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MD Anderson Cancer Center

Protocol Page

Phase II Randomized Study of Lower Doses of Decitabine (DAC; 20 mg/m2 IV daily for 3 days every month) versus Azacitidine (AZA; 75 mg/m2 SC/IV daily for 3 days every month) in MDS Patients with Low and Intermediate-1 Risk Disease 2012-0507

Core Protocol Information

Short Title	DAC vs AZA in MDS Patients with Low and Intermediate-1 Risk
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Full Title:	Phase II Randomized Study of Lower Doses of Decitabine (DAC; 20 mg/m2 IV daily for 3 days every month) versus Azacitidine (AZA; 75 mg/m2 SC/IV daily for 3 days every month) in MDS Patients with Low and Intermediate-1 Risk Disease
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

2012-0507 - DAC vs AZA - May 13 2015.doc

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) in MDS Patients with Low and Intermediate-1 Risk Disease

I. OBJECTIVES

Primary:

Compare the response rates of two different drugs DAC versus AZA on an abbreviated schedule

Secondary:

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

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]

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.

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 in patients with low and intermediate-1 risk MDS.

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.
- de novo or secondary IPSS low- or intermediate-1–risk MDS, including CMML
- ECOG performance status of ≤ 3 at study entry.
- Organ function as defined below:
    - Serum creatinine ≤ 3 x ULN
    - Total bilirubin ≤ 2 x ULN
    - ALT (SGPT) ≤ 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

Patients will be randomized to either arm on an even basis at the beginning, then, based on efficacy and following a Bayesian design, patients will be assigned to the superior arm.

2. Treatment plan

Patients will randomized to receive

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

or

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

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 32 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. All patients may receive erythropoietin for hemoglobin <10 g/dL, and granulocyte-

colony stimulating factor for fever of unknown origin, infection, and/or ANC <0.75 x 10^9/L

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:

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

VI. PRETREATMENT AND PER-TREATMENT EVALUATION

Pre-treatment

1. CBC, differential platelet count.

   Creatinine, bilirubin, ALT or AST, marrow aspirate with cytogenetics (if bone marrow not done within 1 month and cytogenetics (if previously abnormal) within 3 months.
2. Molecular Diagnostic MDS Panel
3. MDS Flow Panel

During therapy

1. CBC, differential, and platelet count once monthly (the differential may be omitted when the WBC is < 0.5 x 10^9/L.)
2. Creatinine, bilirubin, ALT or AST once monthly.
3. Marrow aspirate to confirm response, to be performed after cycle 2 then every 2 to 4 cycles until response observed, then as clinically indicated
4. Molecular Diagnostic MDS Panel, if previously abnormal, if possible. Not all samples will be collected at all times.
5. Sequential MDS Flow Panel to be performed after cycle 2 then every 2 to 4 cycles until response observed, then as clinically indicated.
6. Conventional cytogenetics to be performed after cycle 2 then every 2 to 4 cycles until response observed, then as clinically indicated.

After Cycle 3

If the study doctor decides it is acceptable, you may be allowed to receive treatment from your local cancer doctor. However, you have to return to Houston at least every 3 months for one year, then every 6 months for your study visits for as long as the patient remains on study.

Supportive care

Supportive measures such as prophylaxis for tumor lysis syndrome, erythropoietin, analgesics, blood transfusions, antimicrobials and hematopoietic colony stimulating factors for treatment of cytopenias are permitted

VII. STUDY END POINTS

Primary:

1. Overall improvement rate (OIR), defined as complete remission (CR), partial remission (PR), marrow CR (mCR), or hematologic improvement (HI), measured at the end of each cycle using each patient's best response with the 2 different agents. Response will be assessed using the modified International Working Group 2006 criteria.[11] 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.

Secondary:

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

- 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.

Definitions:

Complete Response (CR):

Normalization of the peripheral blood and bone marrow with <5% bone marrow blasts, a peripheral blood granulocyte count > (1.0×10^9/ L, and a platelet count > 100×10^9/L).

Partial response (PR):

As above except for the presence of 6-15% marrow blasts, or 50% reduction if <15% at start of treatment.

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):

Platelets increase by 50% and to above 30 x 10^9/L untransfused (if lower than that pretherapy); or granulocytes increase by 100% and to above 10^9/L (if lower than that pretherapy); or hemoglobin increase by 2 g/dl; or transfusion independent; or splenomegaly reduction by > 50%; or monocytosis reduction by > 50% if pretreatment > 5 x 10^9/L.

IX. REPORTING REQUIREMENTS

All adverse and serious adverse events will be recorded and reported according to the Department of Leukemia guidelines (appendix C)

X. Randomization

The Department of Biostatistics 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 a Phase II open-label, efficacy and toxicity study of two treatment arms (lower doses of Decitabine versus Azacitidine) in subjects with low risk or intermediate-1 myelodysplastic syndrome. Patients will be enrolled to evaluate the 2 agents. In arm A, Decitabine (DAC) will be administrated 20mg/m^2 IV daily for 3 days every 28 days and in treatment B Azacitidine (AZA) will be administrated 75mg/m^2 SC or IV daily for 3 days every 28 days. For both arms, one course will be considered of 4 weeks. An adaptive randomization design will be employed to compare the efficacy between the two arms. The primary efficacy outcome is the overall improvement rate (OIR), defined as complete remission (CR), partial remission (PR), marrow CR (mCR), or hematologic improvement (HI), assessed after maximum of 2 cycles. At the end of the trial, we will estimate the probability that one arm is superior to the other. We will also evaluate toxicity on each arm. A maximum of 120 patients will be accrued, at an expected accrual rate of 3 patients per month.

Study design

Patients will be assigned to receive Decitabine or Azacitidine, using an adaptive procedure that bases assignment probabilities on observed results in preceding patients. At first, 20 patients will be assigned to each arm with equal probability. As efficacy data accrues, patient assignment to the two arms will become unbalanced in favor of the one that has the higher overall improvement rate (OIR). The OIR for both arms will be estimated with a 95% CI (similar to Bayesian highest posterior density interval).

Based on previous studies, we expect an OIR of about 23% in both arms. Therefore, we assume OIR has a prior Beta distribution (0.46, 1.54) with mean 0.23. Let OIRa and OIRb denote the overall improvement rates for arm A and arm B, respectively. Beginning with the 21st patient in each arm and for each subsequent patient, we will compare OIRa with OIRb, incorporating data from all patients with evaluable response. In order to avoid favoring one arm earlier in a large trial, instead of assigning patients with posterior probability (Pa=Pr(OIRa>OIRb|data) and Pb=1-Pa), we use the following formula to assign patients:

Aa=$\frac{\sqrt{Pa}}{\sqrt{Pa}+\sqrt{Pb}}$, Ab=1-Aa, where Aa is the probability of assigning patients to arm A, Ab is the probability of assigning patients to arm B, Pa is the posterior probability that arm A is superior to arm B and Pb is the posterior probability that arm B is superior to arm A.

If at any point during the trial Pr(OIRa>OIRb|data)>0.95(or <0.05) the schedule A(or B) will be selected as superior. If accruing information gives strong evidence that an OIR of 23% or greater is unlikely to be true for any one of the treatment arms (Pr(OIRa or OIRb>0.23|data)<0.05), assignment to that arm will be stopped. If the maximum of 120 patients is enrolled and evaluated and Pr(OIRa>OIRb|data)>0.9 (or <0.1), we will declare that arm A(or B) has a higher OIR rate than arm B (or A). Otherwise, the trial will be inconclusive. We used simulation (5,000 simulations per scenario) to evaluate the performance of the adaptive randomization procedure under several different scenarios (Table 2). There was an 86% power to select a superior arm (arm B) if the OIR rates are 20% and 40%, respectively.

Toxicity Monitoring

Evidence of Toxicity will be monitored closely in all patients. For each arm, treatment will be terminated if Pr(non hematological grade 3 or higher Toxicity >0.2 | data) >0.95, and the toxicity rate is assumed to follow a non-informative prior of Beta(0.4,1.6). Table 1 shows the simulation of the trial. The treatment will be stopped if the number of patients with study drug related toxicities equal to or greater than indicated (i.e., #pts with tox) among the number of patients accrued (i.e., #pts): 4/5, 5/10, 7/15, 8/20, 9/25, 11/30, 12/35, 13/40, 15/45, 16/50, 17/55, 18/60, 19/65, 21/70, 22/75, 23/80, 24/85, 26/90, 27/95, 28/100, 29/105, 30/110, 31/115, 33/120.

Table 1: Operating characteristics of Safety Monitoring (based on 10000 simulations)

True probability	Stop probability	Average sample size
0.15	0.02	117.7
0.2	0.15	108.1
0.25	0.51	83.3
0.3	0.87	53

Table 2: Operating characteristics of adaptive randomization design to compare DAC with AZA. Randomly assign 20 patients to each arm with equal probability before adapting the randomization, tuning parameter of 0.5, and accrual rate of 3 patients/month.

	Arm A	Arm B
OIR Rate	0.05	0.1
Expected # of Patients	20.8	20.9
Pr(Select)	0.03	0.23

Pr(Select Early)	0.01	0.11
Pr(Stop Early)	0.85	0.51
OIR Rate	0.1	0.23
Expected # of Patients	25.5	28.7
Pr(Select)	0.02	0.52
Pr(Select Early)	0.01	0.38
Pr(Stop Early)	0.86	0.13
OIR Rate	0.2	0.4
Expected # of Patients	28.9	35.9
Pr(Select)	0.01	0.86
Pr(Select Early)	0.01	0.81
Pr(Stop Early)	0.85	0.01
OIR Rate	0.23	0.23
Expected # of Patients	44.3	44
Pr(Select)	0.17	0.18
Pr(Select Early)	0.13	0.13
Pr(Stop Early)	0.26	0.24
OIR Rate	0.3	0.5
Expected # of Patients	30.7	38.6
Pr(Select)	0.01	0.85
Pr(Select Early)	0.01	0.81
Pr(Stop Early)	0.81	0.01

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 OIR for both arms will be estimated by Bayesian posterior estimates, along with the 95% credible intervals. The posterior probability that one treatment is better than the other will be computed, and the 95% credible interval of the posterior probability will also be estimated. Time to event end points, such as response duration, overall survival and

event-free survival, will be analyzed by the Kaplan-Meier method, the log-rank tests and the Cox proportional hazards models.

XI. References:

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Figure 1.

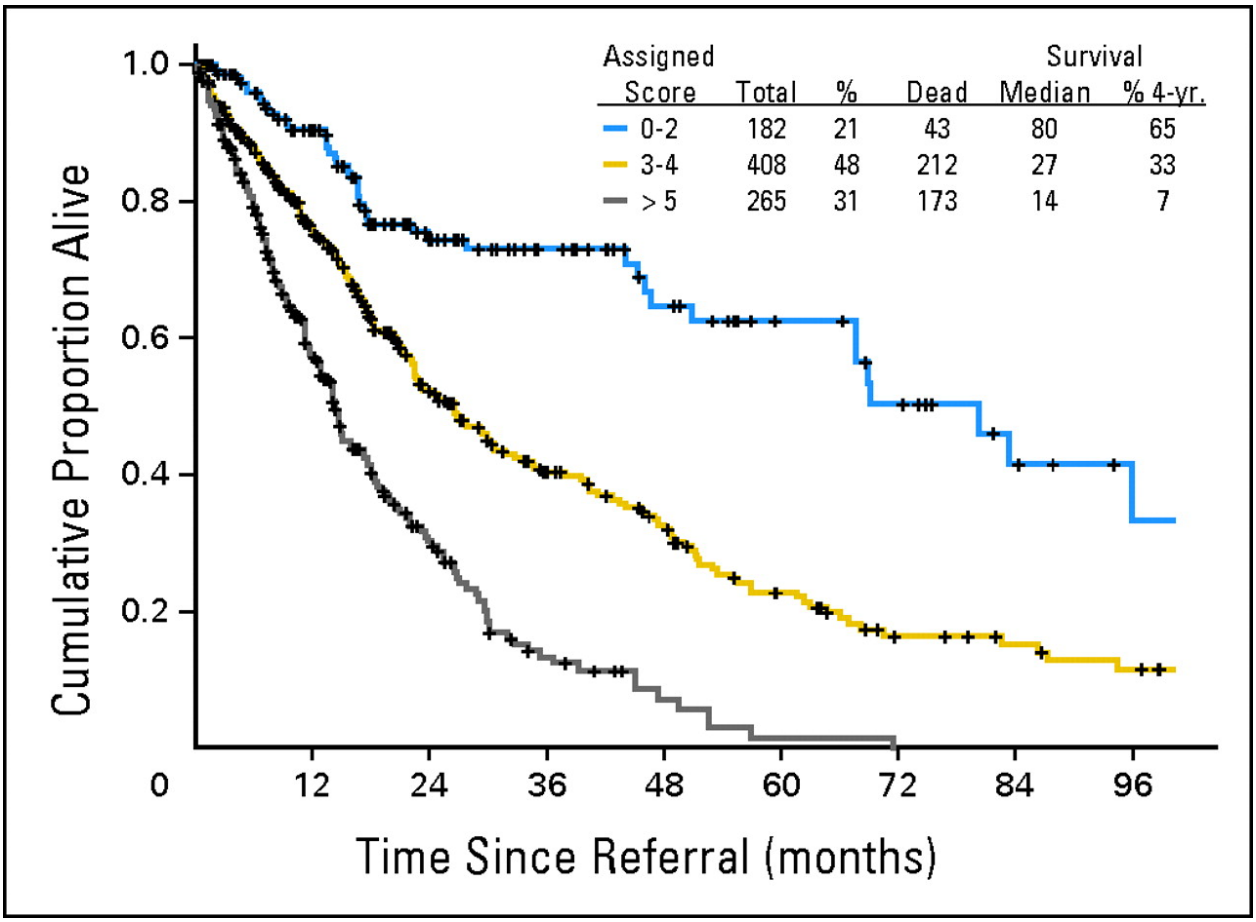
Assigned Score
Total
%
Dead
Survival Median
% 4-yr.
0-2 182 21 43 80 65
3-4 408 48 212 27 33
> 5 265 31 173 14 7
Cumulative Proportion Alive
1.0
0.8
0.6
0.4
0.2
0
12
24
36
48
60
72
84
96
Time Since Referral (months)

Table 1. 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
Hgb < 10 g/dL	< .001	1
Plt, $\times 10^9$/L		
< 50	< .001	2
50-200	< .001	1
BM blasts ≥ 4%	< .001	1

Table 2. 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
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