FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Previous version: 07/05/2018
Current version: 08/19/2019

Title of Protocol:
A Phase II Study of Deferasirox in Patients with Myelodysplastic Syndromes who are Anemic with Iron Overload

Investigators List:		
Investigator	**Professional Title**	**Phone Number**
Bart L. Scott, MD	Associate Member, FHCRC, Associate Professor of Medicine, UW	(206) 667-1990
Karen Schiavo, ARNP	Nurse Practitioner, Seattle Cancer Care Alliance	(206) 288-7242
H. Joachim Deeg, MD	Member, FHCRC, Professor of Medicine, UW	(206) 667-5985
Pamela S. Becker, MD, PhD	Member, FHCRC, Professor of Medicine, UW	(206) 288-6890
Michael L. Linenberger, MD	Member, FHCRC, Professor of Medicine, UW	(206) 667-5021
Sioban B. Keel, MD	Assistant Professor, UW	(206) 685-2196
Jason P. Cooper, MD. PhD	Senior Fellow, UW/FHCRC Hematology-Oncology	(206) 667-2337
Janis L. Abkowitz, MD	Clement A. Finch Professor of Medicine, UW Head, Division of Hematology, UW	(206) 685-7877
Biostatistician:		
Ted A. Gooley, PhD	Member, FHCRC	(206) 667-6533
Research Staff:		
Sheri Fong	Study Coordinator, FHCRC	(206) 667-4963

Emergency number (24 hours):

- **Seattle Cancer Care Alliance: 206-598-6190**
- **Seattle Urgent Care (206) 326-3000 or (206) 326-3341 for paging operator after hours**

TABLE OF CONTENTS **Page**

1.0 INTRODUCTION

Patients with Myelodysplastic Syndromes (MDS) who are red blood cell (RBC) transfusion dependent are known to have a shorter survival in comparison to other MDS patients who do not require RBC transfusions.(1) In addition, there are substantial economic burdens to continued RBC transfusion support(2). While erythroid stimulating agents (ESA, eg, exogenous erythropoietin) are effective in some patients with MDS, many patientsdo not respond and among responders the duration of response on average is one year (3;4). Lenalidomide is effective in reducing RBC transfusion requirements with a 67% transfusion independence rate in patients with deletion of the long arm of chromosome 5 [del(5q)] MDS(5); however in non-del 5 q MDS the response rate is only 27%(6). It is clear that new therapies are needed in this population. Iron chelation therapy (ICT) has been shown to improve hematologic parameters in patients with MDS and in some series there is a demonstrated survival benefit to ICT. Therefore, we propose a phase II prospective trial using ICT with oral deferasirox in patients with MDS with anemia.

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 known preceding insult (*de novo* MDS)(7), 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 8.8 years for patients with very low-risk IPSS-R (Revised International Prognostic Scoring System) scores, to 0.8 years for those with very high-risk scores(8).

The cornerstone of therapy, particularly for lower-risk disease, is centered on improving hematologic parameters thereby reducing the morbidity and mortality associated with low blood counts. At the time of diagnosis over 80% of patients with MDS are anemic, and 50% have a hemoglobin level < 10 g/dL(9). RBC transfusion support is currently the primary management option for MDS-related anemia(2). Transfusions are almost universally effective, ameliorate the patient's symptoms rapidly, and improve health-related quality of life. However, long-term RBC transfusion support can lead to iron overload, which has been associated with an inferior outcome in patients with MDS(1). Strategies to reduce transfusion requirements and subsequent iron overload are imperative to reduce potential harm and to reduce economic and societal costs associated with increased RBC transfusion burdens in MDS patients(2).

2.2 Clinical Data to Date

Other strategies are used to treat MDS-related anemia. Erythropoiesis stimulating agents (ESA; such as erythropoietin or darbepoetin) are the most commonly used agents to treat MDS(10). However, the benefit of ESA are largely restricted to patients with lower erythropoietin levels and minimal RBC transfusion requirements in the presence of low or intermediate risk disease(11). In approximately 5% of patients, del(5q) is the sole cytogenetic abnormality(12). Lenalidomide has been proven to be an effective agent in this population with 67% of the patients achieving transfusion independence in a phase III trial(5). In the absence of the del(5q) abnormality, the rate of transfusion independence is approximately 27% (6). There is data to indicate that combined therapy with lenalidomide and ESA result in improved erythroid responses(13). Combination therapy with lenalidomide and ESA are under current investigation in a multi-center trial phase III randomized trial. Hypomethylating agents (HMA: azacitidine and decitabine) target the aberrant DNA methylation seen in MDS and result in a response in approximately 50% of patients with low-risk MDS (14;15). Azacitidine is FDA-approved for all stages of MDS. Decitabine is not FDA-approved for patients with low risk disease by the original International Prognostic Scoring System (IPSS)(16). While these agents have been shown to alter the natural history of advanced MDS; there is less data to support their routine use in lower risk MDS patients (17;18). Since the route of administration is either IV or SQ and there is significant toxicity, the HMA are generally not the preferred therapeutic choice for patients with early stage MDS.

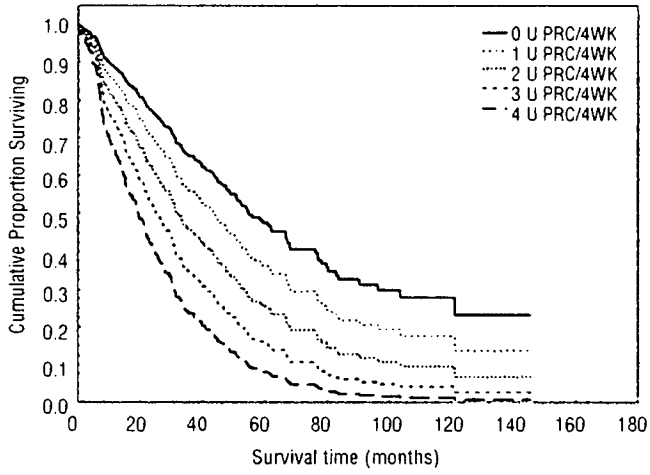

Figure 1: Survival among 426 patients with low risk MDS according to transfusion dependency.

In the absence of widely effective interventions, MDS-related anemia is often mitigated with RBC transfusions. Although it can relieve symptoms, overtime alloantibodies and iron overload can result as a consequence of multiple transfusions(2). Some patients with MDS, in particular RARS, develop iron overload in the absence of multiple transfusion. This may occur through several mechanisms including ineffective erythropoiesis resulting in increased gastrointestinal absorption(19). Concomitant hemochromatosis gene mutations (HFE) and polymorphisms in other regulators of iron metabolism may also influence the predisposition for iron overload in patients with MDS. Consequently, in certain patients with MDS (RARS), iron overload may not correlate well with the number of RBC transfusions and may occur early in the course of disease.

Several reports have noted a higher mortality rate in multiply RBC transfused, iron-overloaded MDS patients treated conventionally or after stem cell transplantation (1;20-25). In a retrospective analysis from 426 patients with low risk MDS the burden of RBC transfusions was significantly associated with overall survival (**Figure 1**). All patients were diagnosed with MDS based upon the WHO criteria between 1992 and 2004. This data set included patients with a diagnosis of RA, RCMD, RARS, or Del 5q (all with less than 5% blasts). Thus, indicating that even among patients who are traditionally thought to have low risk MDS, RBC transfusion dependence was strongly predictive of survival. This finding led to the development of a dynamic prognostic system known as the WHO-based prognostic scoring system (WPSS) which incorporated RBC transfusion dependence(26). Separately, several investigators found that ferritin serum levels were associated with overall survival in low risk MDS(21). In a retrospective analysis, ferritin levels were available in 95 patients with low risk MDS. When stratified by > or ≤ serum ferritin level of 1,000 ng/mL, MDS patients with higher ferritin levels were found to have an inferior survival (**Figure 2**).

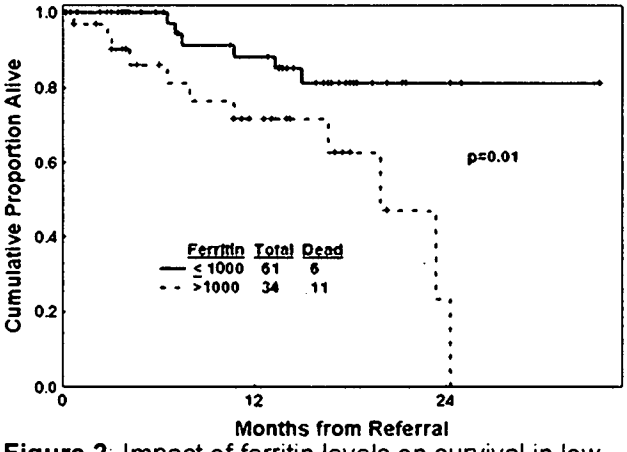

Figure 2: Impact of ferritin levels on survival in low risk MDS patients.

Based on preclinical and clinical data, mechanisms underlying the inferior survival in this population point to excess in labile plasma iron (LPI) as the putative mediator(19). This has prompted the use of ICT to modify the negative effect of iron overload in patients with MDS. Although several reports suggest a survival benefit with ICT (27-31), all of them were non-randomized comparisons and were susceptible to a significant selection bias. We know that patients are selected to receive ICT on the basis of an expected survival; otherwise, they would not life long enough to benefit. Therefore, the improved survival in patients treated with ICT could be completely due to a selection bias that is not necessarily overcome by a matched pair analysis(29). In addition, several trials have confirmed the ability of deferasirox to reduce iron content as measured by serum ferritin and in some patients to improve hematologic parameters (32-36). However, all of these studies are non-randomized and most are retrospective. Currently, there is a prospective randomized controlled trial evaluating the use of iron chelation therapy in red cell transfusion dependent MDS patients (TELESTO). In the absence of randomized prospective studies controversy still surrounds the implementation of ICT for patients with MDS.

In a multicenter, open-label, single-arm, 3-year phase II trial (US03), the safety and tolerability of deferasirox was evaluated in lower-risk MDS who had received at least 20 units of RBC and had a serum ferritin ≥ 1,000 µg/L(34). Of the 173 patients that underwent ICT with deferasirox, 51 (28%) experienced hematologic improvement, only seven of which received other MDS related therapy. Therefore, ICT appears to improve hematologic parameters in some MDS patients with iron overload. Mean labile plasma iron (LPI) was measured at baseline in 163 patients, among these patients 68 had elevated levels (>0.5 LPI units). Concentrations of LPI fell within normal limits in all 47 patients who were assessed at week 13 and remained in the normal range through the duration of the trial (**Figure 3**). Additionally, there was a decline in the median serum ferritin by 23.2% at one year in the patients who completed at least one year of ICT. Therefore, deferasirox was able to reduce the iron burden in iron-overloaded MDS patients. The annual discontinuation rates of deferasirox were 45%, 43%, and 35% during years 1, 2, and 3 respectively. The safety profile of deferasirox in this setting was reasonable with discontinuation in 43 patients (24.8%) because of adverse events (such as gastrointestinal disturbances) or disease progression and 23 patients (13.2%) because of abnormal laboratory values (such as increased serum creatinine). All 28 deaths that occurred during the study were considered unrelated to deferasirox.

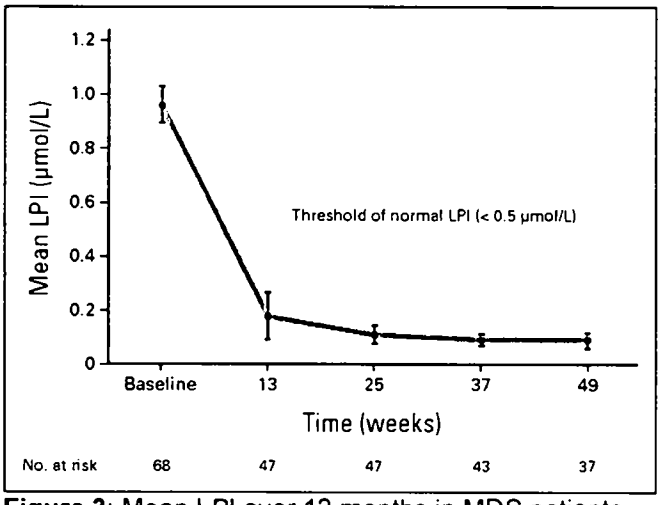

Figure 3: Mean LPI over 12 months in MDS patients with abnormal LPI at baseline.

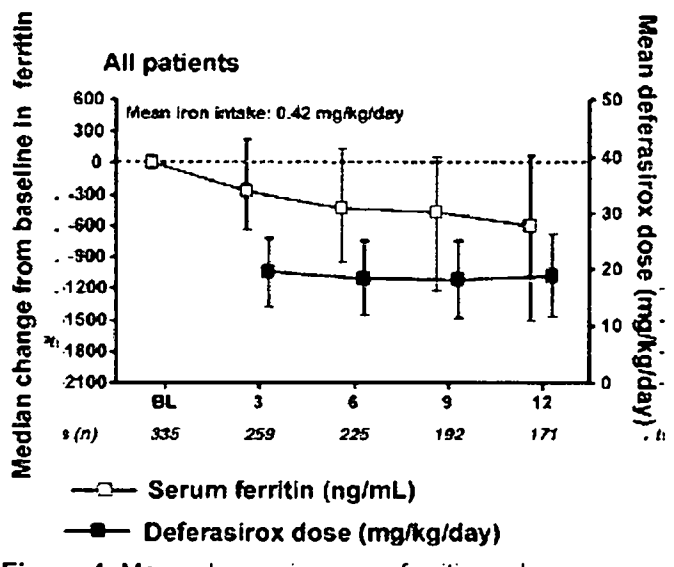

Figure 4: Mean change in serum ferritin and mean deferasirox dose among MDS patients in the EPIC Trial

The EPIC trial was a similar study conducted in Europe. There were 341 MDS patients enrolled in this phase II prospective trial. Patients were treated with 20 mg/kg/day of deferasirox if they received 2-4 U/month of RBC transfusions or 10-30 mg/kg/day if there were less or more RBC transfusion dependent, respectively. Overall, 175 patients completed one year of therapy with deferasirox. Of the 166 patients who discontinued therapy, 78 were for adverse events. The most frequently reported adverse events were gastrointestinal including diarrhea, nausea, vomiting, etc. There were 26 deaths in the study with most common cause being infection. None of the deaths were felt to be drug related. Serum ferritin levels significantly decreased from baseline after 1 year of deferasirox with a median reduction of 606 ng/mL (**Figure 4**). A post-hoc analysis demonstrated that erythroid, platelet and neutrophil responses were observed in 21.5%, 13%, and 22% of the patients after a median of 109, 169 and 226 days, respectively (**Figure 5**)(33).

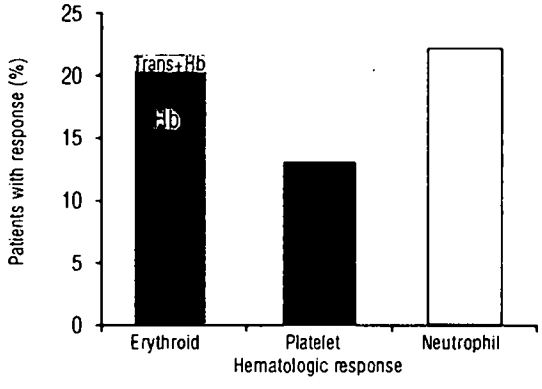

Figure 5: Percentage of MDS patients with hematologic improvement enrolled into the EPIC trial

The improvement seen in hematologic parameters after the initiation of ICT may be a result of improved function of the renal oxygen sensing system for erythropoietin production, reducing the inhibitory effect of oxidative stress on hematopoiesis, or

altering intracellular levels of the nuclear transcription factor NF-kB(19).

There is little clinical data regarding ICT in patients who have received minimal RBC transfusions or in patients with a serum ferritin < 1000 ng/mL. However, these patients may still derive benefit from ICT. As discussed earlier, patients with MDS may be more susceptible to iron overload or have iron overload in the absence of multiple RBC transfusions. Furthermore, ICT may modify disease risk beyond RBC transfusion-related events. ICT in the setting of multiple RBC transfusions for other hematologic conditions such as beta-thalassemia major exerts a survival effect largely though reduction in iron-related end organ damage. However, the expected survival in MDS at baseline, even in the setting of lower-risk disease, is on the order of a few years. Given this short timeframe in contrast to the time required to develop RBC transfusion-related end organ damage, the poorer outcome associated with iron overload in MDS may not be entirely accounted for by this mechanism. Iron overload in patients with MDS has been linked according to several studies to increased infection risk and accelerated transformation to AML in addition to end organ damage (28;37;38). By reducing LPI, ICT may decrease the rates of infection and leukemic transformation, and may result in selective toxicity towards MDS hematopoietic progenitors relative to normal progenitors(19). There is also the possibility that mild iron deficiency may mitigate the ineffective erythropoiesis of MDS since emerging data suggest that ineffective erythropoiesis is due, at least in part, to an excess of heme relative to globin as red cells mature and heme toxicities. Reducing iron and thus heme in maturing red cells might correct this imbalance. With a manageable side effect profile along with its disease-modifying potential it is reasonable to explore the efficacy of aggressive ICT with deferasirox in lower risk MDS patients who do not necessarily have excessive iron burden according to ferritin levels.

2.3 Study Agent

Patients will receive oral deferasirox which has been approved by the FDA for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age or older. Deferasirox will be administered to achieve a ferritin < 100 ng/mL and, since it is approved for chelation and used regularly for this purpose as a standard of care, the dosing and schedule will be at the discretion of the treating clinician based on overall iron loading (ferritin), renal function, hepatic function, blood counts, and clinical condition / performance status. Contraindications include the following: Serum creatinine greater than two-times the upper limit of normal (ULN) or glomerular filtration rate (GFR) of less than 40 mL/min, poor performance status, high risk MDS, advanced malignancies, platelet count of less than 50,000, pregnancy, and/or known hypersensitivity to deferasirox.

2.4 Risks/Benefits

The most frequently occurring adverse reactions are diarrhea, vomiting, nausea, abdominal pain, skin rashes and increases in serum creatinine. Among patients with MDS, the major observed toxicity was an increase in serum creatinine (37%). The most frequent adverse reactions that led to drug discontinuation were increase in serum creatinine, diarrhea, nausea, rash and vomiting. Death was reported in the first year in 8% of the patients. Auditory and ocular disturbances occurred in <1% of participants. Deferasirox is considered pregnancy Category C by the FDA as animal studies have demonstrated potential embryonal fetal toxicities with decreased offspring viability with renal anomalies. The potential benefits of deferasirox are reduction in total body iron with improvement in organ function (liver and heart). Additional benefits include the potential to improve hematopoiesis and bone marrow function in general.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective is to assess the activity of ICT with deferasirox in patients with anemia due to MDS.

3.2 Secondary Objectives

Secondary objectives include a reduction in RBC transfusion requirements, hematologic improvement, change in serum ferritin levels from baseline to the end of the study as measured on a monthly basis and safety and tolerability of deferasirox.

3.3 Exploratory Objectives

Samples will be taken to study erythropoiesis and the impact of iron overload on erythropoiesis on patient samples including blood and marrow.

4.0 STUDY DESIGN

4.1 Description of Study

This study is a single-center open-label prospective phase II trial evaluating deferasirox in patients with very low, low or intermediate risk MDS by the IPSS-R criteria(8).

4.2 Endpoints

4.2.1 Primary Endpoint

The primary endpoint is the proportion of patients that achieve erythroid hematologic improvement as defined by the modified IWG response criteria at 6 months(39).

4.2.2 Secondary Endpoints

1. Change in RBC transfusion requirements.
2. The proportion of patients who achieve granulocyte or platelet hematologic improvement as defined by the modified IWG response criteria(39).
3. Change in serum ferritin levels from baseline to the end of the study as measured on a monthly basis.
4. Safety and tolerability profile as measured by grade 3 and 4 non-hematologic adverse events

5.0 SUBJECT SELECTION

5.1 Inclusion Criteria

1. Capable of giving written informed consent prior to any study-specific procedures
2. Diagnosis of MDS as defined by the WHO diagnostic criteria (40) (**Appendix A**)
3. Have very low, low or intermediate risk disease by the IPSS-R (8) (**Appendix B**)
4. Baseline serum ferritin level ≥ 100 ng/mL
5. Have an ECOG performance status of 0-2 (41) (**Appendix C**)
6. Age ≥ 18
7.
8. Anemia defined as hemoglobin ≤ 10.0 g/dLHave adequate organ function, including:
    a. Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine transaminase (ALT), and aspartate transaminase (AST) ≤ 3.5 times ULN
    b. Renal: Serum creatinine ≤ 1.5 X ULN and estimated GFR > 40 mL/min
9. Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the study and for 3 months following the last dose of deferasirox*
10. Females with childbearing potential* must have had a negative urine or serum pregnancy test ≤ 7 days before the first dose of deferasirox and must also not be breastfeeding
11. Reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

*Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment.

Effective contraception methods include:

- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
- Total abstinence or (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males must use a condom during intercourse while taking drug and for 28 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Please note that deferasirox may reduce the efficacy of hormonal contraception thus it is recommended to use alternative methods of contraception as described above.

5.2 Exclusion Criteria

1. If the patient is currently receiving ESA (for example, erythropoietin) with plans to continue during study: Less than 2 months duration of ESA therapy prior to starting study drug and no dose escalation within 2 months of start of study drug.
2. If the patient is being treated with GCSF and/or a TPO-mimetic (for example, Eltrombopag or Romiplostim) with plans to continue during the study: Less than 2 months duration of GCSF or the TPO-mimetic treatment prior to starting study drug; or GCSF and/or TPO-mimetic has been added to ESA therapy within 2 months of start of study drug.
3. If patient is being treated with Lenalidomide with plans to continue during the study: Stable dose for less than 3 months prior to start of study drug.
4. If patient is being treated with HMA (for example, Azacitidine or Decitabine) with plans to continue during the study: Stable dose for less than 6 months prior to start of study drug.
5. Currently enrolled in, or discontinued within the last 14 days from a clinical trial involving an investigational product or non-approved use of a drug, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
6. Presence of ≥10% blast by morphologic examination of bone marrow aspirate or biopsy
7. Platelets ≤ 50,000
8. Microcytosis on screening CBC (MCV < 81 fL)
9. Active GI ulceration or hemorrhage
10. Have a serious preexisting medical conditions that, in the opinion of the investigator would preclude participation in the study (for example a GI disorder causing clinically significant symptoms such as nausea, vomiting, and diarrhea, or malabsorption syndrome).or that would result in a life expectancy of less than 1 year
11. Known hypersensitivity to deferasirox
12. History of non-transfusional hemosiderosis
13. Prior hematopoietic stem cell transplant for the diagnosis of MDS
14. A second primary malignancy that in the judgment of the principal investigator (PI) or designee may affect the interpretation of results
15. Have an active fungal, bacterial, and/or known viral infection including human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis
16. Currently using aluminum-containing antacid products
17. History of clinically significant auditory or ocular toxicity with ICT

6.0 SUBJECT REGISTRATION

Patients will be recruited to participate in this clinical trial during the regular clinical visits of co-investigators. Patients will be given a copy of the consent form for this trial and will have ample time to review the study. The study will be reviewed with the patient by an experienced co-investigator in detail. Patients will be provided with a signed copy of the consent form. Following the signature of a consent form the FHCRC Research Subject Registration Form (**Appendix D**) will be completed and sent to the FHCRC Research Coordinator along with a copy of the signed consent form and protocol specific HIPAA form. The original consent form will remain in the patient's chart. Once this form has been received and screening has been completed, the eligibility checklist (**Appendix E**) will be completed by study staff. The eligibility checklist must be signed by the PI or designee prior to the start of treatment with deferasirox. Ineligible patient will be considered a screen failure and will not be enrolled; however, they may be reconsidered for enrollment at a later date. Patients must be consented prior to any screening procedures and

must be re-consented with each subsequent attempt at screening. An eligibility checklist must be completed with each screening attempt.

7.0 TREATMENT PLAN

7.1 Agent Administration

Deferasirox is available orally and should be administered per the manufacturer's instructions.

7.2 Treatment Schema

Deferasirox will be administered orally per the manufacturer's instructions to achieve a ferritin < 100 ng/mL and, since it is approved for chelation and used regularly for this purpose as standard of care, the dosing and schedule will be at the discretion of the treating clinician based on overall iron loading (ferritin, serum iron), renal function, hepatic function, blood counts, and clinical condition / performance status.

7.3 Duration of Therapy

1. Screening phase (up to 4 weeks: Day -29 to Day -1)

Screening evaluations will be performed at one or more clinic visits to determine eligibility for the study.
Laboratory Assessments

- CBC with differential
- Creatinine and GFR estimation
- Hepatitis Panel

Screening evaluations include laboratory evaluations as well as a bone marrow aspirate or biopsy. CBC with differential and record of transfusional requirements in the preceding 3 months will be obtained during the baseline screening. Testing for hepatotrophic viruses will be performed during the screening phase to include: Hep A antibody, Hep B surface antibody, Hep B surface antigen, Hep B core antibody, Hep C antibody, and Hep C PCR. Baseline ophthalmologic and audiometric examinations will be performed during the screening phase. It is recommended that the screening bone marrow aspirate or biopsy be performed once a patient has been found to be otherwise eligible. The results from the screening bone marrow aspirate or biopsy will be used as the baseline for analyses. Baseline will be defined as the last assessment or procedure conducted prior to the initiation of deferasirox (Day 1). Baseline evaluations must be performed within 30 days of start of deferasirox except the baseline bone marrow biopsy which can have occurred within 30 days of the start of deferasirox and for pregnancy testing in women of childbearing potential which must be performed within 7 days of the start of deferasirox.

2. Treatment phase (up to 52 weeks: Day 1 to Week 26)

Patients will receive deferasirox at a starting dose at the discretion of the treating clinician based on baseline serum ferritin levels, renal function, hepatic function, blood counts, and clinical condition / performance status The target ferritin level is < 100 ng/mL. The primary endpoint of hematologic improvement in the erythroid lineage will be assessed at 6 months. Nonresponders will be offered the option of alternative treatments including clinical trials if available. The maximum duration of therapy on this protocol is one year.

3. Monitoring (From Start of therapy till day 30 following last dose)

Creatinine and GFR will be assessed every 2 weeks during the first month of therapy and monthly thereafter; more frequent monitoring may be required if clinically indicated. Serum transaminases, bilirubin, and alkaline phosphatase will be checked every 2 weeks during the first month of therapy and then monthly thereafter. The number of RBC transfusions and platelet transfusions will be recorded at each visit, and hematologic response data will be collected monthly. Lab studies may be performed by the local oncologist. Safety assessments will be performed at all study visits with ophthalmologic and audiometric examinations performed at baseline and as indicated (at least yearly). A bone marrow aspirate or biopsy will be obtained after 3 months of treatment and 6 months following initiation of deferasirox. Patients will be followed for an additional 30 days after discontinuation of deferasirox to assess for toxicity.

Table 2 Summary of Study Related Monitoring:

Test	Minimal Frequency*

Serum creatinine, GFR^	Pretreatment (within 30 days) baseline. Every 2 weeks during the first month and then monthly thereafter.
Urine protein/creatinine ratio (spot-check)	Pretreatment (within 30 days) baseline and at 6 months and 12 months
Serum Ferritin	Pretreatment (within 30 days) baseline and then monthly thereafter
Serum transaminases, bilirubin, alkaline phosphatase	Prior to therapy (within 30 days). Every 2 weeks during the first month and then monthly thereafter
CBC with differential	Pretreatment (within 7 days) baseline and monthly thereafter
Bone Marrow Aspirate or Biopsy	Pretreatment (within 30 days) baseline (screening) and at 3 months and 6 months post-initiation
Auditory and ophthalmic testing	Prior to therapy (within 3 months). Annually thereafter.
Hepatotrophic viruses: Hep B surface antibody, Hep B surface antigen, Hep C antibody, and HCV PCR	Pretreatment (within 30 days)
Pregnancy test urine or serum	Pretreatment (within 7 days of start of deferasirox) in women of child bearing potential

*Testing should be performed more frequently if clinically indicated
^Estimated GFR with the MDRD formula

Please see Study Calendar (**Appendix F**) which will be supplied to the patients to assist with follow up and scheduling of necessary testing.

7.4 Duration of Follow-Up

Patients will remain treated on study for a maximum of one year. The primary endpoint of hematologic improvement in the erythroid lineage based upon the modified IWG criteria (**Appendix G**) will be assessed at 6 months. At the end of 6 months patients who do not respond will be offered the option of alternative treatments including enrollment into clinical trials if possible. The goal is for patients to complete at least 6 months of therapy; however, patients may be removed/withdrawn from the study prior to 6 months as detailed in Section 7.7. Patients will be followed for 30 days following last dose of study related therapy. At the end of one year patients may continue to receive deferasirox but not as part of this trial and they will not be followed for outcomes or toxicities.

7.5 Concomitant Medication and Supportive Care Guidelines

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

7.5.1 Permitted Concomitant Therapy

1. All study participants will be allowed, as medically justified, access to RBC and platelet transfusions. Concurrent use of an ESA will be allowed if the patient has been on a stable dose for two months prior to screening and continuation of ESA is medically justified. Combination therapy with a TPO-mimetic (such as Eltrombopag or Romiplostim) and/or G-CSF is allowed as long as the patient has been on a stable dose for two months prior to screening. G-CSF will be allowed in the setting of an acute infection if medically justified. Lenalidomide concurrent use is allowed if they have been on a stable dose for at least 3 months of duration. HMA concurrent use is allowed if they have been on a stable dose for at least 6 months.

7.5.2 Permitted Concomitant Therapy Requiring Caution or Action

- Concomitant use of UGT inducers decreases deferasirox systemic exposure. Avoid the concomitant use of potent UGT inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) with deferasirox. If you must administer deferasirox with 1 of these agents, consider increasing the initial dose of deferasirox by 50%, and monitor serum ferritin levels and clinical responses for further dose modification Concomitant use of bile acid sequestrants decreases deferasirox systemic exposure. Avoid the concomitant use of bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol) with deferasirox. If you must administer deferasirox with 1 of these agents, consider increasing the initial dose of deferasirox by 50%, and monitor serum ferritin levels and clinical responses for further dose modification

- Deferasirox may induce CYP3A4 resulting in a decrease in CYP3A4 substrate concentration when these drugs are coadministered. Closely monitor patients for signs of reduced effectiveness when deferasirox is administered with drugs metabolized by CYP3A4 (e.g., alfentanil, aprepitant, budesonide, buspirone, conivaptan, cyclosporine, darifenacin, darunavir, dasatinib, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, felodipine, fentanyl, hormonal contraceptive agents, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, pimozide, quetiapine, quinidine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, tolvaptan, tipranavir, triazolam, ticagrelor, and vardenafil)
- Deferasirox inhibits CYP2C8 resulting in an increase in CYP2C8 substrate (e.g., repaglinide and paclitaxel) concentration when these drugs are coadministered. If deferasirox and repaglinide are used concomitantly, consider decreasing the dose of repaglinide and perform careful monitoring of blood glucose levels. Closely monitor patients for signs of exposure related toxicity when deferasirox is coadministered with other CYP2C8 substrates
- Deferasirox inhibits CYP1A2 resulting in an increase in CYP1A2 substrate (e.g., alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, theophylline, tizanidine) concentration when these drugs are coadministered. An increase in theophylline plasma concentrations could lead to clinically significant theophylline induced CNS or other adverse reactions. Avoid the concomitant use of theophylline or other CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine) with deferasirox. Monitor theophylline concentrations and consider theophylline dose modification if you must coadminister theophylline with deferasirox. Closely monitor patients for signs of exposure related toxicity when deferasirox is coadministered with other drugs metabolized by CYP1A2.

7.5.3 Prohibited Concomitant Therapy

- Any investigational drug other than study medication is NOT permitted during the study.
- The concomitant administration of deferasirox and aluminum-containing antacid preparations has not been formally studied. Although deferasirox has a lower affinity for aluminum than for iron, avoid use of deferasirox with aluminum-containing antacid preparations due to the mechanism of action of deferasirox.

7.6 Dose Modifications

7.6.1 Based on Concomitant Medications

As stated in Section 7.5.1 deferasirox will be adjusted based upon concomitant medications which interferes with metabolism.

7.6.2 Change in Patient's Weight

The dose of study medication should be adapted using during the study if the change (increase or decrease) in body weight exceeds 10% of the body weight compared to the baseline visit or the last dose adjustment due to change in patient's body weight

7.6.3 Renal Impairment

Serum creatinine and proteinuria should be monitored during the study as stated in Table 2.

Deferasirox can cause acute renal failure, fatal in some patients and requiring dialysis in others. Postmarketing experience showed that most fatalities occurred in patients with multiple comorbidities and who were in advanced stages of their hematological disorders. In the clinical trials, deferasirox-treated patients experienced dose-dependent increases in serum creatinine.
Measure serum creatinine and determine the glomerular filtration rate (GFR, estimated by the MDRD method) before initiating therapy in all patients.

Deferasirox is contraindicated in patients with an estimated GFRless than 40 mL/minute or serum creatinine greater than 2 times the age-appropriate upper-limit-of-normal (ULN). Renal tubular damage, including Fanconi's Syndrome, has been reported in patients treated with deferasirox, most commonly in children and adolescents with beta-thalassemia and serum ferritin levels <1500 mcg/L.

Deferasirox will be administered and dosed at the discretion of the treating clinician based on renal function as measured by serum creatinine and via the estimated GFR.

Intermittent proteinuria of unclear significance was also noted in clinical trials with deferasirox. The level of proteinuria will be measured per **Table 2** (at baseline before treatment, at 6 months and again at 12 months)strictly for monitoring. Deferasirox will be administered and dosed at the discretion of the treating clinician based on the

results of monitoring for proteinuria. However, given the intermittent nature of proteinuria experienced with deferasirox and its unclear significance, there is no contraindication to the administration of deferasirox based on level of proteinuria.

7.6.4 Changes in Serum Ferritin

Goal serum ferritin of < 100 ng/mL and deferasirox dose adjustment will be at the discretion of the treating clinician based on the monthly serum ferritin level (in addition to other variables as detailed above including renal function, hepatic function, blood counts, and clinical condition / performance status).

7.6.5 Skin Disorders

Rashes may occur during deferasirox treatment. For rashes of mild to moderate severity, deferasirox may be continued without dose adjustment, since the rash often resolves spontaneously. In severe cases, interrupt treatment with deferasirox. Reintroduction at a lower dose with escalation may be considered after resolution of the rash. Severe skin reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme, have been reported during deferasirox therapy. If SJS or erythema multiforme is suspected, discontinue deferasirox immediately and do not reintroduce deferasirox therapy.

7.6.6 Hepatic Impairment

Liver function tests should be monitored during the duration of the trial as indicated in **Table 2**.

Deferasirox can cause hepatic injury, fatal in some patients. Hepatic toxicity appears to be more common in patients greater than 55 years of age. Hepatic failure was more common in patients with significant comorbidities, including liver cirrhosis and multiorgan failure.

Consider dose modifications or interruption of treatment for severe or persistent elevations.

Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment may be at higher risk for hepatic toxicity. In a single dose (20 mg/kg) study in patients with varying degrees of hepatic impairment, deferasirox exposure was increased compared to patients with normal hepatic function. The average total (free and bound) AUC of deferasirox increased 16% in 6 patients with mild (Child-Pugh A) hepatic impairment, and 76% in 6 patients with moderate (Child-Pugh B) hepatic impairment compared to 6 patients with normal hepatic function. The impact of severe (Child-Pugh C) hepatic impairment was assessed in only 1 patient.

Avoid the use of deferasirox in patients with severe (Child-Pugh C) hepatic impairment. For patients with moderate (Child-Pugh B) hepatic impairment, the starting dose should be reduced by 50%. Closely monitor patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment for efficacy and adverse reactions that may require dose titration.

7.6.7 Auditory or Ocular Toxicity

Auditory (decreased hearing) and ocular (lens opacities) disturbances have been reported with deferasirox treatment. Auditory and ophthalmic testing (including fundoscopy) is recommended before the start of deferasirox treatment and at regular intervals thereafter (every 12 months). If disturbances are noted, dose reduction or interruption may be considered.

7.6.8 Hypersensitivity Reactions

Cases of serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving deferasirox, with the onset of the reaction occurring in the majority of cases within the first month of treatment. If reactions are severe, deferasirox should be discontinued.

7.6.9 Cytopenias

There have been post-marketing reports (both spontaneous and from clinical trials) of cytopenias in patients treated with deferasirox. Most of these patients had pre-existing hematological disorders that are frequently associated with bone marrow failure. The relationship of these episodes to treatment with deferasirox is uncertain. In line with the standard clinical management of such hematological disorders, complete blood counts will be monitored regularly. Given the nature of this particular clinical trial in the setting of MDS patients, dose interruptions or modifications in patients who develop cytopenias or have worsening of cytopenias are at the discretion of the treating clinician.

7.6.10 Gastrointestinal Ulceration, Hemorrhage, and Perforation

GI hemorrhage, including deaths, has been reported, especially in elderly patients who had advanced hematologic malignancies and/or low platelet counts. Nonfatal upper GI irritation, ulceration and hemorrhage have been reported in patients, including children and adolescents, receiving deferasirox. Monitor for signs and symptoms of GI ulceration and hemorrhage during deferasirox therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. The risk of gastrointestinal hemorrhage may be increased when administering deferasirox in combination with drugs that have ulcerogenic or hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral bisphosphonates, or anticoagulants. There have been reports of ulcers complicated with gastrointestinal perforation (including fatal outcome).

7.6.11 Hypersensitivity

Deferasirox may cause serious hypersensitivity reactions (such as anaphylaxis and angioedema), with the onset of the reaction usually occurring within the first month of treatment. If reactions are severe, discontinue deferasirox and institute appropriate medical intervention. deferasirox is contraindicated in patients with known hypersensitivity to deferasirox.

7.7 Criteria for Removal/Withdrawal

A patient may 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 PI or designee, poses an unacceptable safety risk to the patient;
- If, in the PI or designee'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 PI or designee;
- A positive pregnancy test at any time during the study;
- An intercurrent illness that, in the judgment of the PI or designee, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy, or
- Completion of the study
- Evidence of disease progression to a higher stage of MDS or AML as defined by WHO criteria

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 (**Appendix H**) should be filled out.

- Once completed, the form should be faxed to FHCRC Research Coordinator at 206-667-2284.
- It is the responsibility of the PI or designee to complete the Notice of Withdrawal From a Research Study Form (see **Appendix H**) and fax it to the FHCRC Research Coordinator at (206) 667-2284.

Study treatment is defined as "any activity involving a patient described in a protocol that is not part of their routine medical care". Patients that withdraw from study treatment will be asked permission to continue to record survival data up to the protocol-described end of the subject follow-up period as it is important to the integrity of the final study analysis.

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

8.0 GUIDELINES FOR ADVERSE EVENT REPORTING

8.1 Adverse Event Reporting/Institutional Policy

The following guidelines are the minimum Cancer Consortium IRB adverse event (AE) reporting guidelines. Protocol-specific additional reporting requirements for adverse events are addressed in Section 8.2.

In accordance with institutional policy, all adverse events which in the opinion of the PI are unexpected and related or possibly related to the research and serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized be reported to the IRB within 10 calendar days of learning of the problem.

Definitions:

Adverse Event (AE) - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including

an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to the medicinal product.

Life-threatening AE – Any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.

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

Attribution - The following are definitions for determining whether an adverse event is related to a medical product, treatment or procedure:

- An adverse event is "**related or possibly related to the research procedures**" if in the opinion of the PI, it was more likely than not caused by the research procedures.
- Adverse events 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 adverse event is related or possibly related, the adverse event should be reported.

The Cancer Consortium Expedited Reporting Form should be completed for all adverse events that meet the expedited reporting requirements. The AE form (see **Appendix I**) should be faxed to the FHCRC Research Coordinator at (206) 667-2284 within 10 business days of study staff awareness. All available information should be submitted.

8.2 Study-Specific AE Capture

Please refer to the package insert of deferasirox for a listing of specific expected AEs.

AEs will be reviewed and captured in the source documentation. AEs occurring from enrollment through 30 days after the last administration of the study treatment will be captured in protocol-specific case report forms (**Appendix J**).

The following events are **not** recorded as AEs in this study:

- Disease progression or relapse.
- Planned medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs.
- Abnormal laboratory values grade < 3 (CTCAE v4.03).

In accordance with institutional policy, all SAEs which in the opinion of the PI or designee meet all three of the following criteria will be reported to the IRB within 10 calendar days of learning of the problem:

1. unexpected
2. related or possibly related to the research
3. serious or suggests that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized

All other SAEs and deaths, not meeting the expedited reporting criteria, will be reported to the IRB as part of the annual continuation review report to the IRB.

9.0 Serious Adverse Events

9.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

9.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the study PI and/or study coordinator within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to the study PI and/or study coordinator if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax (206-667-2284) () within 24 hours to the study PI and study coordinator..

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

9.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the study PI and/or study coordinator within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

9.4 Duration and Grade of AE Capture

AEs will be captured starting with the initiation of study treatment through 30 days after the last administration of the study treatment.

9.4.1 AE Grading

Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Citing the website under this section in the protocol rather than printing the entire document is sufficient unless the study is modifying the criteria. The scale in its entirety can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10.0 DATA AND SAFETY MONITORING PLAN

The 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, that all data required for oversight of monitoring are accurately reported to the FHCRC/UW Cancer Consortium Data and Safety Monitoring Committee (DSMC), that all adverse events are reported according to the protocol guidelines, and that any adverse reactions reflecting patient safety concerns are appropriately reported. The PI or designee will personally review with the Research Nurse the clinical course of all the enrolled patients weekly. A delegation log of authority will be kept to delineate the role of co-investigators (**Appendix K**).

Under the provisions of the Institutional Data Safety and Monitoring Plan, the Cancer Consortium Clinical Research Support Office provides monitoring for Good Clinical Practice and compliance by qualified monitors unaffiliated with the conduct of the study. Monitoring visits are conducted in accordance with the Cancer Consortium Data and Safety Monitoring Plan.

This protocol will also be monitored by a dedicated DSMB on a semi-annual basis. Enrollment, response and toxicity data will be reviewed. The DSMB has the authority to terminate the study, hold enrollment, or suggest modifications to the protocol as indicated.

An annual review of the progress of the study with respect to the monitoring plan will be performed by the DSMC. The DSMC will review the number of subjects and unanticipated problems. The DSMC will also review DSMB reports regarding accrual, stopping rules, protocol adherence to the data and safety monitoring plan, as well as DSMB recommendations. If the DSMC finds a study to be continuing accrual in violation of the study design or the recommendation of the DSMB, the DSMC has the authority to suspend trial accrual.

11.0 STUDY AGENT INFORMATION

11.1 Background Investigational drug: Deferasirox

Deferasirox is an orally active chelator that is highly selective for iron (III). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Two molecules of deferasirox form a complete complex with Fe3+.

The high potency of deferasirox in mobilizing tissue iron and promoting iron excretion was demonstrated both in vitro and in vivo model systems. Deferasirox is eliminated from the body by hepatic glucuronidation and biliary excretion. Deferasirox has low affinity for zinc and copper, and does not cause constant low serum levels of these metals.

Deferasirox was first approved for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in adults and pediatric patients aged 2 years and older in the United States in November 2005 and is currently approved for this indication in more than 100 countries, including the European Union, Switzerland and Japan. Deferasirox has also been approved in more than 60 countries for the treatment of chronic iron overload in patients with non-transfusion dependent thalassemia aged 10 years and older.

11.2 Deferasirox Preparation and Administration

Deferasirox is for oral use and will be administered per manufacturers labeling for iron chelation..

12.0 ASSESSMENT OF EFFICACY AND TOXICITY

12.1 Efficacy Parameters

The primary endpoint is the proportion of patients that achieve erythroid hematologic improvement as defined by the modified IWG response criteria(39) at 6 months. Please see **Appendix G** for a table defining the response criteria for this study.

12.2 Method and Timing

All patients will be screened for eligibility following consent. Screening must be completed within 30 days of start of therapy. If the time period between screening assessments and start of therapy is greater than 30 days then screening tests must be repeated. The most recent screening labs prior to start of therapy will be considered the

baseline assessment upon which response by the modified IWG criteria will be based. Screening assessments will consist of CBC with differential, ferritin, hepatic and renal function tests and a bone marrow aspirate or biopsy. Women of child bearing potential must have a urine or serum pregnancy test performed within 7 days of start of deferasirox.

Follow up tests will consist of monthly CBC with differential, monthly ferritin levels, and monthly renal and hepatic function tests while the patient remains enrolled in the trial. Bone marrow aspiration or biopsy will be repeated at 3 months and 6 months following the start of deferasirox, and as clinically indicated. If at any point a patient is suspected to have disease progression, a bone marrow biopsy or aspirate may be obtained to document this progression. Physical exams and detailed history will be obtained on a monthly basis to screen for potential toxicities. The primary endpoint of hematologic improvement in the erythroid lineage will be assessed at 6 months following start of deferasirox. The secondary endpoints of hematologic improvement in granulocytes and platelets will also be assessed at 6 months. At the end of 6 months patients who do not respond will be offered the option of alternative treatment options including enrollment into clinical trials if possible.

12.3 Other Parameters

The secondary endpoints change in RBC transfusion requirements, change in serum ferritin, and safety and tolerability will be assessed in a continuous fashion during the entire duration of the study. Patients will remain on study for a maximum of one year. Patients will be assessed for AE and SAEs while they remain enrolled into the study. Patients will have an end of study visit day 30 following completion or withdrawal from the study.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

Study data will be recorded in a password-protected research database. Case report forms are generated from the database for review by the PI and study monitors. Clinical Statistics maintains a subject database at FHCRC to allow storage and retrieval of subject data collected from a wide variety of sources. The investigator will ensure that data collected conform to all established guidelines for coding, collection, key entry and verification. 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. Subject research files are scanned and stored in a secure database (OWL). OWL records are maintained by the FHCRC data abstraction staff. Access is restricted to personnel authorized by the Division of Clinical Research.

14.0 ETHNIC and GENDER DISTRIBUTION: TARGETED ENROLLMENT

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	1	1	2
Not Hispanic or Latino	9	14	23
Ethnic Category Total of All Subjects*	10	15	25
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	9	14	23
Racial Categories: Total of All Subjects*	10	15	25

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects
The projected accrual is based on demographic trends of the referral population and not on any perceived advantage or disadvantage of the intervention based on race, gender or ethnicity.

15.0 STATISTICAL CONSIDERATIONS

We estimate the rate of hematologic response to iron chelation with deferasirox to be 0.25 based on previously published studies in patients with MDS and iron overload. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. The accrual goal is for a total of 25 patients. The null hypothesis will be rejected if 4 or more responses are observed in 25 patients. This design yields a type I error rate of 0.0336 and power of 0.9008 when the true response rate is 0.25. Descriptive statistics will be performed and the planned number of patients is estimated based on the patients we have that would meet eligibility criteria.

16.0 TERMINATION OF THE STUDY

The PI may terminate the study at any time. The IRB and FDA also have the authority to terminate the study should it be deemed necessary. There is no planned interim analysis of this study and there are no early stopping rules in place for excessive toxicity. The study will be monitored by a designated DSMB which will meet every 6 months to review the protocol accrual and results including toxicity. The DSMB has the independent authority to terminate the study at their discretion. This information will be included in the consent form.

Reference List

(1) Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemia evolution in patients with myelodysplastic syndrome. Haematologica 2006;91(12):1588-90.

(2) Goldberg SL, Chen E, Corral M, Guo A, Mody-Patel N, Pecora AL, et al. Incidence and clinical complications of myelodysplastic syndromes among United States medicare beneficiaries. J Clin Oncol 2010 Jun 10;28(17):2847-52.

(3) Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood 2004 Jul 15;104(2):321-7.

(4) Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 2008 Jan 15;111(2):574-82.

(5) Fenaux P, Giagounidis A, Selleslag D, Beyne-Rauzy O, Mufti G, Mittelman M, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood 2011 Oct 6;118(14):3765-76.

(6) Raza A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1-risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood 2008 Jan 1;111(1):86-93.

(7) Scott BL. Myelodysplastic syndromes: emerging therapies, survival, and alternative outcomes. Managed Care 2009 Nov;18 (Suppl. 9)(11):4-12, discussion 13-4.

(8) Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012 Sep 20;120(12):2454-65.

(9) Scott B, Deeg HJ. Clinical presentation. In: Deeg HJ, Bowen DT, Gore SD, Haferlach T, Le Beau MM, Niemeyer C, editors. Hematologic Malignancies: Myelodysplastic Syndromes.Heidelberg, Germany: Springer; 2006. p. 1-4.

(10) Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst 2008 Nov 5;100(21):1542-51.

(11) Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IM, Dybedal I, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol 2003 Mar;120(6):1037-46.

(12) Haase D, Germing U, Schanz J, Pfeilstöcker M, Nösslinger T, Hildebrandt B, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood 2007 Dec 15;110(13):4385-95.

(13) Komrokji RS, Lancet JE, Swern AS, Chen N, Paleveda J, Lush R, et al. Combined treatment with lenalidomide and epoetin alfa in lower-risk patients with myelodysplastic syndrome. Blood 2012 Oct 25;120(17):3419-24.

(14) Lyons RM, Cosgriff TM, Modi SS, Gersh RH, Hainsworth JD, Cohn AL, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol 2009 Apr 10;27(11):1850-6.

(15) Garcia-Manero G, Jabbour E, Borthakur G, Faderl S, Estrov Z, Yang H, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. J Clin Oncol 2013 Jul 10;31(20):2548-53.

(16) Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002 May 15;20(10):2429-40.

(17) Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009 Mar;10(3):223-32.

(18) Lübbert M, Suciu S, Baila L, Rüter BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011 May 20;29(15):1987-96.

(19) Shenoy N, Vallumsetla N, Rachmilewitz E, Verma A, Ginzburg Y. Impact of iron overload and potential benefit from iron chelation in low-risk myelodysplastic syndrome (Review). Blood 2014 Aug 7;124(6):873-81.

(20) Malcovati L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005 Oct 20;23(30):7594-603.

(21) Garcia-Manero G, Shan J, Faderl S, Cortes J, Ravandi F, Borthakur G, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia 2008 Mar;22(3):538-43.

(22) Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood 2007 May 15;109(10):4586-8.

(23) Platzbecker U, Bornhäuser M, Germing U, Stumpf J, Scott BL, Kröger N, et al. Red blood cell transfusion dependence and outcome after allogeneic peripheral blood stem cell transplantation in patients with de novo myelodysplastic syndrome (MDS). Biol Blood Marrow Transplant 2008;14(11):1217-25.

(24) Alessandrino EP, Della Porta MG, Bacigalupo A, Malcovati L, Angelucci E, van Lint MT, et al. Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. Haematologica 2010 Mar;95(3):476-84.

(25) Armand P, Kim HT, Rhodes J, Sainvil MM, Cutler C, Ho VT, et al. Iron overload in patients with acute leukemia or MDS undergoing myeloablative stem cell transplantation. Biol Blood Marrow Transplant 2011 Jun;17(6):852-60.

(26) Malcovati L, Germing U, Kuendgen A, Della Porta MG, Pascutto C, Invernizzi R, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007 Aug 10;25(23):3503-10.

(27) Leitch HA, Leger CS, Goodman TA, Wong KK, Wong DHC, Ramadan KM, et al. Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy. Clinical Leukemia 2008 Aug;2(3):205-11.

(28) Leitch HA. Improving clinical outcome in patients with myelodysplastic syndrome and iron overload using iron chelation therapy (Review). Leuk Res 2007 Dec;31 (Suppl. 3):S7-S9.

(29) Neukirchen J, Fox F, Kundgen A, Nachtkamp K, Strupp C, Haas R, et al. Improved survival in MDS patients receiving iron chelation therapy - a matched pair analysis of 188 patients from the Dusseldorf MDS registry. Leuk Res 2012 Aug;36(8):1067-70.

(30) Rose C, Brechignac S, Vassilief D, Pascal L, Stamatoullas A, Guerci A, et al. Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A multicenter study by the GFM (Groupe Francophone des Myelodysplasies). Leuk Res 2010 Jul;34(7):864-70.

(31) Lyons RM, Marek BJ, Paley C, Esposito J, Garbo L, DiBella N, et al. Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry. Leuk Res 2014 Feb;38(2):149-54.

(32) Gattermann N, Finelli C, Porta MD, Fenaux P, Ganser A, Guerci-Bresler A, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. Leuk Res 2010 Sep;34(9):1143-50.

(33) Gattermann N, Finelli C, Della Porta M, Fenaux P, Stadler M, Guerci-Bresler A, et al. Hematologic responses to deferasirox therapy in transfusion-dependent patients with myelodysplastic syndromes. Haematologica 2012 Sep;97(9):1364-71.

(34) List AF, Baer MR, Steensma DP, Raza A, Esposito J, Martinez-Lopez N, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. J Clin Oncol 2012 Jun 10;30(17):2134-9.

(35) Improta S, Villa MR, Volpe A, Lombardi A, Stiuso P, Cantore N, et al. Transfusion-dependent low-risk myelodysplastic patients receiving deferasirox: Long-term follow-up. Oncology Letters 2013 Dec;6(6):1774-8.

(36) Maurillo L, Breccia M, Buccisano F, Voso MT, Niscola P, Trapè G, et al. Deferasirox chelation therapy in patients with transfusion-dependent MDS: a 'real-world' report from two regional Italian registries: Gruppo Romano Mielodisplasie and Registro Basilicata. Eur J Haematol 2015 Mar 12;[Epub ahead of print; doi: 10.1111/ejh.12476].

(37) Jabbour E, Garcia-Manero G, Taher A, Kantarjian HM. Managing iron overload in patients with myelodysplastic syndromes with oral deferasirox therapy (Review). Oncologist 2009 May;14(5):489-96.

(38) Gattermann N. Guidelines on iron chelation therapy in patients with myelodysplastic syndromes and transfusional iron overload (Review). Leuk Res 2007 Dec;31 Suppl 3:S10-S15.

(39) Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans P, Nimer SD, et al. Clinical applications and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006 Jul 15;108(2):419-25.

(40) Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009 Jul 30;114(5):937-51.

(41) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982 Dec;5(6):649-55.

APPENDIX A: World Health Organization (WHO) Classification of Myelodysplastic Syndromes[40]

Disease	Blood findings	BM findings
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia* No or rare blasts (< 1%)†	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)† No Auer rods < 1 × 10^9/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts† No Auer rods < 1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts† No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts‡ Auer rods ±‡ < 1 × 10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts‡ Auer rods ±‡
Myelodysplastic syndrome—unclassified (MDS-U)	Cytopenias < 1% blasts†	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (see Table 6) < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

*Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

†If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.

‡Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have < 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rod+ and/or 5% to 19% blasts in the blood.

Recurring Chromosomal Abnormalities Considered as Presumptive Evidence of MDS

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.

APPENDIX B

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) [8]

IPSS-R Cytogenetic Risk Groups

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate (Int)	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Int	Poor	Very Poor
BM Blast %	≤ 2		>2 - <5%		5-10%	> 10%	
Hemoglobin	≥ 10		8 - <10	< 8			
Platelets	≥100	50 - <100	< 50				
ANC	≥ 0.8	< 0.8					

IPSS-R Prognostic Risk Categories/Scores

RISK CATEGORY	RISK SCORE
Very Low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

IPSS-R: Prognostic Risk Category Clinical Outcomes*

	Total	Very Low	Low	Int	High	Very High
Pts (%)	7012	1332(19)	2665(38)	1402(20)	912(13)	701(10)
Survival*		8.8	5.3	3.0	1.6	0.8
AML 25%^		NR	10.8	3.2	1.4	0.7

*Medians, years ^Median time to 25% AML evolution

APPENDIX C: Eastern Cooperative Oncology Group Performance Status[41]

ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

APPENDIX D

Clinical Research Division
Research Subject Registration Fax Coversheet

Date: _____

TO: MDS Protocol 9422 Research Coordinator

FAX: (206) 667-2284

RE: RESEARCH SUBJECT REGISTRATION FORM

FROM: _____

FAX: _____

PHONE: _____

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

IF YOU HAVE RECEIVED THIS INFORMATION IN ERROR, PLEASE NOTIFY THE SENDER BY TELEPHONE, AND RETURN THE ORIGINAL AND ANY COPIES OF THE MESSAGE BY MAIL TO THE SENDER AT FRED HUTCHINSON CANCER RESEARCH CENTER, 1100 FAIRVIEW AVE N. LF-210, SEATTLE, WA 98109

FRED HUTCH
CURES START HERE™

Clinical Research Division
Research Subject Registration Form

16.1 Protocol Number: 9422

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 or Refused to Report**

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.

Appendix E: Protocol 9422 Eligibility Checklist

A. **Inclusion Criteria:** *All answers must be yes for the patient to be eligible*

1. Yes ☐ No ☐ Patient signed IRB approved consent form.
   Date: _____
   IRB file number: _____
   Date of IRB approval: _____
2. Yes ☐ No ☐ Diagnosis of MDS by WHO criteria (**Appendix A**)
3. Yes ☐ No ☐ IPSS-R of very low, low or intermediate risk (**Appendix B**).
4. Yes ☐ No ☐ Baseline serum ferritin level ≥ 100 ng/mL
5. Yes ☐ No ☐ ECOG PS 0-2 (**Appendix C**)
6. Yes ☐ No ☐ Age ≥ 18 years
7. Yes ☐ No ☐ Hemoglobin ≤ 10.0 g/dL
8. Yes ☐ No ☐ Adequate organ function. Please check **yes** if patient meets **ALL** of the following criteria.

   Yes ☐ No ☐ Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine transaminase (ALT), and aspartate transaminase (AST) ≤ 3.5 times ULN

   Yes ☐ No ☐ Renal: Serum creatinine ≤ 1.5 X ULN and estimated GFR > 40 mL/min
9. Yes ☐ No ☐ Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the study and for 3 months following the last dose of deferasirox
10. Yes ☐ No ☐ Females with childbearing potential must have a negative urine pregnancy test ≤ 7 days before the first dose of deferasirox and must also not be breastfeeding
11. Yes ☐ No ☐ Reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

B. **Exclusion criteria:** *Each of the following questions must be marked no for the patient to be eligible*

1. Yes ☐ No ☐ If the patient is currently receiving ESA (for example, erythropoietin) with plans to continue during study: Less than 2 months duration of ESA therapy prior to start of study therapy and no dose escalation within 2 months of start of study therapy.
2. Yes ☐ No ☐ If the patient is being treated with GCSF and/or a TPO-mimetic (for example, Eltrombopag or Romiplostim) with plans to continue during the study: Less than 2 months duration of GCSF or the TPO-mimetic treatment prior to start of study therapy; or GCSF and/or TPO-mimetic has been added to ESA therapy within 2 months of start of study therapy.
3. Yes ☐ No ☐ If patient is being treated with Lenalidomide with plans to continue during the study: Stable dose for less than 3 months prior to start of study therapy.
4. Yes ☐ No ☐ If patient is being treated with HMA (for example, Azacitidine or Decitabine) with plans to continue during the study: Stable dose for less than 6 months prior to start of study therapy..
5. Yes ☐ No ☐ Currently enrolled in, or discontinued within the last 14 days from a clinical trial involving an investigational product or non-approved use of a drug, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

6. Yes ☐ No ☐ Presence of ≥10% blast by morphologic examination of bone marrow aspirate or biopsy

7. Yes ☐ No ☐ Platelets ≤ 50,000

8. Yes ☐ No ☐ Presence of microcytosis on screening CBC (MCV < 81 fL)

9. Yes ☐ No ☐ Active GI ulceration or hemorrhage

10. Yes ☐ No ☐ Have serious preexisting medical conditions that, in the opinion of the PI or designee would preclude participation in the study (for example a GI disorder causing clinically significant symptoms such as nausea, vomiting, and diarrhea, or malabsorption syndrome)

11. Yes ☐ No ☐ Known hypersensitivity to deferasirox

12. Yes ☐ No ☐ History of non-transfusional hemosiderosis.

13. Yes ☐ No ☐ Prior hematopoietic stem cell transplant for the diagnosis of MDS

14. Yes ☐ No ☐ A second primary malignancy that in the judgment of the PI or designee may affect the interpretation of results

15. Yes ☐ No ☐ Have an active fungal, bacterial, and/or known viral infection including human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis

16. Yes ☐ No ☐ Currently using aluminum-containing antacid products

17. Yes ☐ No ☐ History of clinically significant auditory or ocular toxicity to ICT

Signature of person completing this form: _____ Date:_____

Signature of PI or Designee

_____ Date: _____

APPENDIX F

9422 Study Calendar

Procedure	Screening Phase	Treatment Phase			Follow-up phase		
	Screening within 30 days	**Cycle 1** Day 1	**Cycle 2-6** Day 1	**Cycle 7-12** Day 1	**At End of 6 cycles Primary Endpoint**	**At End of 1 year**	**30 days after last dose**
Medical History	X						
Physical Exam	X	X	X	X	X	X	X
Transfusion History	X	X	X	X	X	X	X
Pregnancy Test*	X						
CBC with differential	X	X	X	X	X	X	X
Serum Creatinine, estimated GFR^	X	X (every 2 weeks)	X	X	X	X	X
Urine protein/creatinine ratio (spot-check)	X				X	X	X
Serum Ferritin	X	X	X	X	X	X	X
Bone Marrow Aspiration or Biopsy	X**		X** (at 3 and 6 months)		X		
Hematologic Improvement according to modified IWG criteria	X	X	X	X		X	
Hepatotrophic Virology¥	X						
Serum transaminases, bilirubin, alkaline phosphatase	X	X (every 2 weeks)	X	X	X	X	X
Auditory and Ophthalmic Testing	X					X	

*Pregnancy test only in women of child baring potential may consist of urine or serum pregnancy test and must be completed within 7 days of day 1
^Estimated creatinine clearance with the MDRD formula;
¥Hep B Surface antibody, Hep B surface antigen, Hep C antibody, and HCV PCR
** Research samples: use preservative-free heparin in the syringe and place in sterile, preservative-free red-top tube. Send to hematopathology lab at SCCA

9422

APPENDIX G

Modified IWG Response Criteria[39]

Modified IWG Response Criteria for Hematologic Improvement

Hematologic Improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 × 10^9/L)	Absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L platelets Increase from < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase > 0.5 × 10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Modified IWG Response Criteria for altering natural history of MDS

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

9422

APPENDIX H

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

FRED HUTCH
CURES START HERE™

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.
9422	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 (206-667-2284).
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 on _____(date)

APPENDIX I

Fred Hutchinson Cancer Research Center
Clinical Research Division
Institutional Review Office
SERIOUS ADVERSE EVENT REPORT

FHCRC Unique Patient Number:
☐ FHCRC/SCCA ☐ Other
Gender ☐ Male ☐ Female Age:
FHCRC Principal Investigator Bart Scott, MD

FHCRC Protocol Number: 9422
FHCRC IR File Number: 9422

Phone number: 206-667-1990
Mail stop: D1-100

Date of Report:

☐ Initial Report ☐ Follow-up Report # ☐ Other:

Date Serious Adverse Event Started:

Date Ended: or ☐ Ongoing (if ongoing- must submit follow-up report)

Adverse Event:

Date Study Staff became aware of event:

Outcomes attributed to adverse event: (Check all that apply)
☐ Death ____/____/_____
☐ Life-threatening
☐ Hospitalization (initial or prolonged)
☐ Disability
☐ Congenital Anomaly
☐ Required intervention to prevent permanent impairment/damage

Describe the Serious Adverse Event including a summary of all relevant clinical information.
(Or attach a Med Watch Form or other SAE reporting form if one has been completed.)

☐ Continued next page

☐ Follow-up Report Required ☐ Final Report (PI must sign final report)

Completed by: Date:

The PI has determined that the consent form must be revised: ☐ Yes ☐ No

Signature of PI or Designee: Date:

APPENDIX J

Protocol 9422 ADVERSE EVENTS

Patient Name: _____

CTC Category	Adverse Event	Start Date	End Date	Ongoing Y/N	Grade 3, 4, Death	SAE Y/N

FHCRC/UW Study Personnel Signature and Delegation of Authority Log

Sponsor:	FHCRC / UW
Principal Investigator:	Bart L. Scott, MD
Protocol Number/Title:	9422 / A Phase II Study of Deferasirox in Patients with Myelodysplastic Syndromes who are Anemic with Iron Overload
IND #:	N/A

Name (print)	**Title and Position (*e.g. Investigator, Study Coordinator*)**	**Initials**	**Signature**	**Responsibilities *See Codes below *List all that apply***	**Start Date of Study Responsibility**	**End Date of Study Responsibility**	**PI's Initials and Date ****

*Responsibility Codes:

01=Administer informed consent	05=Data base entries & corrections	09=
02=Determine eligibility	06=Study drug accountability	10=
03=Assess adverse events	07=SAE reporting	11=
04=CRF entries & corrections	08=IRB submission, renewals, modifications	12=

**Investigator's initials indicate review and approval of responsibilities for the person listed on that line