A single arm phase II trial of maintenance low dose 5'-azacitidine post T cell depleted allogeneic stem cell transplantation for patients with Myelodysplastic Syndrome and Acute Myelogenous Leukemia with high risk for post-transplant relapse

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	Consent and Followup
Westchester	Consent and Followup
Nassau	Consent and Followup
Commack	Consent and Followup
Monmouth	Consent and Followup

Bergen	Consent and Followup

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

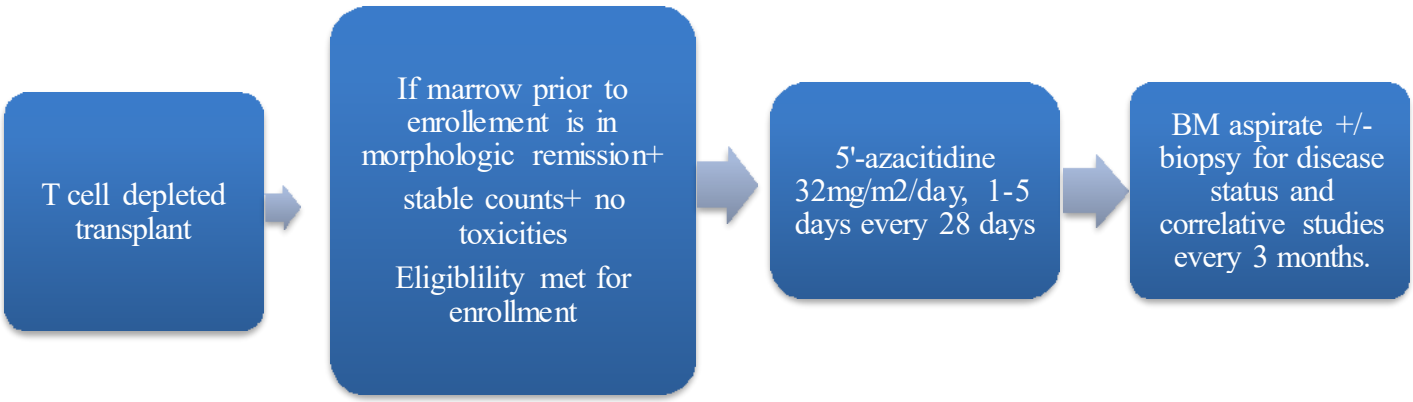
This is a single arm phase II trial to assess the efficacy of 5'-azacitidine to reduce the high relapse rate after T cell depleted (TCD) hematopoietic stem cell transplant (HSCT) from histocompatible matched or mismatched related or unrelated donor for patients with Myelodysplastic syndrome (MDS) and Acute Myelogenous Leukemia (AML) who are at high risk for relapse. Candidates for this trial will include MDS patients who have an International Prognostic Scoring System (IPSS) Intermediate-1 with poor cytogenetics and higher IPSS as well as AML patients with high risk cytogenetics and molecular mutations who on day +28-30 post T cell depleted transplant and prior to enrollment are in remission with no evidence of excess blasts or cytogenetics and/or molecular abnormalities.

Hematopoietic stem cell donors for this trial will include individuals who are 10/10 HLA matched and up to two-antigen mismatched at the HLA A, B, C DRB1 and DQB1 loci, as defined by high-resolution methods. The stem cell source can be either PBSC or bone marrow.

Patients will be prepared for transplantation with a chemotherapy only myeloablative regimen or a total body irradiation (TBI)-containing myeloablative regimen.

Maintenance therapy with 5'-azacitidine will be given at a dose of 32 mg/m^2/day for 5 consecutive days subcutaneously, every 28 days (a cycle). This treatment can start between 60-120 days posttransplant depending on patient's clinical and hematological status and will be given for up to a year post transplant.

The primary endpoint of the study is the relapse rate after treatment initiation. Patients will also be monitored for regimen related toxicities, incidence of infections, incidence and severity of acute and chronic graft versus host disease (GvHD), marrow and T cell chimerism and characteristics of immune reconstitution. Correlative studies will look at the effects of DNA methylation and relapse risk in response to treatment with 5'-Azacitidine, the effect of maintenance 5'-azacitidine on expression of cell markers that are highly specific and sensitive for the detection of residual MDS/leukemic cells as well as the effect of treatment with 5'-Azacitidine on augmenting GVL by increasing regulatory T cells.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

The aim of this prospective phase II trial is to evaluate the efficacy and confirm the safety of 5'-azacitidine after allogeneic T cell depleted (TCD) hematopoietic stem cell transplant (HSCT) from histocompatible matched or mismatched related or unrelated donor in patients with Myelodysplastic syndrome (MDS) and Acute Myelogenous Leukemia (AML) who are at high risk for relapse.

Primary objective:

To evaluate whether maintenance treatment post transplant with 5-azacitidine can reduce the relapse rate over the current standard of care for high-risk MDS and AML patients.

Secondary objectives:

1. To assess overall survival from the time of 5-azacitadine initiation.

2. To confirm the safety and tolerability of low dose 5'-azacitadine by measuring the frequency of transfusions, frequency of bleeding, frequency of serious infections, and use of G-CSF support.

3. To evaluate graft function and myeloid and T cell chimerism after administration of low dose 5'-azacitdine

4. To evaluate the incidence of acute and chronic GvHD following the initiation of 5-azacitadine.

Correlative Objectives:

Correlate treatment with low dose 5'-Azacitidine with:

1. Gene specific methylation in the hematopoietic stem cell (HSC) compartment in CD 34 cells subpopulations.

2. Recurrence of cytogenetic abnormalities in the hematopoietic stem cell (HSC) compartment in CD34 cells subpopulations.

3. Normalization of myeloid progenitor frequencies known to be altered in MDS.

4. Level of regulatory T cells (CD4+CD25-FoxP30).

3.0 BACKGROUND AND RATIONALE

3.1 Advanced Myelodysplastic Syndrome and high risk Acute Myelogenous Leukemia

Myelodysplastic syndromes (MDS) are hematopoietic stem cell disorders characterized by cytopenias with a variable risk of transformation to acute leukemia. The median survival of MDS patients with refractory cytopenias without an excess of blasts is about 5 years. The more advanced forms of MDS, defined by an increase in the blast count and presence of several cytogenetics changes, have much worse prognosis and shorter survival. The median survival for patients with refractory anemia with excess of blasts (RAEB-1, blasts 5-9%) is 1.5 years and for patients with RAEB-2 (blasts 10-19%) is one year[1]. These patients are more likely to develop and die from acute myelogenous leukemia (AML). Although a variety of non-transplant options are currently being developed and survival has improved, none of these treatments is curative in patients with advanced MDS and AML evolved from MDS.[2,3,4]

AML is also a group of heterogeneous disorders with regard to morphology and chromosome aberrations detected in the leukemic cells. Slovak et al in a SWOG/ECOG study looked at the correlation between cytogenetic changes at presentation and outcome after therapy for de-novo AML and identified 3 prognostic groups based on cytogenetics; low, intermediate and high risk with 5 years overall survival of 55%, 38% and 11%, respectively.[5] These prognostic differences among the three groups remained also after achieving remission, with worse outcome seen in the

unfavorable group, which is the group that benefited the most from allogeneic hematopoietic stem cell transplantation. Although progress has been made in defining prognostic markers for AML, a substantial percentage of patients lack a specific cytogenetic abnormality of prognostic significance. Recent studies have identified several recurrent somatic mutation in patients with AML including mutations in FLT3, NPM1, CEBPA, TETA, ASXL1, IDH1/IDH2, DNMT3A, PHF6 and many more that have prognostic implications for patients with AML, and in specifics to the intermediate cytogenetic risk group [6,7,8,9,10,11,12,13]. More recently Patel et al reported the prognostic relevance of integrated genetic profiling in AML which has a very important impact on understanding the biology of the disease, improving prognostic models and affecting therapeutic decision making.[14]

3.2 Allogeneic Hematopoietic Stem cell Transplantation for MDS and AML

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment available for patients with myelodysplastic syndrome and high risk acute leukemia[15,16,17,18,19,20,21,22,23,24,25]. However, the success rate in these patients has been hindered by two major problems: (i) a high transplant-related mortality secondary to graft-versus-host disease (GvHD) and infectious complications and (ii) a high post transplant disease relapse, particularly in patients with advanced MDS and AML.

The two main strategies that have been used to reduce GvHD are: (i) Pharmacologic manipulation of donor T cells in the patient after administration of the allograft with immunosuppressants: calcineurin inhibitors, methotrexate, mycophenolate, monoclonal antibodies such as alemtuzumab (anti CD52 antibody –Campath), and polyclonal anti T cell antibodies such as antithymocyte globulin. Although the incidence of GvHD has improved by combining these agents, this complication still remains a significant problem in HLA matched transplant and more notable in non-HLA matched transplants. (ii) Removal of donor T cells of the allograft before infusion to the recipient. This approach also removes the cells that in part mediate the graft versus-leukemia-effect and potentially could increase the risk of relapse secondary to possible loss of graft versus leukemia effect (GVL).

The MSKCC HSCT program has focused its research on T cell depletion and methods of T cell depletion that have been investigated includes: agglutination of T cells with first soybean lectin and then sheep red blood cells to deplete the T cells from marrow grafts and CD34 positive selection in peripheral blood stem cell grafts. Our initial experience with T cell depletion transplants demonstrated significant decrease in the incidence of GvHD even in mismatched transplants without increase in the incidence of relapse in patients transplanted in remission or with minimal residual disease. In our series of 232 consecutive adult leukemic patients (median age 41) transplanted with marrow grafts from HLA-matched siblings depleted of T-cells with soybean agglutinin and E rosette depletion, the incidence of grade II-IV GvHD was 3% and the incidence of chronic graft vs. host disease was 5% [24]. Similarly, in over 100 recipients of T cell depleted unrelated marrow grafts, the incidence of grade II-IV aGvHD and of chronic GvHD was 8%. In two recent studies[26,27] using ex-vivo TCD with the Miltenyi ClinMACS device in patients

with hematologic malignancies with favorable and unfavorable risk disease who received a matched[28] related donor (MRD) or matched unrelated donor (MUD) graft the incidence of GvHD was also low (aGvHD-23% and cGvHD- 7% in the MRD and aGvHD- 9% and cGvHD- 29% in the MUD).

The second main obstacle to successful allogeneic HSCT is the high relapse rate, particularly in patients with advanced MDS and AML, in whom the relapse rate can be as high as 40% in the first 2 years post transplant [29,30] and even higher-60%, for patients who are not at remission at time of transplant. [31,32]

Strategies to reduce relapse rates after allogeneic stem cell transplantation include interventions (i) before transplantation, for instance therapy with induction chemotherapy or hypomethylating agents [32], to achieve remission prior to transplant, and (ii) post transplant interventions usually involving some form of immune manipulation such as withdrawal of immunosuppression, use of cytokines in order to enhance the immune response, or infusion of donor lymphocytes (DLI). These strategies have been successful at decreasing relapse rates, but on the expense of higher rates of graft-versus-host disease. [33,34,35]

Our early experience with TCD in MDS established that optimization of the patient's disease status, that is induction of remission prior to transplant, can result in a lower incidence of posttransplant relapse.[32] The relapse rate at 1-year posttransplant for patients transplanted with active disease was 60% whereas patients transplanted in remission was 20%. Further analysis of our early experience with our most recent experience demonstrated that the relapse rate was similar whether the patient was conditioned for transplant with a TBI containing preparative regimen or a chemotherapy containing preparative regimen combining Busulphan, Melphalan, and Fludarabine. Moreover, recent analysis (unpublished data) of transplant outcomes in children and adults who underwent T cell depleted transplant at MSKCC between 1985-2011 for MDS and AML demonstrated that poor risk cytogenetics at diagnosis is a very strong predictor of relapse (figure 1).

Since the focus of the MSKCC transplant program has been T cell depletion, patients with MDS and AML have been transplanted with this type of allograft. A few studies have looked at preemptive/maintenance intervention post transplant to reduce the risk of relapse, though, to the best of our knowledge not in the unique setting of T cell depleted transplant. Despite the common perception that TCD transplant is associated with higher risk of relapse, due to loss of GVL effect, the relapse rate after T cell depleted myeloablative transplants in our MDS/AML patients in remission or second refractory cytopenia phase is lower or at least similar to that seen in recipients of T cell replete myeloablative transplants reported by other centers. We therefore believe that with our long term experience with TCD transplant for MDS and AML this is an optimal setting to evaluate the potential benefit of post transplant intervention to reduce the risk of relapse.

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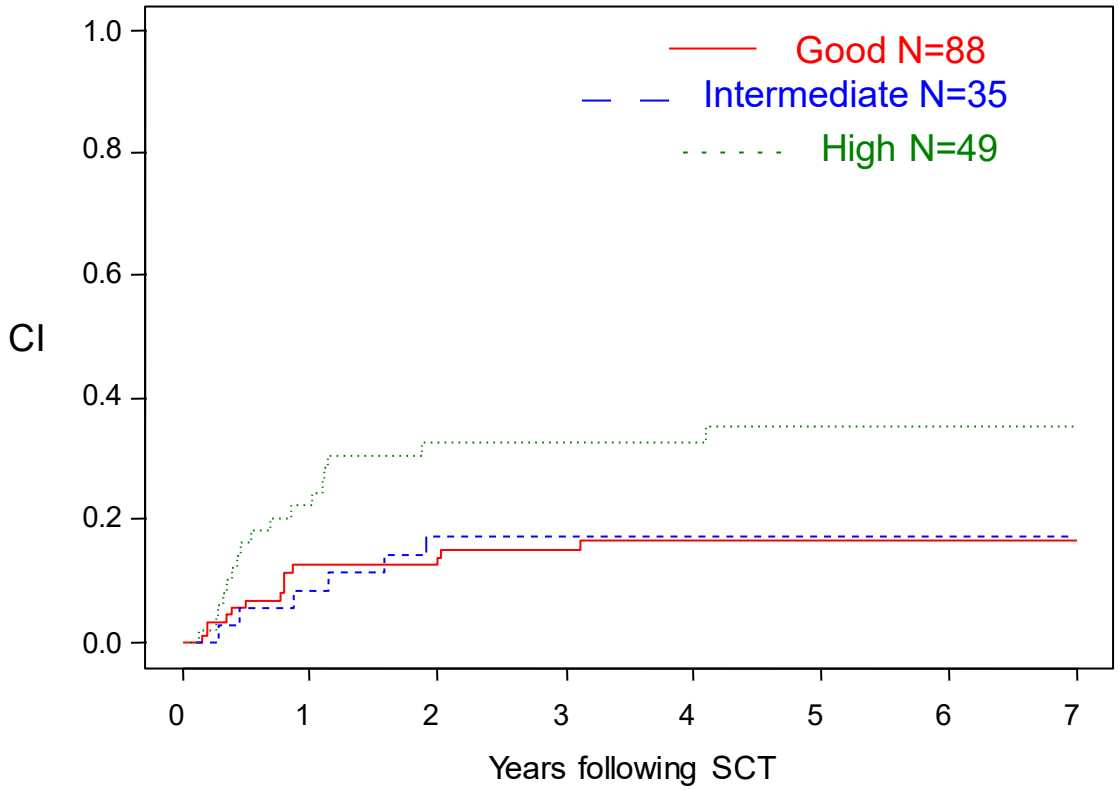
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Intermediate N=35
High N=49
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1
2
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4
5
6
7
Years following SCT

Risk for relapse based on cytogenetic changes (as per IPSS criteria) at diagnosis in 172 patients who underwent T cell depleted transplant at MSKCC between 1985-2011.

3.3 5-Azacitidine and summary of results of trials in patients with MDS and AML

Azacitidine (5-azacytidine) is a chemical analogue of the cytosine nucleoside used in DNA and RNA. Azacitidine is thought to induce antineoplastic activity via two mechanisms; inhibition of DNA methyltransferase at low doses, causing hypomethylation of DNA, and direct cytotoxicity in abnormal hematopoietic cells in the bone marrow through its incorporation into DNA and RNA at high doses, resulting in cell death.

Epigenetics changes consist of biochemical modifications to chromatin that do not alter the sequence of the DNA itself. The primary epigenetic modifications are DNA methylation and histone modification, both of which are potentially reversible. [36,37] DNA methylation plays an important role in gene regulation, and aberrant methylation of promoter regions can occur in malignancies, and is correlated with gene silencing, particularly of tumor suppressor genes [38]. MDS and AML appear to be more amenable to hypomethylating agents, compared to solid tumors, though the exact mechanism of response in unknown. Currently, two DNA hypomethylating agents have been approved for patients with MDS: 5'-azacitadine and Decitabine (5-aza-2'-deoxycitidine). Both drugs are DNA methyltransferase (DNMT) inhibitors that have demethylating effects.

Two randomized trials comparing 5'-azacitadine to best supportive and conventional care regimens in patients with MDS, demonstrated that 5'-azacitadine was superior in terms of time to progression to AML and in overall survival. [2,3]

Only small phase II studies have investigated the use of 5'-azacitadine or decitabine to induce remission prior to allogeneic SCT. Lubbert, et al treated 15 patients with MDS or AML at a median age of 65 with low dose decitabine before allogeneic SCT [39] and showed that this can be effective treatment, which can induce response and even remission prior to allogeneic HSCT. With a median of 5 cycles, 33% of the patients achieved a CR and 6% achieved a PR prior to transplantation.

Data on use of 5'-Azacitadine in pediatric patients is much more limited; however several studies have incorporated 5'-azacitadine in combination with other chemotherapies for pediatric myeloid leukemia patients in either the up-front setting at a dose of 100mg/m2 X 4 days or in relapsed or refractory patients at doses of 250-300 mg/m2/day for 2 days with improvement in response rates and overall well tolerated, though with high incidence of myelosuppression. [40,4142]

3.4 Summary of results of phase I-II trials of 5'-azacitadine post allogeneic HSCT in patients with MDS/AML

Several studies have assessed the safety and efficacy of 5'-azacitadine after allogeneic HSCT in patients with MDS and AML as salvage therapy at disease recurrence or as a preventive measure to reduce the risk of relapse. A retrospective study by Jabbour et al in 17 AML patients who received an allogeneic SCT and then 5'-azacitidine at the time of relapse (n=9) or as maintenance (n=8) [43] showed a significant response. 5'-azacitadine was given at different doses: 16, 24 and 40 mg/m^2/day for 5 consecutive days every 4 weeks, with median of 8 cycles. Among the patients in the relapsed disease group, the response rate was 55% (5/9). The 8 patients who received 5'-azacitadine as maintenance treatment remained in CR for median of 17 months (range 14-26 months), however 37.5% (3/8) relapsed eventually. The one-year EFS and OS were 55% and 90%. The majority of patients experienced grade 1-2 hematologic toxicity but no dose reductions were required.

In a phase I study by De Lima et al, 45 patients with AML (n=37) and MDS (n=8) received different dosages of 5'-azacitadine (8, 16, 24, 32 and 40mg/m^2/day for 5 days) for 1-4 cycles. [44]This study showed that 5'-azacitadine is safe and well tolerated after allogeneic SCT, with a recommended dose of 32mg/m^2/day for 5 days.

The Relaza study in Europe looked at patients with MDS (n=3) and AML (n=17) with evidence of MRD by CD34+ donor chimerism <80% without evidence of hematologic relapse who were treated with 5'-azacitadine at a dose of 75 mg/m^2 /day for 7 days for 4 cycles followed by more cycles depending on response. After the initial 4 cycles, 50% of patients had a major response. Grade 3-4 hematologic toxicity, mostly neutropenia and thrombocytopenia, resulted in dose reduction in 45% of patients.[45]

Two main conclusions can be drawn from the above studies: (i) Low dose of 5'-Azacitidine - 32 mg/m^2/day was found to be tolerable in the post transplant setting with relatively safe toxicity profile. (ii) 5'-Azacitidine was effective in inducing remission in patients who relapsed after allogeneic HSCT as well as maintaining remission when given for maintenance. Of note is that the patients enrolled in these studies were patients at very high risk, as majority were not in CR at time of transplantation, which is different from patients undergoing T cell depleted HSCT.

3.5 Mechanism of activity of 5'-azacitidine post allogeneic hematopoietic stem cell transplant

The administration of 5'-azacitidine to recipients of allogeneic HSCT can affect both stem cells and T cells, irrespective of origin, donor derived or residual host cells and therefore consolidate the effect of the transplant by two different pathways;

(i) *Eliminating residual leukemic stem cells*- Following myeloablative conditioning, the stem cell population will consist of largely donor derived normal hematopoietic stem cells and very minimal residual host MDS and AML stem cells. This latter cells are the ones shown to be the disease initiating cells and are likely responsible for relapse. [46,47,48, 49] Since 5'-azacitidine and other hypomethylating agents have their preferential effect on leukemic stem cells as it has been well documented in MDS

patients receiving these agents [50,51] we hypothesize that early administration of this agent post transplant can act upon the residual MDS and AML HSC and prevent its expansion, while awaiting donor derived GVL effect which is a later event.

(ii) *Augmenting GVL effect*- Regulatory T cells (Tregs) are known to contribute to the maintenance of self-tolerance by regulating inflammatory responses and suppression of autoimmunity and GvHD in mouse models. The major population of Tregs is naturally occurring Tregs (nTreg). These cells are generated in the thymus and defined by CD4+CD25+FOXP3+. Small numbers of Treg can also be generated in the periphery from naïve CD4+CD25- T cells by T cell receptor stimulation. FOXP3 is a transcription factor exclusively expressed in nTregs. Mutation in FOXP3 lead to autoimmune disease due to loss of functional nTregs and forced expression of FOXP3 in CD4+CD25- T cells induce regulatory properties. Recent reports demonstrated that the *FoxP3* locus in both humans and mice is unmethylated in Tregs while heavily methylated and silenced in CD4+CD25-T cells. Choi et al demonstrated in a mouse model that hypomethylating agents (both 5'-azacitidine and decitabine) are able to induce FOXP3 expression in $CD4^{+}CD25^{-}$ T cells. Interestingly, 5'-azacitidine given to mice after HLA mismatched transplant resulted in less GVHD while preserving GVL by peripheral conversion of alloreactive T cells into $FOXP3^{+}$ Tregs and epigenetic modulation of genes downstream of Foxp3 required for the suppressor function of Tregs. [52]

Goodyear et al, have recently shown that the administration of 5'-azacitidine post-transplant increased peripheral Tregs and suggested another mechanism of anti-leukemic effect, through up regulation of expression of epigenetically silenced tumor antigens such as MAGE-A1 (melanoma-associated Ag1) and WT-1 (Wilm tumor Ag1). 5'-azacitidine has the capacity to induce a CD8+ T cell response to tumor antigens in patients with hematologic malignancies. This effect of 5'-azacitidine on Tregs expression was confined to the immediate period after transplant.[53]

These effects on T cells were observed in recipients of unmodified transplant and are unknown in the setting of TCD transplant. When Tregs recovery was studied after T cell depleted transplant, in adult patients who received myeloablative conditioning regimens in combination of ATG, slow recovery of Tregs was associated with higher incidence of opportunistic infections and extensive chronic GVHD. This study demonstrated Treg recovery, at least age appropriate, by the second year post transplant.[54]

3.6 Correlative studies

Methylation- Although, in their study, De Lima et al did not demonstrate an effect on DNA methylation using unfractionated marrow cells it is possible that the shorter period of treatment (4 cycles) as well as lower average doses (16-40mg/m^2) were responsible for that.

In this proposed study, the gene specific methylation in sorted hematopoietic and leukemic stem cells from marrow samples will be analyzed at several points: at diagnosis (if available), prior to transplant, posttransplant prior to initiation of 5'-azacitadine and every 3 months. The purpose to this part of the study is to determine if maintenance 5'-Azacitadine post transplant has an effect on methylation.

Minimal Residual Disease (MRD)- Currently there is still no one acceptable test with high specificity and sensitivity for detection of minimal residual myeloid disease. We plan to assess disease status by morphologic evaluation and immunophenotyping.

Moreover, In collaboration with Stephen Chung, MD and Christopher Y Park, MD PhD, a panel of aberrantly expressed cell surface proteins that are highly specific and sensitive for the detection of cells bearing these antigens will be used to assess for residual MDS/AML cells. This will allow us to determine whether persistence of cells bearing these antigens can predict for relapse after transplant. This analysis will be performed by multi-parameter flow cytometry.

Cytogenetic changes in the stem cells- In collaboration with Christopher Y Park, MD PhD, and Steve Chung, MD fluorescence activated cell sorting (FACS) and FISH technique will be used to assess for residual involvement of the HSC compartment following transplantation, assessing for the effect of 5'-azacitadine therapy on residual MDS HSC over serial time points (e.g. every three months).

Graft-versus-Leukemia- Last, we'll assess the effect of 5'-Azacitadine on T cell differentiation with specific interest on Tregs. This will be done by the flow cytometry lab and will be part of routine post transplant "FLOW7 BMT" which assess for CD4, CD8 and cD19. In addition, the effect of treatment with post transplant 5'-Azacitadine on T regs will be studied.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single arm phase II trial to assess the efficacy and confirm the safety of maintenance therapy with 5'-azacitadine compared to historical control after TCD allogeneic hematopoietic stem cell transplant for patients with MDS and AML who are at high risk of relapse.

4.3 Intervention

5'-azacitadine will be given at a low dose of 32mg/m^2 S.C for 5 days every 28 days (a cycle). Dose de-escalation will be permitted for hematologic and non- hematologic toxicities.

Patients will start taking the study drug between days 60-120 post TCD allogeneic hematopoietic stem cell transplant and up to a year post-transplant or until there is a toxicity that requires cessation of therapy. Therefore patients will get between 8-10 cycles. Patients who come off-study for reasons unrelated to toxicities before completing 4 cycles will be replaced. Since most cases of relapse occur early post transplant, in the first year, this is the most appropriate time to intervene. Treatment will start as soon as possible.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5'-azacitadine- Vidaza ™

Source and pharmacology: 5'-azacitadine contains AZA, which is a pyrimidine nucleoside analog of cytidine. AZA is a 4-amino-1-a-D-ribofuranosyl-s-triazin-2(1H)-one. The empirical formula is C8H12N4O5. The molecular weight is 244. The finished product is supplied in a sterile form for reconstitution and subcutaneous injection only. Vials of 5'-azacitadine contain 100 mg of 5-azacitadine and 100 mg mannitol as a sterilized lyophilized powder.

Solution preparation: 5'-azacitadine should be reconstituted aseptically with 4ml sterile water for injection. The diluent should be injected slowly into the vial. The vial should be inverted 2-3 times and gently rotated until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain 5'-azacitadine 25mg/ml.

Preparation for immediate release: doses greater than 4 mL should be divided equally into the syringes. The product may be held at room temperature for up to 1 hour, but must be administrated within 1 hour after reconstitution.

Preparation for delayed release: the reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into two syringes. The product must be refrigerated immediately, and may be held under refrigerated conditions (2^0C-8^0C, 36^0F-46^0F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Storage: Store un-reconstituted vials at 25^0C (77^0F); excursions permitted to 15^0-30^0C (59^0F-86^0F)

Stability: reconstituted 5-azacitadine may be stored for up to 1 hour at 25^0C (77^0F) or for up to 8 hours between 2-8^0C (36^0F-46^0F). The 5-azacitadinevial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. Do not save any unused portions for later administration.

Administration: to provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2-3 times and gentle rolling the syringe between the palms for 30 seconds immediately prior to administration. 5-azacitadine is administrated subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate

sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas were the site is tender, bruised, red, or hard.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Patients who have undergone T cell depleted allogeneic hematopoietic stem cell transplantation at MSKCC for**:**

1. De novo myelodysplastic syndromes (MDS): IPSS-1 with poor risk cytogenetics or higher IPSS.
2. Acute myelogenous leukemia (AML) in first remission that required more than 1 cycle of treatment to achieve remission or with the following cytogenetic abnormalities: FLT3 mutation, deletion/monosomy of chromosome 5 or 7, MLL gene rearrangement, or more than or equal to 3 cytogenetics abnormalities. Also patients in second or greater remission.
3. Patients with Secondary MDS/AML.
4. Patients will be considered eligible for the study if after transplant they achieved hematologic (<5% blasts) and cytogenetic remission.
5. Patients will be eligible to enter the study between 60-120 days post transplant.

6.2 Subject Inclusion Criteria

1. Age: pediatrics and adults patients – 1 year old-75 years old.
2. Karnofsky performance status >=60% for patients >16yo and Lansky performance status >=60% for patients ≤16yo
3. Stable blood counts (ANC>1000/uL, Hb>8gr/dL, Plt>50,000/ uL) not supported by transfusions.
4. Renal: Serum creatinine <1.5 ULN
5. Hepatic: <3xULN ALT and <1.5 total serum bilirubin, unless there is congenital benign hyperbilirubinemia.
6. Cardiac: Adequate cardiac function measured by LVEF>50%. If asymptomatic, pre-transplant echocardiogram is adequate. If symptomatic, echocardiogram needs to be repeated.
7. Each patient must be willing to participate as a research subject and must sign an informed consent form.

Patients who were treated with 5'-azacitadine without response prior to transplant would be eligible to participate on this protocol.

6.3 Subject Exclusion Criteria

Patients will be excluded from the trial if at time of enrollment:

1. Active uncontrolled bacterial, fungal or viral infection.
2. Evidence of uncontrolled graft-versus-host disease.
3. Pulmonary: new onset hypoxia
4. Known or suspected hypersensitivity to 5'-azacitadine or mannitol.
5. Evidence of residual disease either by increased blasts count (>5%) or persistence of previous known cytogenetics abnormalities.
6. Peripheral blood neutrophil chimerism: less than 95% donor.

7.0 RECRUITMENT PLAN

Patients who fulfill the eligibility criteria as listed in section 6.0 will be recruited for this study by an attending physician of the allogeneic BMT services in Medicine and Pediatrics. In the period of time between 60-120 days post-transplant, patients who are eligible for the study protocol will be offered to participate. A discussion will take place about the need for treatment with 5'- azacitidine which involves 5 days of subcutaneous injection every month for a year post transplant, the rational of decreasing risk of relapse, and the potential side effects, which at this part are mostly known to be related to myelosuppression and decreased blood counts. This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research population.

8.1 PRETREATMENT EVALUATION

The patient will undergo comprehensive medical evaluation after stable engraftment has been documented. This evaluation includes:

1. Complete physical exam and medical history
2. Bone marrow tests post HSCT will be performed to determine remission status by morphology, cytogenetics and molecular studies (if indicated) and chimerism as part of routine post transplant assessments. At the same time, bone marrow sample will also be taken for baseline correlative studies under the biospecimen protocol. Any bone marrow sample collected prior to starting treatment with Azacitidine can be used as baseline for correlative studies.
3. Complete blood counts (CBC)
4. Complete metabolic panel
5. Pregnancy test will be checked for women at child bearing age prior to initiation of treatment

6. Cardiac: Adequate cardiac function measured by LVEF>50%. If asymptomatic, pre-transplant echocardiogram is adequate. If symptomatic, echocardiogram needs to be repeated.

9.1 TREATMENT/INTERVENTION PLAN

1. 5'-azacitadine will be given at a dose of 32mg/m^2 for 5 consecutive days subcutaneously. Treatment will be given every 28 days (cycle). Treatment will be given up to a year post transplant.
2. CBC will be checked weekly during the first 2 cycles, and if stable every 2 weeks with following cycles. CBC results from tests performed externally will be accepted for Days 8, 15, and 22 of C1 and C2 and Day 15 of subsequent cycles. Comprehensive metabolic panel will be checked at the beginning of every cycle.
3. Pregnancy test will be checked for women at child bearing age prior to start of each cycle.
4. Bone marrow studies (day 100, and 6, 12, 18 and 24 months post transplant) for assessment of disease status and chimerism. Peripheral blood chimerism status at day 100, and 6, 12, 18 and 24 months post transplant will be tested as part of routine post transplant evaluation
5. Peripheral blood lymphocytes phenotyping and in-vitro response to standard panel of mitogen will be assessed as part of routine post transplant assessment
6. Bone marrow samples for correlative studies will be tested at the same time that patients are undergoing routine BM studies. These tests are considered experimental.
7. Peripheral blood samples for correlative studies will be collected prior to start of Azacitidine treatment on C1D1 and at 12 and 18 months post transplant. These tests are considered experimental.

Dose modifications

Event	Modification
ANC <1000/uL for > 4 days,	Drug held until resolved (ANC 1500) and up to 60 days. If after 60 days there is no neutrophils recovery the treatment will be permanently discontinued.
• If by next cycle ANC is 1000-1500, not G-CSF dependent	Resume therapy with 50% dose reduction
• If by next cycle ANC fully recovered, >1500 not G-CSF dependent	Resume full therapy dose
Platelets <10,000/uL for > 4 days, or if transfusion dependent to keep count>10,000/ uL	Drug held until resolved (>50,000) and up to 60 days.

• If by next cycle Platelets are 10,000-50,000, not transfusion dependent	Resume therapy but with 50% dose reduction
• If by next cycle Platelets >50,000	Resume full therapy dose
Hemoglobin < 8g/dL for > 4 days or if transfusion dependent	Drug held until resolved (> 8g/dL) and up to 60 days.
• If by next cycle hemoglobin >8g/dL	Resume full therapy dose
Hepatic toxicity – Drug related grade 3-4	Drug stopped
Drug related grade 1-2	Next cycle delayed up to 60 days for resolution or reduced by 25% on subsequent cycles (resume full dose on next cycle once resolved)
Creatinine > 50% above age-adjusted ULN	Drug held
Creatinine ≤ 50% above age-adjusted ULN after a maximum delay of 45 days	Dose reduced 50% on next cycle (resume full dose on next cycle once resolved)
Serum bicarbonate level (CO2) - Unexplained reduction; < 20mEq/L	Dose reduced by 50% on next cycle
Cardiac, pulmonary, dermatologic, or neurologic toxicity - Drug related grade 3-4	Drug stopped
Acute infection	Drug held (resume full dose once resolved)

10.0 EVALUATION DURING TREATMENT/INTERVENTION

During the treatment patients will be seen in clinic every 4 weeks (prior to every cycle) and more frequently if required by primary BMT attending. All patients will be closely monitored and evaluated as per MSKCC BMT standard of care guidelines. Evaluations may be withheld if the treating physician feels that there is a strong contra-indication to perform the study (e.g. patient has relapsed or is terminally ill). Also, additional tests will be performed as clinically indicated. Study specific assessment schedule listed in table below.

Schedule of Study Assessments

Procedures	**Pre-Treatment**	**Post Treatment Start**					
		C1 & C2				C3+	
		D1	D8	D15	D22	D1	D15
Window	45	(+/-) 7	(+/-) 3	(+/-) 3	(+/-) 3	(+/-) 7	(+/-) 3
Eligibility	X						
Informed consent	X						
History/Physical	X						
Pregnancy Test (1)	X	X				X	
Blood Chemistry/CMP (2)	X	X				X	
CBC (2)	X	X	X	X	X	X	X
Echo- **if no new symptoms, pretransplant is adequate**	X						
Toxicity assessment (3)		X				X	
Correlative studies – Peripheral blood for Tregs expression studies (4)		X*					

Procedures	**Post Transplant**				
	100 days	6 months	12 months	18 months	24 months
Window	(+/-) 21	(+/-) 14	(+/-) 14	(+/-) 14	(+/-) 14
Chimerism (Peripheral Blood) (5)	X	X	X	X	X
Bone marrow aspirate and/or biopsy (6)	X	X	X	X	X
Peripheral blood lymphocytes phenotyping and in-vitro response (7)	X	X	X	X	X
Correlative studies - BM sample for methylation assays, flow studies for MRD (8)	X	X	X	X	X
Correlative studies – Peripheral blood for Tregs expression studies			X	X	

*Peripheral blood samples will be collected prior to start of Azacitidine treatment on C1D1 only

(1) Pregnancy Test – Not required for Cycle 1 Day 1 if done at screening, but required for Day 1 of each subsequent cycle for FCBP.
(2) CBC – checked weekly during the first 2 cycles, and if stable, every 2 weeks with subsequent cycles. Outside CBC results will be accepted for D8, 15 and 22 of C1 and C2 and for D15 of subsequent cycles. CBC/Chemistry must result prior to IP administration on or within 7 days of Day 1 of each cycle. If a CBC is performed within overlapping windows for two time-points, it is not necessary to repeat unless clinically indicated.
(3) Toxicity Assessment - Not required for Cycle 1 Day 1, but required for Day 1 of each subsequent cycle or within 7days of Day 1 of each cycle. Patients who pass away, complete treatment or end treatment before the start of the next cycle will have toxicities captured at the end of the last cycle started.
(4) Peripheral blood samples (2 GTT) will be collected and stored at HOTB prior to start of Azacitidine treatment on C1D1 and at 12 and 18 months post-transplant
(5) Peripheral blood will be checked for neutrophil, B cells, and T cell chimerism
(6) In the first year bone marrow tests will be performed to assess disease status by morphology, cytogenetics, and molecular as per BMT standard of care time-points. Following the first year these studies will be performed at 18 and 24 months post transplant.
(7) Peripheral blood will be checked for lymphocytes phenotyping as well as in-vitro response to standard panel of mitogens as per BMT standard of care.
(8) Correlative studies include global and specific genes methylation status, Fluorescence activated cell sorting (FACS) and FISH assays will be used to assess for residual involvement for the HSC compartment

10.1 Correlative Studies

Bone marrow samples will be obtained on Day+100 and at 6, 12,18 and 24 months post transplant as part as our routine post transplant follow up. In addition, another BM aspirate sample, 3 cc, will be sent to HOTB.

Using a panel of aberrantly expressed cell surface proteins that are highly specific and sensitive for the detection of cells bearing these antigens, the samples will be assessed for residual MDS/AML cells. This analysis will be performed by multiparameter flow cytometry.

By using fluorescence activated cell sorting (FACS) and FISH technique, the samples will be assessed for residual involvement of the HSC compartment following transplantation.

Global methylation assay will also be assessed on the sorted cells by using anti- 5'-methylcytosine monoclonal antibody which will be provided by Dr. Ari Melnick.

Peripheral blood sample will be obtained prior to start of Azacitidine treatment on C1D1 and at 12 and 18 months post transplant and will be stored at the Hematology-Oncology Tissue Bank (HOTB).

These samples will be sent to the clinical lab to assess azacitidine's effect on Tregs expression- peripheral blood will be examined by flow using the markers CD3+CD4+CD25HICD127NEG.

11.1 TOXICITIES/SIDE EFFECTS

Toxicities will be graded according to NCI CTAE version 4.0 grades 3-4 only, except grades 1-4 hepatic toxicity (increased AST, ALT, alkaline phosphatase and bilirubin) and grades 1-4 GI toxicity (nausea, vomiting, diarrhea). The side effects and toxicities related to 5-azacitadine are listed below.

5'-azacitadine

Likely

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Lowered white blood cell count that may lead to infection
- Lowered platelet count that may lead to an increase in bruising or bleeding
- Lowered red blood cells that may cause anemia, tiredness, or shortness of breath
- Chest pain
- Fever
- Fatigue and weakness
- Headache
- Dizziness
- Bruising
- Rash
- Dry skin
- Skin nodules
- Erythema
- Weight loss
- Abdominal pain
- Loss of appetite
- Joint pain
- Muscle Pain
- Breathlessness
- Upper respiratory tract infections as well as infections of the throat and sinuses
- Pneumonia

- Injection site bruising, pain or reaction
- Anxiety
- Insomnia

Less Likely:

- Abnormal heart beat
- Fainting spells
- Skin infections
- Upper abdominal pain
- Bleeding from the gums
- Difficulty eating
- Hemorrhoids
- Pain when urinating
- Urinary tract infection
- Muscle cramps
- Wheezing
- Fluid on the lungs
- Increased sweating
- Night sweats

Rare But Serious:

- Convulsions
- Anaphylaxis
- Bone marrow depression
- Congestive Heart Failure
- Stupor
- Coma

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Definitions of events in the study period that are important for analysis and treatment

1. Disease relapse

Relapse of MDS or AML will be analyzed as to type and genetic origin of the leukemic cells. These will be defined by morphologic and/or cytogenetic criteria: an increasing number of blasts in the marrow over 5%, by presence of circulating blasts, or by presence of blasts in any extramedullary site as well as presence of previous cytogenetic abnormalities. Other

studies assessing for MRD, FACS and FISH assays will be evaluated but would not be considered disease relapse if positive since they are experimental..

2. Transplant related mortality

Includes fatal complications resulting from the therapy such as severe infection, hemorrhages and graft failure.

3. Immunologic reconstitution

Our previous studies have identified time points at which the various immunologic functions can be expected to return. Immunophenotyping and NK cell function will be performed on circulating lymphocytes of all patients.

T cell proliferation in response to PHA, candida, viral antigens and tetanus following immunization will be performed at approximately 6 months post transplant and every 3-6 months thereafter until normal values are reached.

4. Engraftment and chimerism

Engraftment will be documented by analysis of bone marrow cells as well peripheral blood cells for chimerism by standard karyotype or short tandem repeat analysis every 3 up to one year posttransplant.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility, the patient will be removed from the study. Intolerable toxicity would take a subject off protocol therapy, but not off study to continue to follow them since overall survival is a secondary objective. Also patients may be removed from the study if requested by the patient. Patients will need to receive a minimum of 4 cycles to be considered evaluable for protocol objectives. Patients who receive less than 4 cycles due to treatment-related toxicities will be considered evaluable for toxicity only and will not be replaced on study. Patients who relapse prior to receiving 4 cycles are considered evaluable per protocol. Patients who come off-study for reasons unrelated to toxicities before completing 4 cycles are considered inevaluable per protocol and will be replaced. Management will continue as per standard allogeneic HSCT guidelines.

14.1 BIOSTATISTICS

This phase II trial will explore the efficacy of treating high-risk MDS and AML patients with 5'-azacitidine following TCD-HSCT. Based on historical MSKCC data for patients with advanced MDS and AML (adults and pediatrics) with high relapse risk, who meet the entry criteria, the two-year

cumulative incidence of relapse is 35%. Therefore, this intervention would be considered promising if the two-year relapse proportion is 15% or less. If the relapse proportion is 35% or greater, the 5-azacitibine intervention would not be considered promising. Therefore, using a single stage exact design, a total of 32 patients will accrue on study. At the end of the trial, if seven or fewer patients relapse by two years post treatment initiation, the trial will be considered promising. If, however, more than 8 patients relapse at any point the study will be considered unpromising and will be closed for further accrual. The type I and type II errors for this trial are 0.08 and 0.10, respectively. It is anticipated that enrollment will be completed in 5 years with an accrual of approximately 6-7 patients/year.

If a patient is found to be ineligible for reasons unrelated to disease relapse or progression, or is lost to follow-up, s/he will be replaced for the primary endpoint. If a patient dies for reasons unrelated to disease relapse or progression (i.e., treatment related mortality), s/he will remain as part of the 32 patient cohort. Treatment-related mortality will be monitored as part of the stopping rules discussed below.

In order to reduce patient risk and confirm the safety of 5'-azacitidine in this setting, the study design includes early termination in event of severe neutropenia, severe thrombocytopenia, and treatment-related mortality. The boundaries are based on accrual of 32 patients. The calculations in the table below are based on marginal probabilities.

Failure Type	**# of failures needed to stop the study**	**Failure rate in the population**	**Probability boundary is crossed**
Neutropenia (Grade III-IV)	3 in the first 8 patients 4 in the first 14 patients 5 in the first 20 patients	0.1	0.1
	6 in the first 27 patients 7 at any point	0.3	0.92
Thrombocytopenia (Grade III-IV)	3 in the first 8 patients 4 in the first 14 patients 5 in the first 20 patients	0.1	0.1
	6 in the first 27 patients 7 at any point	0.3	0.92
	3 in the first 5 patients 4 in the first 8 patients 5 in the first 12 patients	0.15	0.07

Treatment-related mortality	6 in the first 16 patients 7 in the first 20 patients 8 in the first 25 patients 9 in the first 29 patients 10 at any point	0.4	0.93

In addition to the primary endpoint, there are a number of secondary and correlative objectives.

Secondary Objectives:

1. Kaplan-Meier methodology will be used to compare overall survival.
2. The safety will be described by tabulating the number of transfusions, frequencies of bleeding and serious infections, and the use of G-CSF support.
3. We will also evaluate the following metrics: graft function; myeloid and T-cell chimerism; and acute and chronic GVHD incidence. Graft function will be examined after enrollment by summary statistics of hemoglobin levels, neutrophils and platelets. Myeloid and T-cell chimerism will be summarized as a continuous measurement at enrollment, 6, 9,12,18 months post-transplant and 24 months post-transplant. Cumulative incidence function will be used to estimate grade II-IV acute GVHD and chronic GVHD incidence.

Correlative Studies:

1. The global DNA methylation status will be evaluated at baseline, and the change from baseline will be explored among individuals who do and do not relapse by the 24 month BM evaluation. . This continuous measurement will be compared using a rank-sum test.
2. The reoccurrence of cytogenetic abnormalities will be evaluated in the CD34 subpopulation of cells at the time of trial enrollment. This exploratory measure is calculated as the proportion of involved cytogenetic cells out of the total number of stem cells and may be a marker of disease burden following transplant. This proportion will be categorized and relapse will be contrasted across these categories using a permutation-based logrank test.
3. The composition of myeloid progenitor cells will be compared pre- and post- 5'-azacitidine treatment to explore whether normalization occurs following treatment. These paired measurements will be compared using McNemar's test.
4. The levels of regulatory T-cells and CD8+ will be graphically displayed across baseline and post-treatment time points.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study and will be responsible for both pediatric and adult accruals. The responsibilities of the RSA and principal investigator include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into The Clinical Research Data Base (CRDB), a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The

committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Risks: From the studies that have been done so far it was demonstrated that post transplant 5'-Azacitadine can be safely given in patients with myelodysplastic syndrome and acute myelogenous leukemia and that these patients may benefit from the treatment. However, given this is a new treatment approach in T cell depleted transplant, it is possible that there are side effects that have not yet been seen.

Benefits: The information from this study will help future cancer patients.

Possible toxicities/side effects: Toxicities and side effects of the agents used are listed in section 11 and reporting of serious adverse events is found in section 17.2.

Consent Process: Participation in this study is voluntary. All patients will be required to sign a statement of informed consent which must conform to MSKCC IRB guidelines. For minors consent will be obtained from parents or guardians of unemancipated minors. Minors between 7-17 years old will be assented. This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research population.

Alternatives: Alternative treatment options will be presented to the patient prior to taking part in this study. Alternative treatment options may include not participating in this study and follow up as per regular standard of care post transplant, or taking part in another study of post transplant maintenance therapy, should that becomes available.

Costs: The patient's health plan/insurance company will need to pay for all of the costs of standard medical care. Patients will not be paid for taking part in this study. Research tests will be done at no cost to the patient.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred

- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

All patients will be followed for safety and toxicity related to the study. The reportable serious adverse events (SAEs) will be defined according to the current MSKCC Adult and Pediatric BMT Adverse Event Reporting Guide..

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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[2] Silverman LR, Demakos EP, Peterson BL, et al. Randomized control trial of azacitidine in patients with myelodysplastic syndrome; a study of the cancer and leukemia group B J Clin oncol 2002;20:2494-2440

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