Phase II Randomized Study of Lower Doses of Decitabine (DAC; 20 mg/m^2 IV daily for 3 days every month) versus Azacitidine (AZA; 75 mg/m^2 SC/IV daily for 3 days every month) versus Azacitidine (AZA; 75 mg/m2 SC/IV daily for 5 days every month) in MDS Patients with Low and Intermediate-1 Risk Disease Transfusion-Dependent versus Best Supportive Care (BSC) in MDS Patients with Low and Intermediate-1 Risk Disease Transfusion-Independent

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I. OBJECTIVES

Primary:

Compare the event-free survival rates of two different drugs: DAC versus AZA on an abbreviated schedule to a standard arm of AZA given over 5 days in patients with low-risk MDS transfusion-dependent and to BSC in patients with low-risk MDS transfusion-independent.

Secondary:

Compare the response rates for the transfusion independent and the transfusion dependent patients. For example the response rate of two different drugs DAC versus AZA on abbreviated schedule to a standard arm of AZA given over 5 days.

Evaluate the durability of response, the overall and transformation-free survival rates, and the safety profile of 2 different drugs.

The quality of life protocol (2014-0636) titled “Interventional Validation of an MDS-Specific Measure of Quality of Life: Assessing the Responsiveness of the QUALMS-1 to Different Hypomethylating Agent Regimens for Low and Intermediate Risk Disease” was written specifically as a companion study to protocol 2014-0112 and may be offered as an optional assessment to patients enrolled onto this protocol.

II. RATIONALE

Myelodysplastic syndromes (MDS) are clonal hematopoietic stem-cell disorders characterized by ineffective hematopoiesis, peripheral-blood cytopenias, and increased tendency to progress to acute myeloid leukemia (AML).[1] Median age of patients with MDS is approximately 70 years.[2] This patient population is frequently affected by other comorbid conditions, a factor that often influences treatment decisions.

Treatment of MDS is based on prognostic factors that predict survival and progression to AML. The most widely used prognostic system for therapeutic decision making is still

the International Prognostic Scoring System.[3] This system stratifies patients into the following four groups: low, intermediate-1, intermediate-2, and high risk. Risk is based on number of cytopenias, percentage of bone marrow blasts, and karyotype. Low risk and intermediate-1 risk are usually grouped together as lower-risk disease, whereas intermediate-2 risk and high risk are grouped together as higher-risk disease. Several other factors have recently been shown to have prognostic value. These include, among others, the need for RBC transfusions[4] and the presence of reticulin marrow fibrosis.[5] Analysis of recently identified genetic and immunophenotypic alterations has not yet been introduced in the therapeutic decision making of MDS.[1]

The survival of patients with higher-risk MDS is significantly different than that of patients with lower-risk disease. Without intervention, median survival of higher-risk patients is close to 12 months.[3] Survival of patients with lower-risk disease is more diverse and ranges from a few months (poor-prognosis, lower-risk disease) to more than a decade (Fig 1 and Tables 1 and 2).[3,6] Risk of transformation to AML in lower-risk MDS is less than 30%.[6] A recent analysis has indicated that most patients with lower-risk MDS die from causes directly related to complications of MDS.[7]

Therefore, the objectives of therapy are different in lower- versus higher-risk disease. In higher-risk MDS, treatment options should impact survival as a primary end point. In lower-risk MDS, therapies should be adapted to specific patient situation, including severity and type of cytopenias and expected survival.[6] Therefore, in lower-risk MDS,

therapies should have the capacity to improve transfusion needs and potentially survival.

Until recently, treatment approaches in patients with lower-risk MDS have focused on improving transfusion needs. It should be noted that we consider transfusions as part of supportive care in MDS. In general, patients with lower-risk MDS do not receive therapy until they become transfusion dependent. This notion could be challenged by the recent report that the prognosis of patients with lower-risk MDS is heterogeneous, ranging from 9 months to more than a decade.[6] This model may allow the identification of patients with lower-risk disease and poor prognosis (Fig 1). The question is whether the more aggressive treatment of these patients, can favorably change the natural history of this group of patients with poor prognosis and lower-risk disease.

In MDS, tumor suppressor genes are silenced by the effects of irregular DNA hypermethylation.[8-9] Two hypomethylating agents (HMA), decitabine at 20 mg/m^2 IV daily for 5 days every months, and azacitidine at 75 mg/m^2 IV/SC daily for 7 days every month, are approved for treatment of patients with higher-risk MDS.[8-9] The use of the hypomethylating agent azacitidine, has been formally shown in a randomized clinical trial to improve survival of patients with higher-risk MDS.[8] Furthermore, azacitidine given over 5 days was found to be equivalent to a regimen given over 7 days in a phase II randomized trial.[11]

We assessed the use of decitabine in patients with lower risk MDS. In a phase II trial, decitabine given at lower dose, 20 mg/m^2 IV daily for 3 days every month induced an objective response rate of 23% in 43 patients with low and intermediate-1 risk disease. The median overall survival (OS) was not reached; about 70% of patients were alive at 500 days. The safety profile was adequate.[10]

Results from a study investigating alternative SC azacitidine dosing schedules in lower-risk patients with MDS suggested that a lower dose schedule (375 mg/m^2 total dose) was beneficial.[11] Furthermore, clinical responses were reported in patients who received oral azacitidine, a formulation proven to have lower drug exposure and DNA hypomethylation relative to SC azacitidine.

We have recently initiated a phase II randomized trial comparing decitabine to azacitidine given in an abbreviated way of 3 days in patients with low-risk MDS. So far, 34 patients were enrolled (19 treated with azacitidine and 15 with decitabine). 24 patients are evaluable for response. The response rates were 31% and 36% for patients treated with azacitidine and decitabine respectively with no significant toxicity.

Given our previous experience and considering the above data in support of lower doses regimen we propose to evaluate in a phase II Bayesian design the efficacy of DAC versus AZA versus standard AZA (5 days) in patients with low and intermediate-1 risk MDS transfusion-dependent versus BSC in patients with low and intermediate-1 risk MDS transfusion-independent .

III. BACKGROUND DRUG INFORMATION

A. Decitabine:

Decitabine (Dacogen™, 5-aza-2'-deoxycytidine) is an analogue of the natural nucleoside 2'- deoxycytidine. It is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro,* which is achieved at concentrations that do not cause major suppression of DNA synthesis. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

In solid tumor patients who received 72-hour infusion of decitabine at 20 to 30 mg/m^2/day, decitabine pharmacokinetics were characterized by a biphasic disposition. The total body clearance (mean ± SD) was 124 ± 19 L/hr/m2, and the terminal phase elimination half-life was 0.51 ± 0.31 hr. The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. *In vitro* metabolism studies have suggested that decitabine is not a substrate for the human liver cytochrome P450 enzymes. As plasma protein binding of decitabine

is negligible (<1%), interactions due to displacement of more highly protein bound drugs from plasma proteins are not expected.

Decitabine has been approved by the Food and Drug Administration (FDA) in the United States for treatment of patients with MDS including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups.

The major toxicity is myelosuppression. Decitabine may also cause fever, cough, constipation, diarrhea, nausea, vomiting, edema, headache, insomnia and hyperglycemia. Rarely, decitabine can cause allergic reactions.[4]

B. Azacitidine (AZA)

Azacitidine, a ring analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and DNA synthesis and metabolism. Since the early 1970s, azacitidine has been investigated in the US for the treatment of acute leukemia. Clinical trials have focused primarily on patients with disease refractory to conventional chemotherapy. These investigations indicated azacitidine has activity in the treatment of acute myelogenous leukemia (AML). Clinical trials subsequently have been conducted to evaluate the effects of azacitidine in a variety of other malignant and hematologic

disorders, including solid tumors, hemoglobinopathies (thalassemia and sickle cell anemia), and myelodysplastic syndromes (MDS).

Toxicology studies have been conducted in mice, rats, dogs, and Rhesus monkeys. Most of the studies were performed during the 1970s and early 1980s according to existing guidelines and standards in place during that period. The nonclinical studies identified the bone marrow, liver, kidneys, and lymphoid tissues (spleen, lymph nodes) as the main target organs of toxicity. In single-dose studies, the lethal dose of azacitidine after intravenous (IV) administration in mice, rats, and dogs was approximately 250 mg/m^2. Repeated daily dosing appears to increase the toxicity of azacitidine. The genotoxicity of azacitidine is consistent with that of other nucleoside analogs that interact with nucleic acids. Likewise, similar to other agents with cytostatic properties, azacitidine was embryotoxic and reduced the reproductive performance in mice and rats. It is important to note that animal study data is superseded in many respects by the extensive clinical safety data collected in the last two decades.

Limited azacitidine pharmacokinetic data are currently available. Based on plasma concentrations of total radioactivity (which represent parent drug plus circulating metabolites), azacitidine is rapidly absorbed when given subcutaneously (SC), with maximum plasma concentrations found 0.5 to 2 hours after dosing. Azacitidine and/or its by-products are rapidly cleared by the kidneys. The half-lives and percent radioactivity recovered in urine are similar for the IV and SC routes of administration.

The effects of renal or hepatic impairment, gender, age, and race on the pharmacokinetics of azacitidine have not been studied.

In 1985, the Cancer and Leukemia Group B (CALGB) study investigators began clinical trials with azacitidine in MDS patients under the auspices of the National Cancer Institute (NCI). Results from the three studies conducted by the CALGB (Protocols 8421, 8921, and 9221) have been published. The first two CALGB studies (Protocol 8421 and Protocol 8921) were uncontrolled Phase 2 investigations. The most recent CALGB study (Protocol 9221) was a Phase 3 investigation that compared azacitidine to supportive care alone. The azacitidine dose investigated in the CALGB studies was 75 mg/m2/day for 7 days, repeated on a 28-day cycle. Azacitidine was administered by continuous IV infusion in the first study (Protocol 8421), and by SC injection in the two studies that followed. The dose was adjusted based on toxicity and clinical response. In the Phase 3 investigation (Protocol 9221), azacitidine produced higher response rates than supportive care alone. In addition, azacitidine prolonged the time to transformation to AML or death.

The efficacy of azacitidine to treat MDS also was evaluated in 7 open-label studies conducted outside the CALGB protocols. The dosage regimen used in 6 of these studies was 75 mg/m^2 given daily for 7 days every 3-4 weeks by SC injection in 4 studies, SC or IV in 1 study, and the route was not specified in the last study. The dosage regimen used in the seventh study was 5-35 mg/m^2/day given by continuous IV infusion for 14 days. The lowest response rate was found in this seventh study, which

suggests the mechanism of 5-azacitidine's activity requires repeated administration of a minimally effective dose to achieve improvement in hematologic parameters.

As with other antimetabolites, bone marrow suppression (leukopenia, thrombocytopenia) is a common adverse event associated with azacitidine. However, myelosuppression generally occurs more often and with greater severity at doses higher than those used to treat MDS. Gastrointestinal toxicity (ie, nausea, vomiting, and diarrhea) can limit the dose of azacitidine in any patient population. Infrequent adverse effects include neuromuscular aches, generalized weakness, renal tubular acidosis, and liver enzyme abnormalities. Erythema and burning at the injection site can occur following SC administration, which usually resolves within 24-72 hours.

Azacitidine is approved for all patients with MDS using FAB criteria (up to 30% blasts).

IV. Eligibility criteria

Inclusion criteria:

- Sign an IRB-approved informed consent document.
- Age ≥18 years.
- IPSS low- or intermediate-1–risk MDS, including CMML-1
- ECOG performance status of ≤ 3 at study entry.
- Organ function as defined below:
    - Serum creatinine ≤ 2 mg/dL
    - Total bilirubin ≤ 2 x ULN
    - ALT (SGPT) ≤ 2 x ULN
    - AST (SGOT) </= 2 x ULN

- Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days and will also need to use contraceptives. Men must agree not to father a child and agree to use a condom if his partner is of child bearing potential.

Exclusion Criteria:

- Breast feeding females
- Prior therapy with decitabine or azacitidine

V. Treatment plan

1. Study design

Transfusion-dependent subjects will be randomized to AZA 75 mg/m^2 IV/SC for 5 days, AZA 75 mg/m^2 IV/SC for 3 days, or DAC 20 mg/m^2 IV for 3 days on an even basis at the beginning, then, based on efficacy and following a Bayesian design, patients will be assigned to the superior arm.

Transfusion-independent subjects will be randomized to either BSC or one of the 3 arms mentioned above on an even basis at the beginning, then, based on efficacy and following a Bayesian design, patients will be assigned to the superior arm.

Transfusion-independent subjects assigned to BSC will be assigned to one of the 3 above arms once they start requiring blood transfusion. That would be considered an event.

Transfusion-dependent group will be defined as patients requiring blood transfusion for MDS or CMML-1 at any time.

2. Treatment plan

Patients will be randomized to receive:

Decitabine 20 mg/m^2 IV daily for 3 days (days 1-3) approximately every 28 days

or

Azacitidine 75 mg/m^2 SC or IV daily for 3 days (days 1-3) approximately every 28 days

or

Azacitidine 75 mg/m^2 SC or IV daily for 5 days (days 1-5) approximately every 28 days

or

BSC (for transfusion-independent subjects only)

Patients may receive their second course of therapy without interruption, regardless of their degree of myelosuppression. After the first course of therapy, the interval between subsequent cycles of therapy could be shortened or prolonged at the discretion of the investigator. Subsequent cycles can be given prior to peripheral blood count recovery if considered to be in the best interest for the patient and after discussion with the principal investigator and the discussion documented in the patient's medical record. If study drug related prolonged myelosuppression (≥42 days of absolute neutrophil count [ANC] <1 x 10^9/L and platelet count <30 x 10^9/L) is observed after cycle 2, subsequent cycles may be given at the next lower dose (DAC, 15 mg/m^2/day, then 10 mg/m^2/day, then 5 mg/m^2/day; AZA, 56 mg/m^2/day, then 37 mg/m^2/day, then 18 mg/m^2/day) after recovery (ANC ≥1 x 10^9/L and platelet count >50 x 10^9/L) and subsequent cycles of

AZA. Granulocyte-colony stimulating factor for fever of unknown origin, infection, and/or ANC <0.75 x 10^9/L can be administered.

Dose reductions can also be made in other clinical situations where this step is considered to be in the best interest for the patient and after discussion with the principal investigator and the discussion documented in the patient's medical record. The following table is a suggestion for dose modifications in subsequent treatment courses:

Table 1: Dose levels adjustment

Dose level	AZA (mg/m^2)	DAC (mg/m^2)
-1	56	15
-2	37	10
-3	18	5

VI. BASELINE AND PER-TREATMENT EVALUATION

Baseline

1. A complete history and physical examination within 14 days prior to study entry.
2. CBC, differential platelet count.
3. Creatinine, bilirubin, ALT or AST,
4. Bone marrow aspirate and/or biopsy with cytogenetics (if bone marrow not done within 6 weeks and cytogenetics (if previously abnormal) within 3 months prior to study entry.

5. Serum or urine pregnancy test within 7 days of treatment start for women of childbearing potential
6. Documentation of frequency of transfusions (PRBC and Platelets) prior to start of each cycle
7. Documentation of any prior administration of growth factors and ESA

Prestudy laboratory tests must be obtained within 14 days of registration.

During therapy

1. CBC, differential, and platelet count once monthly prior to start of each cycle (the differential may be omitted when the WBC is < 0.5 x 10^9/L)

2. Creatinine, bilirubin, ALT or AST once monthly prior to start of each cycle.

3. Bone marrow aspirate and/or biopsy to confirm response, to be performed after cycle 2 then every 3 cycles for the first year, then every 6 cycles thereafter. All bone marrows will be performed by the registering center, not in the local MD office.

4. Conventional cytogenetics to be performed after cycle 2 then every 3 cycles for the first year, then every 6 cycles thereafter

5. Documentation of frequency of transfusions (PRBC and Platelets) prior to start of each cycle.

6. Documentation in the medical record of any grade 3 or higher possibly, probably, definitely related adverse events that have occurred prior to start of each cycle. For guidelines on SAE Reporting and AE entry for Case Report

Forms (CRF), please refer to Appendix A (for MD Anderson) and Appendix G (for Participating Institutions).

7. Documentation of any prior administration of growth factors and ESA prior to start of each cycle

Table 2: Evaluation

Test	Pre-treatment	During treatment
CBC, differential platelet count	within 14 days of treatment start	Monthly prior to start of each cycle (+/- 7 days)
Creatinine, bilirubin, ALT or AST	within 14 days of treatment start	Monthly prior to start of each cycle (+/- 7 days)
Bone marrow aspirate	Within 6 weeks prior to study entry	after cycle 2 then prior to every 3 cycles for the first year, then prior to every 6 cycles thereafter
Cytogenetics	Within 3 months prior to study entry	after cycle 2 then prior to every 3 cycles for the first year, then prior to every 6 cycles thereafter
Serum or urine pregnancy test for woman of childbearing potential	within 7 days of treatment start	
Transfusion history documented	Prior to study entry	Prior to start of each cycle
Growth factors and ESA documentation	Prior to study entry	Prior to start of each cycle

Follow-Up

Following completion of active treatment and while still on study, patients will be followed for survival approximately every 6 to 12 months for up to 5 years. This follow up can either be done as a visit to the study doctor's clinic or via telephone call to the patient.

Chemotherapy administration

If the study doctor decides it is acceptable, enrolled subjects may be allowed to receive treatment from their local cancer doctor following cycle 1 (appendix B). However, enrolled subjects will have to return to the study doctor's clinic at least every 3 cycles for study visits.

Supportive care

Supportive measures such as prophylaxis for tumor lysis syndrome, analgesics, blood transfusions, antimicrobials and G-CSF for fever/infection are permitted as clinically indicated. Growth factor and ESA administration while on study will be documented.

VII. STUDY END POINTS

Primary:

1. Event-free survival rates of two different drugs DAC versus AZA on an abbreviated schedule and a standard arm of AZA given over 5 days in patients with low-risk MDS transfusion-dependent and to BSC in patients with low-risk MDS transfusion-independent. Events are defined as no response, loss of response, progression to higher risk category MDS, transformation to AML, discontinuation of therapy due to side effects, or death.

Secondary:

1. Overall improvement rate (OIR), defined as complete remission (CR), partial remission (PR), marrow CR (mCR), or hematologic improvement (HI), measured using each patient's best response with the 2 different agents. Response will be

assessed using the modified MDS International Working Group 2006 criteria. The best response within the first two cycles will be the OIR for each treatment arm that will be used in the adaptive randomization algorithm.

2. Transfusion independence (defined as being transfusion-free for ≥8 consecutive weeks between the first dose and study treatment discontinuation)
3. Cytogenetic response, if applicable
4. Clinical benefit
5. Duration of response
6. Time to transformation into AML
7. Overall survival
8. Safety profile

VII. CRITERIA FOR WITHDRAWAL

Reasons for withdrawal include:

• Withdrawal of consent or the subject refuses to continue treatment and/or procedures/observations.

• Relapse/progression unless the treating physician determines that the patient has achieved clinical benefit, at which time further therapy on protocol may be permitted with approval from the PI and the discussion documented in the patient's medical record.

• No response after at least 6 courses unless the treating physician determines that the patient has achieved clinical benefit, at which time further therapy on protocol may be permitted with approval from the PI and the discussion documented in the medical

record. A bone marrow biopsy and/or aspirate is required to confirm that the patient has not achieved a response.

• Intercurrent illness preventing further administration of protocol treatment,

• Unacceptable toxicity that in the opinion of the investigator makes continued therapy unsafe.

VIII. CRITERIA FOR RESPONSE

The response criteria recommended by the MDS International Working Group 2006. Responses must be verified, documented, and signed in the local medical record by the local PI. (Patients are considered non evaluable if they have received less than 2 courses of treatment, unless there is clear disease progression.)

Definitions:

Complete Response (CR):

Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines; persistent dysplasia will be noted

Peripheral blood:

Hgb ≥ 11 g/dL

Platelets ≥ 100×10^9/L

Neutrophils ≥ 1.0×10^9/L

Blasts 0%

Partial response (PR):

All CR criteria if abnormal before treatment except: bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%

Marrow CR:

Blasts ≤ 5% and decrease by ≥ 50% from baseline (baseline blasts should be above 5% to be eligible for marrow CR)

Hematologic Improvement (HI): (responses must last at least 8 weeks)

Erythroid response [HI-E; (if pretreatment Hgb < 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 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.

Platelet response [HI-P; ((if pretreatment Platelet count < 100 x 10^9 /L)]: Absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L platelets, or increase from < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%.

Neutrophil response [HI-N; (pretreatment, ANC < 1.0 × 10^9/L)]: At least 100% increase and an absolute increase > 0.5 × 10^9/L

Progression/Relapse after hematological improvement: ≥1 of the following: ≥50% decrement from maximum response levels in granulocytes or platelets; ↓ in Hgb by ≥1.5 g/dL; transfusion dependence

Stable Disease: Not satisfying criteria for Complete Remission, Partial Response, Marrow CR, Hematologic Improvement or Progression/Relapse.

IX. REPORTING REQUIREMENTS

All adverse and serious adverse events will be recorded and reported according to the Leukemia-Specific Adverse Events (appendix A). The MD Anderson Leukemia

Department will report SAEs in accordance with MD Anderson IRB policies and procedures and Appendix A of the protocol.

Participating Multicenter Institutions SAE requirements will be followed as written in the Data Quality Management Plan.

X. Randomization

The Department of Biostatistics at MD Anderson will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) for patients enrolled on this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

XI. Data Safety Monitoring

A data safety monitoring board (DSMB) at MD Anderson will monitor the trial for the safety.

XII. STATISTICAL CONSIDERATIONS

General Description

This is an adaptive randomized phase II trial for low-risk MDS patients. Regarding the patients transfusion status, patients can be categorized as transfusion dependent and transfusion independent patients. It is expected that there will be half of the transfusion-dependent patients and half of transfusion-independent patients. For transfusion dependent patients, the goal is to compare three treatment arms: 1) DAC, 2) AZA3 (treatment of 3 days), and 3) AZA5 (treatment of 5 days). For transfusion independent patients, the goal is to compare four treatment arms: 1) best supportive care (BSC) 2) DAC, 3)AZA3 (treatment of 3 days), and 4) AZA5 (treatment of 5 days). The primary outcome is event free survival (EFS) defined as the time from beginning of treatment till an event occurs or last follow-up. For transfusion independent patients, the events includes lack of response, requirement of blood transfusion, progression to advanced stages of disease, transformation into AML, discontinuation of therapy due to side effects, and death. The patients who change from transfusion independence to transfusion dependence under BSC will be enrolled in transfusion-dependent group and adaptively assign to the three treatment arms, that is, DAC, AZA3, or AZA5. For transfusion dependent patients, the events includes lack of response, progression to advanced stages of disease, transformation into AML, discontinuation of therapy due to side effects, and death.

Study design

The maximum number of patients accrued will be 240. There will be two parallel adaptive randomization trials for transfusion dependent (N=120) and transfusion independent (N=120) patients respectively. Since we are expecting patients under BSC

will eventually become the transfusion dependent, it is assumed that initially there will be 120 patients under transfusion-dependent group, and the total number increases to about 150 after enrolling the approximate 30 patients under BSC.

Part I Transfusion dependent patients (N=150)

Design

Patients will be randomized using a Bayesian adaptive algorithm. Patients will be randomized fairly among the three arms at the start of the trial (for the first 30 patients), that is, 10 patients per arm. Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of event free survival. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 30 and a maximum of 150 patients will be accrued. There will be 12 months follow up after the last patient is accrued with an anticipated accrual rate of 5 patients per month.

Denote the event free survival for the patients in the three arms (DAC; AZA3; AZA5) as T_i for i=1,2,3. Assume the T_i is independent exponential with median μ_i. And each μ_i independently follows an inverse gamma distribution with parameter α=2.05, β=7.34. The parameters were chosen to set the mean of the prior equal to 7 (the historical median EFS in months) and a variance of 1000. For each patient, the randomization probability for treatment arm i will be based on the posterior probability that it has the largest median EFS. For example, for arm 1, the posterior probability is $\pi_1=Pr(\mu_{1>} \mu_i)$ for i=2,3. In order to avoid aggressively favoring one arm too early in a large trial, instead of

assigning patients with posterior probability, we use its square root transformation as in the following formula to assign patients:

$Aa=\frac{\sqrt{\pi_1}}{\sqrt{\pi_1}+\sqrt{\pi_2}+\sqrt{\pi_3}}$, where Aa is the probability of assigning patients to arm 1, π_1 is the posterior probability that arm 1 is superior, etc.

If at any point during the trial $Pr(\mu_i>\max\{u_j, \text{ for all } j \neq i\} \mid data) > 0.975$, the trial will be terminated and treatment i will be selected as superior. If at any point during the trial $Pr(\mu i>\max\{uj, \text{ for all } j \neq i\} \mid data)<0.025$, then accrual to the arm i will be suspended, and will be reopen if in the future, the changes in other arms make this probability $Pr(\mu i>\max\{uj, \text{ for all } j \neq i\} \mid data) \geq 0.025$. If the maximum accrual is reached and $Pr(\mu_i>\max\{u_j, \text{ for all } j \neq i\} \mid data) > 0.8$ (< 0.2), treatment i will be selected as superior (inferior). A treatment arm will be dropped at any point during the trial if $Pr(\mu_i > 7 \mid data) < 0.1$, for i=1,2,3. Table 3 given below summarizes operating characteristics of the design. The historical median EFS is assumed to be 7 months with the accrual rate of 5 patients per month. The trial will be stopped early and a treatment selected as being “better” if the probability that one treatment’s median EFS is larger than the other’s EFS exceeds 0.975. If the trial does not stop early and the maximum 150 patients are accrued, a treatment is selected as being “better” if the probability that one treatment’s median EFS is larger than the other’s EFS exceeds 0.8. A treatment arm will be dropped at any point during the trial if the probability that the treatment’s median EFS is larger than 7 months is less than 0.1. The “# of patients treated” row is

the average number of patients treated on a given arm under the given scenario. When the medians all equal to 7 months (scenario 1), the probability of selecting one of the three arms (i.e., a false positive result) is at most 9.8%. The probability of selecting the best treatment (i.e., a true positive result) for scenario 2, when the medians EFS are 7, 7, and 12 months for the arms, respectively, are 0.7%, 0.7%, and 88%.

Table 3: simulation results (simulation=5000) for transfusion dependent patients with the minimum randomization probability set as 0.1 and tuning parameter as 0.5

		treatment		
		DAC	AZA3	AZA5
1	True Median EFS	7	7	7
	# of patients treated	40.1	40.6	40.5
	Pr(selected)	0.086	0.095	0.098
	Pr(selected early)	0.003	0.006	0.005
	Pr (stopped early)	0.321	0.317	0.316
2	True Median EFS	7	7	12
	# of patients treated	28.5	28.6	54.2
	Pr(selected)	0.007	0.007	0.88
	Pr(selected early)	0.0002	0.001	0.188
	Pr (stopped early)	0.806	0.814	0.028
3	True Median EFS	3	3	3
	# of patients treated	10.5	10.5	10.5
	Pr(selected)	0.046	0.043	0.045
	Pr(selected early)	0.001	0.001	0.001
	Pr (stopped early)	0.779	0.779	0.777
4	True Median EFS	7	9	14
	# of patients treated	23.6	36.2	57.4
	Pr(selected)	0.003	0.013	0.882
	Pr(selected early)	0.0002	0.003	0.217
	Pr (stopped early)	0.921	0.686	0.0162
5	True Median EFS	7	12	12
	# of patients treated	23.1	56.6	55.6
	Pr(selected)	0.001	0.242	0.235
	Pr(selected early)	0.0002	0.04	0.036
	Pr (stopped early)	0.877	0.12	0.13

6	True Median EFS	4	7	12
	# of patients treated	13.3	29.5	45.3
	Pr(selected)	0.001	0.014	0.883
	Pr(selected early)	0	0.002	0.357
	Pr (stopped early)	0.994	0.866	0.036
7	True Median EFS	4	7	10
	# of patients treated	13.9	34.1	48.1
	Pr(selected)	0.001	0.039	0.757
	Pr(selected early)	0	0.004	0.194
	Pr (stopped early)	0.987	0.661	0.083

Toxicity Monitoring

Evidence of toxicity will be monitored closely for all patients. As expected, there will be 150 transfusion-dependent patients enrolled which includes the 120 patients initially recruited and another 30 patients who have changed from transfusion independence to dependence. With 10 patients fairly randomized to each arm, there will be at most 120 patients being adaptively assigned to any of the three arms. Taking the initial 10 patients assigning to each arm, the maximum number of patient per treatment arm will be 130. For each treatment, treatment will be terminated if $Pr((\theta_E > 0.2 \mid data) > 0.9$, where θ_E is the proportion of any grade 3 or higher treatment related non-hematologic toxicities. It is assumed to follow a non-informative prior of Beta (0.4, 1.6) That is, the trial will be terminated if at any time during the study, there is a more than 90% chance that the average rate of grade 3 or greater treatment related non-hematologic toxicity is more than 20%. Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for toxicity. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer

Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

Table 4: stopping boundaries for toxicity

Number of patients evaluated	Stop the trial if there are this many treatment related toxicities
10	5-10
20	7-20
30	10-30
40	12-40
50	15-50
60	17-60
70	19-70
80	21-80
90	24-90
100	26-100
110	28-110
120	30-120

Table 5: Operating characteristics of safety monitoring

True Toxicity Rate	Prob (stop the trial early)
0.15	0.04
0.2	0.25
0.25	0.68
0.3	0.94

Part II: Transfusion independent patients (N=120)

Design

Patients will be randomized using a Bayesian adaptive algorithm. Patients will be randomized fairly among the four arms at the start of the trial (for the first 40 patients), that is, 10 patients per arm. Thereafter, as the trial progresses and data accrue, the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of event free survival. Therefore, each successive patient is more likely to receive the treatment with better results, on average. A minimum of 40 and a maximum of 120 patients will be accrued. There will be 12 months follow up after the last patient is accrued with an anticipated accrual rate of 4 patients per month.

Denote the event free survival for the patients in the four arms (BSC; DAC; AZA3; AZA5) as T_i for i=1,2,3,4. Assume the T_i is independent exponential with median μ_i. And each μ_i independently follows an inverse gamma distribution with parameter α=2.14, β=13.73. The parameters were chosen to set the mean of the prior equal to 12 (the historical median EFS in months) and a variance of 1000. For each patient, the randomization probability for treatment arm i will be based on the posterior probability that it has the largest median EFS. For example, for arm 1, the posterior probability is $\pi_1=Pr(\mu_1 > \mu_i)$ for i=2,3,4. In order to avoid favoring one arm earlier in a large trial, instead of assigning patients with posterior probability, we use the following formula to assign patients:

$Aa=\frac{\sqrt{\pi_1}}{\sqrt{\pi_1}+\sqrt{\pi_2}+\sqrt{\pi_3}+\sqrt{\pi_4}}$, where Aa is the probability of assigning patients to arm 1, π_1 is the posterior probability that arm 1 is superior, etc.

If at any point during the trial $Pr(\mu_i > \max(u_j \text{ for all } j \neq i) | \text{data}) > 0.975$ (< 0.025), the trial will be terminated and treatment i will be selected as superior (inferior). If the maximum accrual is reached and $Pr(\mu_i > \max\{u_j \text{ for all } j \neq i\} | \text{data}) > 0.8$ (< 0.2), treatment i will be selected as superior (inferior). A treatment arm will be dropped at any point during the trial if $Pr(\mu_i > 12 | \text{data}) < 0.1$, for i=1,2,3,4. Table 6 given below summarizes operating characteristics of the design. The historical median EFS is 12 months. The tables below assume an accrual rate of 4 patients per month. The trial will be stopped early and a treatment selected as being "better" if the probability that one treatment's median EFS is larger than the other's EFS exceeds 0.975. If the trial does not stop early and the maximum 120 patients are accrued, a treatment is selected as being "better" if the probability that one treatment's median EFS is larger than the other's EFS exceeds 0.8. A treatment arm will be dropped at any point during the trial if the probability that the treatment's median EFS is larger than 12 months is less than 0.1. The "# of patients treated" row is the average number of patients treated on a given arm under the given scenario. When the medians all equal to 12 months (scenario 1), the probability of selecting one of the three arms (i.e., a false positive result) is at most 3.7 %. The probability of selecting the best treatment (i.e., a true positive result) for scenario 5, when the medians TTP are 12, 12, and 24 months for the arms, respectively, are 0.1%, 0.04%, 0.2%, and 79.7%.

Table 6: simulation results (simulation=5000) for transfusion dependent patients with the minimum randomization probability set as 0.1 and tuning parameter as 0.5

			treatment		
		BSC	DAC	AZA3	AZA5
1	True Median EFS	12	12	12	12
	# of patients treated	29	28.9	28.8	28.6

	Pr(selected)	0.037	0.036	0.034	0.029
	Pr(selected early)	0.001	0.001	0.001	0.0004
	Pr (stopped early)	0.235	0.233	0.253	0.244
2	True Median EFS	7	7	7	7
	# of patients treated	14.2	14.3	14.3	14.4
	Pr(selected)	0.029	0.024	0.027	0.027
	Pr(selected early)	0.0002	0	0.0002	0.0002
	Pr (stopped early)	0.764	0.774	0.773	0.755
3	True Median EFS	7	12	15	20
	# of patients treated	13.2	24.2	32.3	42
	Pr(selected)	0	0.003	0.035	0.496
	Pr(selected early)	0	0.0004	0.003	0.036
	Pr (stopped early)	0.971	0.58	0.296	0.032
4	True Median EFS	12	12	12	20
	# of patients treated	24	24.3	23.8	40.7
	Pr(selected)	0.003	0.004	0.006	0.572
	Pr(selected early)	0	0.0002	0.0002	0.027
	Pr (stopped early)	0.538	0.533	0.544	0.014
5	True Median EFS	12	12	12	24
	# of patients treated	22.3	22.3	22	42.5
	Pr(selected)	0.001	0.0004	0.002	0.797
	Pr(selected early)	0	0.0002	0	0.059
	Pr (stopped early)	0.713	0.719	0.721	0.006

The design software adaptive Randomization version 4.1.1. developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the OC table.

Toxicity Monitoring

Evidence of Toxicity will be monitored closely for all patients except for the patients under the BSC. With 10 patients fairly randomized to each arm of the four arms, there will be at most 80 patients being adaptively assigned to any arm. Taking the initial 10 patients assigning to each arm, the maximum number of patient per treatment arm will be 90. For each treatment, treatment will be terminated if $Pr((\theta_E > 0.2 \mid \text{data}) > 0.88$. where θ_E is the proportion of any grade 3 or greater treatment related non-hematologic toxicities attributed to study drug and is assumed to follow a non-informative prior of Beta (0.4, 1.6) That is, the trial will be terminated if at any time during the study, there is a more than 88% chance that the average rate of grade 3 or greater treatment related

non-hematologic toxicity is more than 20%. Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for toxicity. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the futility/toxicity stopping boundaries and the OC table.

Table 7: stopping boundaries for toxicity

Number of patients evaluated	Stop the trial if there are this many treatment related toxicities
10	4-10
20	7-20
30	9-30
40	12-40
50	14-50
60	17-60
70	19-70
80	21-80

Table 8: Operating characteristics of safety monitoring

True Toxicity Rate	Prob (stop the trial early)
0.15	0.08
0.2	0.28
0.25	0.62
0.3	0.88

Analysis Plan

Data analysis will be performed using SAS or S-plus, as appropriate. All patients will be included in the intent-to-treat analysis for efficacy. Demographic and disease characteristics of the patients at registration will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. The EFS under different treatment will be estimated by Kaplan-Merier method, along with the 95% credible intervals, and logrank test will be used to assess the EFS differences under different treatments. The Cox proportional hazards model will be used to analyze the effects of treatments and other covariates.

Figure 1. Survival of Patients with Low Risk MDS According to the Lower Risk Prognostic Model

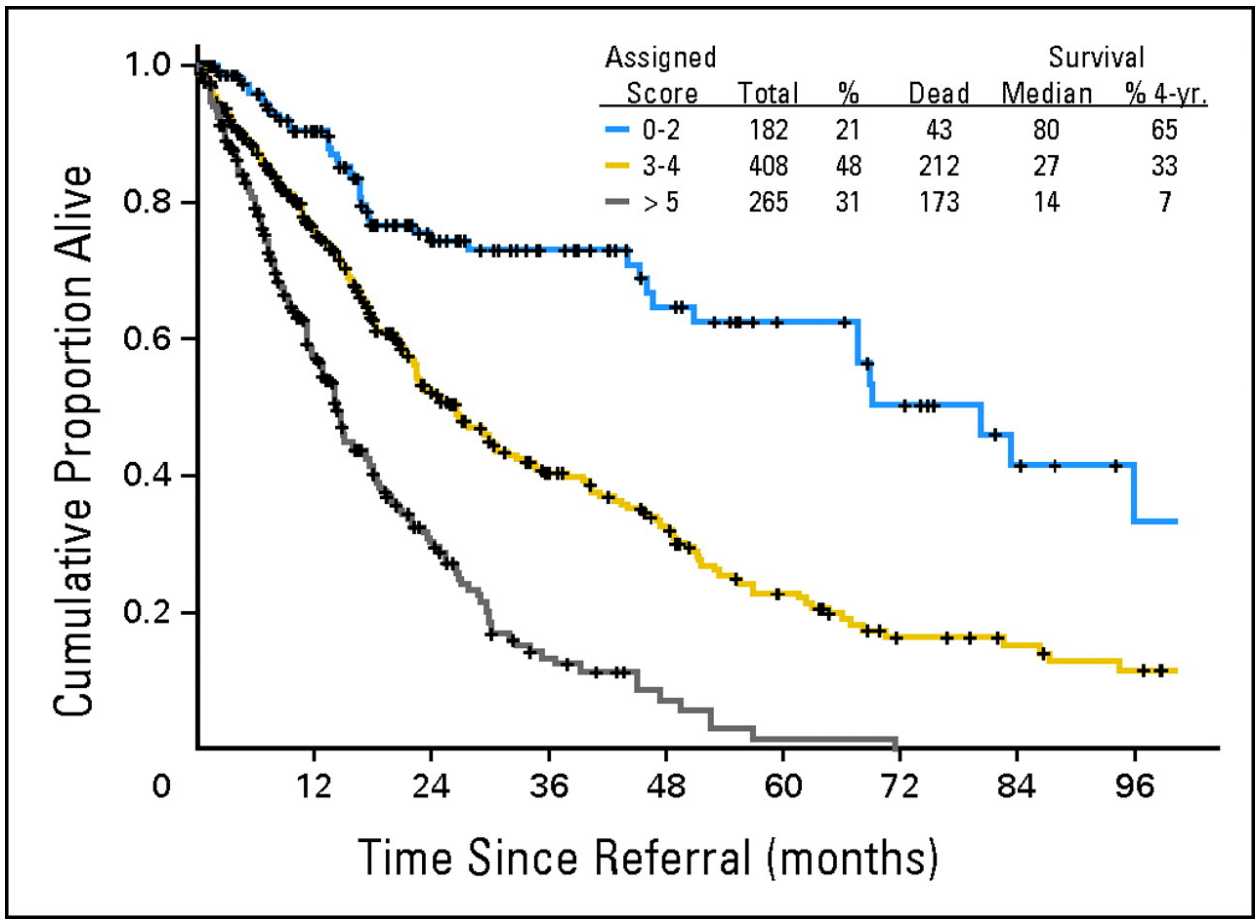

Table 9. Prognostic Model of Lower-Risk Myelodysplastic Syndrome: Multivariate Analysis Poor-Prognosis Parameters and Assigned Score

Adverse Factor	*P*	Assigned Score
Unfavorable cytogenetics	< .001	1
Age ≥ 60 years	< .001	2

Adverse Factor	*P*	Assigned Score
Hgb < 10 g/dL	< .001	1
Plt, $\times 10^9$/L		
< 50	< .001	2
50-200	< .001	1
BM blasts ≥ 4%	< .001	1

Table 10. Prognostic Model of Lower-Risk Myelodysplastic Syndrome: Estimated Survival Outcome Within Each Score Range

Score	No. of Patients	Median Survival (months)	4-Year Survival Rate (%)
0	11	NR	78

Score	No. of Patients	Median Survival (months)	4-Year Survival Rate (%)
1	58	83	82
2	113	51	51
3	185	36	40
4	223	22	27
5	166	14	9
6	86	16	7
7	13	9	NA

XI. References:

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Appendix A

Appendix Subtitle:

Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-" All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment" and Guideline for Good Clinical Practice 4.11.1 "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting".

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Adverse Events (AEs) will be evaluated according to current CTC version in each protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

1. *Myelosuppression related events (due to disease or leukemia therapy)*
    a. *febrile or infection episodes not requiring management in the intensive care unit*
    b. *epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage*
    c. *anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis*
2. *Disease related events*
    a. *symptoms associated with anemia*
        i. *fatigue*
        ii. *weakness*
        iii. *shortness of breath*
    b. *electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)*
    c. *chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)*
    d. *coagulation abnormalities*
    e. *disease specific therapy (induction, maintenance, salvage, or stem cell therapy)*

f. alopecia
g. bone, joint, or muscle pain
h. liver function test abnormalities associated with infection or disease progression
i. disease progression

3. General therapy related events
a. catheter related events
b. renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy
c. rash related to antibiotic use

4. Hospitalization for the management of any of the above expected events

Abnormal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Serious Adverse Event Reporting (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose

Results in death
Is life-threatening
Requires inpatient hospitalization or prolongation of existing hospitalization
Results in persistent or significant disability/incapacity
A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

(Sections relating to ORERM are for MDACC held IND studies only.)

Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported to the IRB as an SAE if deemed appropriate by the Principal Investigator, the IND Sponsor, or the Office of Research Education and Regulatory Management (ORERM).

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to ORERM, regardless of attribution (within 5 working days of knowledge of the event). **Hospitalizations for the management of any expected adverse events (previously described) will not have an**

expedited report but it will be included in the annual report via the SAE log.

All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in ORERM.

The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to ORERM.

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse event that occur after the 30 day time period that is related to the study treatment must be reported to IRB and ORERM. This may include the development of a secondary malignancy.

Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager ORERM) according to 21 CFR 312.32.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Reporting of external SAEs

The MDACC institutional policy for reporting of external SAEs will be followed.

Version 1.0/ Sept 09

IRB Approval Date: September 23, 2009

Appendix B

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

mm/dd/yyyy

Dear Doctor,

_(Name)___ is a mutual patient of ours who has been enrolled on Protocol 2014-0112: Phase II Randomized Study of Lower Doses of Decitabine versus Azacitidine (3 day schedule) versus Azacitidine (5 day schedule) in MDS Patients with Low and Intermediate-1 Risk Disease Transfusion-Dependent versus Best Supportive Care (BSC) in MDS Patients with Low and Intermediate-1 Risk Disease Transfusion-Independent at M.D. Anderson Cancer Center in Houston, TX from _____ to present.

The patient was randomized to treatment arm with _____. The patient's current treatment course is course ___ of this regimen. Following one cycle performed here at MD Anderson Cancer Center, this study requires enrolled patients to return to be seen in our clinic at least every three months for study visits.

__(Name)__ would like to come home for the _____treatment and interim tests, however, in order for us to support follow up at home we will need the following:

1. A confirmation of your center feasibility to perform required testing of CBC with differential and platelets at least monthly and serum bilirubin, creatinine, SGPT or SGOT once per month. More frequent testing may be performed at your discretion.
2. A faxed copy of the documented dictated or handwritten findings of visits as soon as they became available including the above monthly laboratory results, weekly progress notes/clinic notes, physician order for _____ administration, _____ medication administration records, hospital admission summary, hospital discharge summary.
3. A copy of your lab's certification.

If the above protocol requirements are not feasible to be performed at your center, please let us know so that we may arrange for other plans.

If you agree, we would ask you to sign and return this letter as confirmation that we will receive by fax, a copy of all labs, medication administration records, and a copy of the dictated or handwritten clinic visit notes regarding assessments.

The study requires enrolled patients to return to be seen in our clinic at least every three months for study visits.

A follow up visit at MDACC, for evaluation of response and additional testing is scheduled for:

_____

We have included a copy of the abstract for your convenience.

By signing below, I agree to perform all tests and evaluations as noted above, and fax all documentation to 713-745-2232.

Please fax all the above protocol documents as soon as possible to 713-745-2232.
For any questions please call the PI Guillermo Garcia-Manero, MD at 713-745-3428

Thank you for your assistance.

_____
Guillermo Garcia-Manero, M. D.
(PI of the study)

Appendix – C

MDS Clinical Research Consortium

Information to be included in all MDS CRC protocols

MDS CRC PI information

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