to distinguish between important and non-important things in life?	1	2	3	4
53. Were you worried about your health in the future?	1	2	3	4
54. Have you felt physically less attractive as a result of your illness or treatment?	1	2	3	4

Please mark the box, if the next question does not apply to you ☐

55. Have you been concerned about your ability to have children?	1	2	3	4

Please, complete the following questions only if you have completed your hospital treatment and are currently at home.

During the past <u>four weeks</u>:	**Not at all**	**A little**	**Quite a bit**	**Very much**
56. Did having to take your drugs regularly interfere with your daily life?	1	2	3	4
57. Have you been watching yourself closely for any new symptoms?	1	2	3	4
58. Have you felt less interest in sex?	1	2	3	4
59. Have you felt less sexual enjoyment?	1	2	3	4

APPENDIX H

Data Collection (an excel spreadsheet will be used)

UPN or Study ID	Date consent signed	Date Screened & diagnosis	ARM A or B	Date started & regimen	SCRN QLQ-30 Done Y/N	Post treatment/ pre transplant QLQ-30 & C29	Date of transplant	Post-transplant QLQ-30 & C29 ~ Day 100 (+/- 14 days)	Off Study Date	F/U status

APPENDIX I deleted with 28 May 2019 revision