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Protocol Page

A Phase II Study of Omacetaxine (OM) in Patients with Intermediate-1 and Higher Risk Myelodysplastic Syndrome (MDS) post Hypomethylating Agent (HMA) Failure

2013-0870

Core Protocol Information

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Study Chair:	Elias Jabbour
Additional Contact:	Jhinelle L. Graham Vicky H. Zoeller Leukemia Protocol Review Group
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) None **Study Staff Recipients** None
Department:	Leukemia
Phone:	713-792-4764
Unit:	0428
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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A Phase II Study of Omacetaxine (OM) in Patients with Intermediate-1 and Higher Risk Myelodysplastic Syndrome (MDS) post Hypomethylating Agent (HMA) Failure

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A Phase II Study of Omacetaxine (OM) in Patients with Intermediate-1 and Higher Risk Myelodysplastic Syndrome (MDS) post Hypomethylating Agent (HMA) Failure

1.0 Objectives

1.1 Primary Objectives:

a. To assess overall survival and
b. To assess overall response rate (ORR)

1.2 Secondary objectives

a. To assess duration of response
b. To assess relapse-free survival
c. To assess the safety profile

2.0 Background

2.1 Myelodysplastic Syndromes

The standard of care for patients with intermediate-1 and above myelodysplastic syndrome (MDS) is a hypomethylating agent, either decitabine or azacitidine.[1-2] Although these agents are effective and result in clinical improvement in over 60% of patients, it is now accepted that a large majority of patients will lose response. Median number of cycles with this class of agents in front line MDS is 8 months. It is now established that the prognosis of patients that fail a hypomethylating agent is very poor. MD Anderson (MDACC) was the first to report that the median survival of such patients is less than 5 months.[3] Results confirmed now by multiple centers.[4] Of importance, the mechanisms of resistance are not understood. At the present time, there is no drug approved for patients that have failed this class of agents and because of the very poor prognosis of these patients there is an urgent need for an active and safe compound.

A number of agents have been used in the treatment of these patients. These include high dose chemotherapy, clofarabine, sapacitabine but have not been formally tested in this indication.[3] A phase III study of ON1910 (rigorsetib) has been completed and results are expected in 2014. Of interest, the FDA allowed a concept of modest improvement in survival (from 4 to 6 months) in the design of this trial.

We believe that agents with potential in this context of hypomethylating failure MDS cannot be very cytotoxic and allow for gradual responses and stabilization of the disease resulting in prolonged survival. This is important because early responses associated with significant cytopenias have been associated with short survival, an example being cloretazine.[5] Based on our experience with omacetaxine (OMA) in CML and more recently in AML,[6-8] we believe that OMA has the potential to have significant activity in this context without excess toxicity..

2.2 Omacetaxine (OM) in Myeloid Malignancies

OM is a semisynthetic version of a plant alkaloid extracted from Cephalotaxus fortunei, a species of evergreen tree that is indigenous to China. It is available in China for the treatment of hematological malignancies. OM mechanisms of action include protein synthesis inhibition [9] and induction of differentiation[10] and apoptosis. [10-12-14] Recent studies indicate OM is affecting histone deacetylase and is also a potent angiogenesis inhibitor. OM has shown activity in AML and other hematologic cancers, including acute promyelocytic leukemia (APL), chronic myeloid leukemia (CML), and MDS. [13-22] Studies from China reported high response rates in patients with leukemia. Trials in the U.S. have shown significant activity as well. In a Phase I-II trial, Warrell et al. treated 49 patients with refractory AML with OM, 5 or 7 mg/m^2 daily for 7 days and 5 mg/m^2 daily for 9 days (25-49 mg/m^2 per course), in a continuous infusion schedule. [23] Dose escalation beyond 5 mg/m^2 daily resulted in frequent interruption of OM infusion because of hypotension. Hypotensive episodes occurred in approximately 30% of patients; myalgias occurred in 20% of patients and hyperglycemia in 57% of patients (it

was severe in 23%). A schedule of 5 mg/m^2 daily for 9 days was judged reasonable. Of 28 evaluable patients with AML who were treated with cumulative doses of 45-49 mg/m^2, 7 (25%) achieved a CR. At lower dose levels, none of nine patients achieved a CR.[24] The recommended dose schedule of OM was 5 mg/m^2 daily for 9 days.

Two additional studies of OM in AML showed similar results with CR rates of 20% - 30%.[25] Stewart et al. did not obtain any CRs in 20 patients with advanced AML who were treated with OM, 3.5 mg/m^2, on Day 1 and 6 mg/m^2 daily × 7, on Days 2-8.[26]

In their study, Kantarjian et al.[20] investigated OM in a lower dose, longer infusion schedule of 2.5-3 mg/m^2 by continuous infusion daily for 14-21 days in patients with refractory-recurrent acute leukemia in an attempt to demonstrate efficacy without hypotensive events. While the response rate was low in this AML refractory group of patients, the longer infusion lower daily dose schedule averted cardiovascular toxicity. The summary Phase I-II trials of OM conducted at the Memorial Sloan-Kettering Cancer Center, New York Medical College, and the Eastern Cooperative Oncology Group included 117 patients with refractory AML treated at doses of 5-7 mg/m^2 daily by continuous infusion. Among 91 evaluable patients, 14 achieved a CR (15%) and 1 achieved a partial response.[23, 25-26]

In the New York Medical College studies, Feldman et al.[27] used OM, 5 mg/m^2, by continuous infusion daily for 9 days in patients with refractory-recurrent acute leukemia or blastic phase CML. Sixty-six patients were treated; their median age was 41 years. CRs were achieved in 7 of 43 patients (16%) with recurrent AML, in none of 11 patients with AML that primarily was resistant to anthracycline-cytarabine combinations, and in 2 of 3 patients whose disease was resistant to low-dose cytarabine. Side effects included significant hypotensive events, fluid retention, weight gain (29%), and hyperglycemia (63%).[27] Other studies have also demonstrated the activity of OM in AML.[28-30]

Studies with subcutaneous dose schedules of omacetaxine in AML established its safety and efficacy. Dose ranges of 0.5-5 mg/m^2 daily for 9 days were used. The

regimen was myelosuppressive.[31] In the MD Anderson experience doses of more than 2.5 mg/m^2 SQ daily for longer than 5 day exposures were associated with significant myelosuppression.

2.3 Myelodysplastic Syndrome (MDS)

Twenty-eight patients with MDS or MDS evolved into AML were treated with OM 5 mg/m^2/daily by continuous intravenous infusion for 9 days.[22] Their median age was 67 years. Seven patients achieved CR, and 1 had a PR, for an overall response rate of 28%. Complete response occurred in 3 of 15 patients with MDS and in 4 of 13 patients with MDS that evolved to AML. Median duration of remission was 7 months. In this study group, induction death was high (13 of 28 patients), mainly because of myelosuppression-related infections. Myelosuppression was prolonged and severe, but other toxicities were mild. [22] The dose schedule of OM used in this study of elderly patients was effective but toxic. Lower dose schedules of OM may demonstrate similar efficacy and lower toxicity in MDS.

2.4 Human toxicology

In the early trials of brief OM infusions (10-360 minute infusion daily for 1-10 days), delayed hypotension and reflex tachycardia were the dose-limiting and dose-dependent toxic effects of the drug. [24, 32-35] These effects were most prominent at doses above 3 mg/m^2 and appeared approximately 4-6 hours after bolus drug administration. Subsequent studies using lower dose longer infusion schedules resulted in complete elimination of the cardiovascular problems.

Administration of OM by continuous intravenous infusion schedules in Phase I-II studies has resulted in a dramatic decrease in the incidence of cardiovascular complications with an increased antiproliferative effect producing prolonged granulocytopenia and thrombocytopenia.[23] In a Phase I-II study of refractory AML dose of 2.5 mg/m^2 daily for 15 to 21 days (n = 13) or 3.0 mg/m^2 daily for 15 days (n =18).[20] Cardiovascular

complications were minimal, consisting of asymptomatic hypotension (drop of systolic blood pressure by 20 mm Hg) in one patient and supraventricular arrhythmias in two patients. While hypotension is still observed when OM is administered by continuous infusion, temporary interruption of dosing and/or fluid administration is usually successful in reversing this side effect. When OM was given by continuous IV infusion, hypotension appeared within 24-48 hours after starting treatment. With continuous infusion schedules, myelotoxicity becomes the dose-limiting toxicity.[24,32-35] Hyperglycemia, associated with increased plasma insulin levels, has been observed in adult patients treated with OM. Patients receiving OM therapy by continuous infusion, particularly at doses >5 mg/m^2, as well as diabetics and patients concurrently receiving asparaginase and/or prednisone should have their blood glucose levels routinely monitored. Therapy with insulin may be required; however, the effect is usually mild and reversible following completion of OM therapy.

2.6 Justification for study treatment plan

This study is a simple phase II study assessing the efficacy of OM in patients with MDS.. OM will be administered via subcutaneous injection at a dose of 1.25 mg/m^2 twice daily for 3 consecutive days every 28 days. This dosage route and schedule have been used in previous clinical studies both as a single agent and in combination with other therapies. Although many early studies administered OM using both bolus IV and continuous infusion, the subcutaneous route of administration is being used to provide better convenience to patients to allow administration at home. We have recently reported our experience using OM for 3 days in combination with low-dose cytarabine. This combination was found to be safe and effective in inducting an objective response rate of 50% (CR rate of 30%) with a median survival of 9.3 months.[6]

The pharmacokinetics and safety of this route has been evaluated in a dose escalation study in patients with AML. Dose dependent Cmax and AUC were observed, and an MTD of 5 mg/m^2/d for 9 days was reported. Based on these data and results as well as safety and efficacy data from previous studies, the dose of 1.25 mg/m^2 was selected as

it was associated with the greatest number of responses and had an acceptable safety profile.

2.7 Summary of risk and benefits

The safety profile of OM has been well documented in many clinical studies. The principal toxicities associated with subcutaneous OM have been myelosuppression, diarrhea, fatigue, nausea, fever, and infection which are not unexpected in patients with MDS.[36] There will be ongoing safety monitoring during the study and SAE and AE data will be reviewed in conjunction with the other safety measures.

3.0 Drug Descriptions

3.1 OM

OM is a cephalotaxine ester. It is an alkaloid derived from the plant Cephalotaxus fortunei. Cephalotaxines have the empirical composition C18H21NO4 and contain a methylenedioxypheno group, a secondary hydroxyl group, double bond and a vinyl methoxyl group. A variety of esters of cephalotaxine are known and the two which have been investigated clinically are harringtonine, ester-2 and homoharringtonine, ester-3. Homoharringtonine differs from harringtonine in having a methylene group inserted in the side chain. Homoharringtonine can be totally synthesized. OM is commercially available in China from Hangzhou Minsheng Pharmaceutical Group (Hangzhou, China) for the treatment of hematological malignancies. There are no known drug incompatibilities.

The study medication, OM will be provided to the principal investigator by the supporter, Cephalon, Inc. OM is approved by the FDA for use in the United States. OM drug product is a lyophilized vial containing 3.5 mg OM, 10 mg mannitol in a 10-mL clear glass vial, sealed with rubber stopper and aluminum flip-off seal. Drug is stored at controlled room temperature, 15ºC to 30ºC. The study drug will be provided as individual vials of 3.5 mg OM.

OM is administrated by the subcutaneous injection. Each 3.5-mg OM vial must be reconstituted with 1.0 mL of 0.9% NaCl (isotonic saline) before subcutaneous injection. Constituted OM can be stored at ambient temperature and must be used within 12 hours. If refrigerated, constituted OM can be stored for up to 6 days and must be used within those 6 days.

4.0 Study Design and Eligibility

4.1 Study design

This will be a single arm, single center, open label phase II study assessing OM in patients with intermediate-1 and higher risk MDS post HMA failure. OM will be administered at the dose of 1.25 mg/m^2 subcutaneously every 12 hours for 3 days. If patient is in the hospital a nurse will administer the treatment. If patient is at home then the treatment can be self-administered or administered by a family member. This Phase II study will include up to a total of 80 patients. The primary endpoint of this Phase II study is achievement of objective response and overall survival. Early stopping rules will be implemented for low CR rates and survival (please refer to section 11.2)

4.2 Patient eligibility

4.2.1 Inclusion

1. Age >/= 18 years

2. Diagnosis of MDS confirmed within 10 weeks prior to study entry according to WHO criteria. Patients are either not eligible for or choose not to proceed with a stem cell transplant.

3. MDS classified as follows: RAEB-1 (5%-9% BM blasts); RAEB-2 (10%-19% BM Blasts); CMML (5%-19% BM blasts); RAEB-t (20%-29% BM blasts) AND/OR by IPSS: intermediate-1 and high risk patients.

4. No response, progression, or relapse (according to 2006 IWG criteria) following at least 4 cycles of either azactidine or decitabine, which were completed within the last 2 years - AND/OR - intolerance to azacitidine or decitabine defined as drug-related >/= grade 3 hepatic or renal toxicity leading to treatment discontinuation during the preceding 2 years.

5. Eastern Cooperative Oncology Group (ECOG) performance status of </= 2.

6. Willing to adhere to and comply with all prohibitions and restrictions specified in the protocol.

7. Patient (or patient's legally authorized representative) must have signed an informed consent document indicating that the patient understands the purpose of and procedures required for the study and is willing to participate in the study.)

4.2.2 Exclusion

1. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

2. Active infection not adequately responding to appropriate antibiotics (i.e. ongoing temperatures of >/= 38 degree Celsius).

3. Total bilirubin >/= 1.5 mg/dL and not related to hemolysis or Gilbert's disease. Patients with total bilirubin >/= 1.5 mg/dL to 3 mg/dL are eligible if at least 75% of the bilirubin is indirect.

4. Alanine transaminase (ALT/SGPT) or aspartate transaminase (AST/SGOT) >/= 2.5 x the upper limit of normal.

5. Serum creatinine > 1.5 mg/dL.

6. Female patients who are pregnant or lactating.

7. Patients with reproductive potential who are unwilling to following contraception requirements (including condom use for males with sexual partners, and for females: prescription oral contraceptives [birth control pills], contraceptive injections, intrauterine devices [IUD], double-barrier method [spermicidal jelly or foam with condoms or diaphragm], contraceptive patch, or surgical sterilization) throughout the study.
8. Female patients with reproductive potential who do not have a negative urine or blood beta-human chorionic gonadotropin (beta HCG) pregnancy test at screening.

9. Patients receiving any other concurrent investigational agent or chemotherapy, radiotherapy, or immunotherapy.
10. Prior hydroxyurea for control of leukocytosis or use of hematopoietic growth factors (eg, G-CSF, GM-CSF, procrit, aranesp, thrombopoietins) is allowed at any time prior to or during study if considered to be in the best interest of the patient.
11. Psychiatric illness or social situation that would limit the patient's ability to comply with study requirements.

5.0 Treatment Plan

5.1 Treatment Plan

In this Phase II study 80 patients will be treated with OM for the first 3 days of every 4-7 week cycle. The primary endpoint of this study will be efficacy as measured by objective response rate and overall survival. Early stopping rules will be implemented for excessive toxicity or lack of efficacy. Please refer to statistical section 11 for details.

5.2 General study treatment plan

The intent of the study design is for all patients to receive up to 12 courses. Treatment will be continued during the duration of the study unless patients exhibit evidence of treatment failure, disease progression, experience an unacceptable toxicity, or the investigator determines that discontinuation of treatment is in the best interest of the patient.

Patients will be treated with study drugs based on a calculation determined from the patient's body surface area (BSA). BSA will be calculated before each cycle and will be based on the patient's height (measured at baseline) and weight (measured each cycle) and will be adjusted downward to "ideal" weight.

"Patients will be instructed to self-administer OM at home and return unused intact drug syringes to be disposed of by the study staff or dropped off to the Investigational Pharmacy. Patients will be given a Research Medication Diary to record the medication taken each day. Patients will be instructed to bring the diary and any unused intact medication syringes with them to all study visits. Any unused drug will be disposed of per institutional standard practice.

5.3 Dose modifications:

Patients will receive their OM treatment every 4-7 weeks:

a. OM 1.25 mg/m^2 SQ every 12 hours (+/- 3 hours) for 3 days.

Courses will be repeated every 4-7 weeks. Subsequent courses can be given with modified schedules as detailed below:

a. Stable or improved MDS with grade 2 or less toxicity: use same dose schedule as previous course.
b. MDS not improved with grade 2 or less toxicity, increase dose schedule to 4 days of OM if needed.
c. MDS stable/improved or not improved with grade 3-4 toxicity, give subsequent course with 2 days of OM if clinically indicated; otherwise may take patient off study.
d. Other modifications in the dose schedule based on response and toxicity of individual patient are allowed if in the patient best interest, after discussion with principal investigator.
e. Missed doses will not be made up.

In addition, any drug-related, non-hematologic toxicity experienced by a patient should return to ≤ grade 2 or the baseline grade before the patient continues treatment.

Other dose modifications may be permitted if in the patient's best interest after discussion with the Principal Investigator. Up to a total of 12 courses. Additional chemotherapy courses may be given if felt to be in the patient's best interest for an additional total of 12 courses (total 24 courses).

5.4 Supportive measures during treatment

Supportive care measures will be according to institutional and Leukemia Department guidelines.

5.5 Management of toxicities and dose modifications

5.5.1 At all cycles

All dose delays, reductions, and modifications for hematologic and non-hematologic toxicities will be assessed according to Sections 5.5.2 and 5.5.3.

5.5.2 Hematologic (blood/bone marrow) toxicity

No dose reductions, delays, or modifications are required for hematologic toxicities during the first cycle. It is assumed that low counts at diagnosis are due to involvement by the disease process and require therapy for improvement. Likewise, patients with persistent disease who are considered for more therapy can be expected not to have a recovery of their hematologic parameter and thus, no dose reductions, delays, or modifications are required for hematologic toxicities unless it is considered to do so in the best interest of the patient and after discussion with the Principal investigator.

5.5.3 Non-hematologic toxicity

If grade 2 toxicity occurs during any course of therapy, and it is unresponsive to optimal treatment and is possibly related to OM treatment, OM treatment may be withheld after the onset of an event until the AE has returned to baseline or ≤ grade 1. If the AE has returned to baseline or ≤ grade 1 within the 3 days of the first course or subsequent cycles, treatment may resume at the same dose, but missed doses will not be made up.

If grade 3 or greater toxicity occurs during any course of therapy, and it is unresponsive to optimal treatment and is possibly related to OM treatment, OM treatment may be withheld after the onset of an event until the AE has returned to baseline or ≤ grade 1. If the AE has returned to baseline or ≤ grade 1 within the 3 days of the first course or subsequent courses, treatment may resume but at a reduced OM subcutaneous dose of 1.0 mg/m^2 twice daily for the remainder of that cycle only. Missed doses will not be made up. In subsequent cycles of therapy, the dose of OM will be the original dose, but the number of consecutive days of OM treatments should then be reduced by 1 day for all subsequent treatment cycles.

If persistent grade 2 toxicity occurs after completion of a cycle of therapy (i.e., after day 3 of each course), and it is unresponsive to optimal treatment and is possibly related to OM treatment, OM treatment may be delayed up to 21 days after the onset of an event or until the AE has returned to baseline or ≤ grade 1. Then administer 100% of the planned dose. If toxicity persists longer than 21 days or recurs, the dose may be delayed and the number of consecutive days of OM treatments should then be reduced by 1 day for all subsequent treatment cycles.

If grade ≥3 toxicity occurs after completion of the OM treatment (i.e., after day 3 of each course) and it is suspected that OM played a role in toxicity, the next scheduled cycle of OM therapy should be withheld until toxicity returns to grade 0 or 1 or to baseline. The dose of OM will then remain the same, but the treatments may then be reduced by 1 day for all subsequent treatment cycles. Additional repeat dose reduction of 1 day will be made if toxicity recurs or persists. The number of consecutive days of OM may be reduced and the intervals between cycles may be shortened or increased, if clinically indicated. Missed doses of OM will not be made up.

Dose modifications different from those stated in the protocol will be decided jointly by the principal investigator and the treating physician.

Adverse events which are moderate to severe in intensity and which are assessed as possibly or probably related to study drug, may result in the termination of study treatment in the affected study patient.

Such termination should be reviewed with the principal investigator at the earliest possible time. Following review with the principal investigator, the study patient may be permanently withdrawn from the study depending upon the nature and severity of the event.

5.6 Supportive care

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

6.0 Pretreatment Evaluation

History and physical (including weight and blood pressure), CBC with differential and platelets, chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT, uric acid, LDH, potassium, magnesium, glucose), and an ECG within 14 days of therapy start.

Serum or urine HCG at screening for women of childbearing potential and within 3 days prior to treatment start.

Bone marrow aspirate and/or biopsy within 28 days of therapy start. The bone marrow evaluation will include immunophenotyping by flow cytometry and cytogenetic studies.

MDS flow panel

7.0 Evaluation During Study

Patient will have physical examination prior to each course. In addition:

1. CBC with differential and platelet counts at least once a week until remission, then every 2 to 4 weeks during active treatment, and every 4 to 8 weeks thereafter as long as on study. No differential is needed if the WBC is < 1.0 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. If pre-treatment MDS Flow Panel was initially abnormal, sequential MDS Flow Panel to be performed after cycle 2 then every 2 to 4 cycles until response observed, then as clinically indicated if possible.

5. Conventional cytogenetics to be performed after cycle 2 then every 2 to 4 cycles until response observed, then as clinically indicated.

The patient may have the laboratory work done by their home physician and the results reported to the research nurse for the study.

Patient will be followed for survival at MDACC every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MD Anderson Cancer Center the follow-up visits may be conducted via telephone.

8.0 Criteria for Response

The response criteria recommended by the MDS International Working Group.

Definitions:

8.1 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).

8.2 Partial response (PR):

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

8.3 Hematologic Improvement (HI):

Meets all criteria for CR except for platelet recovery to ≥100 x 10^9/L.

8.4 Marrow CR:

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

8.5 Clinical benefit:

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 1.0 x 10^9/L (if lower than that pretherapy); or hemoglobin increase by 1.5 g/dl ; or transfusion independent; or splenomegaly reduction by > 50%; or monocytosis reduction by > 50% if pretreatment > 5 x 10^9/L.

8.6 Relapse-free survival (RFS)

- Time from date of response until the date of first objective documentation of disease-relapse.

8.7 Overall survival (OS)

- Time from date of treatment start until date of death due to any cause.

9.0 Criteria for Removal from the Study

Patients are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. Patients may be discontinued from the study for the following reasons:

1. Patient requests discontinuation.
2. There is unacceptable toxicity (i.e., NCI CTCAE version 4 grade 4 drug-related non hematologic toxicity).
3. Patient experiences an NCI CTCAE version 4 >/= grade 3 drug-related non-hematologic toxicity or clinically significant infection of any grade that is not recovered by Day 75 from the onset of the toxicity.
4. Patient experiences a third occurrence of an NCI CTCAE version 4 grade 3 drug-related non-hematologic toxicity.
5. Patient experiences asymptomatic grade 2 total bilirubin or creatinine abnormality that is not recovered by Day 75 from the onset of the toxicity.
6. There is a need for any treatment not allowed by the protocol.
7. Treatment failure or disease relapse.
8. Investigator discretion.

10.0. Regulatory and Reporting Requirements

Adverse event reporting will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) most current version will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

10.1 Expedited adverse event reporting

Refer to **Appendix C** for 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.

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.

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***

11.0 Statistical Considerations

The proposed study is a single-arm phase II clinical trial study in patients with MDS who have failed therapy with hypomethylating agents. The primary endpoint is to determine the overall survival, defined as the time from treatment start to the time of death A maximum of 80 patients will be accrued at a rate of 1 to 5 patients per month (maximum accrual period 3.33 years). Additional 12 months of follow-up is planned after the last patient is accrued into the trial. It is anticipated that treatment with OM will prolong the

median OS from 4.2 months, as shown in the current standard therapy, to 6 months. The CR, overall survival and toxicity will be monitored during the study, and all data will be used to update the prior distributions for toxicity and efficacy parameters. It will be postulated that the treatment can achieve a CR rate of 20 percent.

We compare median survival time among patients in this study to historical median survival time of 4.2 months. We assume an exponential distribution of failure in the study group and a two-sided significance level of 0.05. Given one additional year of follow up after study recruitment and an accrual rate of 1-5 patients per month, 80 patients will yield a power of 84% to test for a 1.8 months improvement in median survival from 4.2 months.

11.1 Overall Survival Monitoring

The efficacy endpoint, OS, will be continuously monitored using the Bayesian method by Thall et al.[37] Let Ts and Te represent the OS times for the historical regimen and the experimental regimen OM, respectively. We assume Ts|Ms and Te|Me follow an exponential distribution with respective median Ms and Me. Furthermore, we assume that the prior for Ms follows an inverse gamma distribution IG (5.0, 16.8) to reflect our knowledge of OS in patients treated historically with standard regimen. This prior distribution has a mean of 4.2 months, and a variance of 5.88. The prior for Me is assumed to be IG (2.18, 4.94), which has the same mean of 4.2 months and a larger variance of 100 to reflect our uncertainty about the median OS of the proposed experimental regimen, OM.

The OS will be continuously monitored, and the study will be terminated early if, based on the available data, there is less than 5% chance that the median OS in patients treated with OM will improve by more than 1.8 months, compared to the historical regimen. The futility stopping rule is as follows:

$$Pr(Me > Ms + 1.8 \text{ months} \mid data) < 0.05$$

The operating characteristics of this decision rule are summarized in Table 1 using the one-arm TTE software developed by the Department of Biostatistics at M.D. Anderson Cancer Center.

Table 1. Operating characteristics for the design (based on 5000 simulations)

Scenario	True Median (months)	Pr(Stopped Early)	Mean No. patients	Average Trial Duration (months)
1	2.0	0.9999	13	16.26
2	3.0	0.8882	32	22.54
3	4.2	0.2332	66	34.00
4	5.0	0.1088	73	36.29
5	6.0	0.0478	77	37.58
6	7.0	0.0236	78	38.05

The monitoring for OS will be carried out through the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) which is housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics. Training on the use of the CTC will be provided by the biostatistical collaborator of the study, with emphasis on the importance of timely updating of follow-up times and recording of events. The monitoring rule for OS will be applied continuously when a new patient is enrolled or an existing patient's data is updated. If the stopping rule is met, an automatic email will be sent out to the study PI, RN and the study statistician to keep them informed and the CTC website will not allow enrollment of any new patients.

11.2. CR Rate and Toxicity Monitoring

Complete response rate and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) and the extension by Thall and Sung (1998). This regimen of the experimental treatment will be considered worthy of further investigation if it elicits an increase in CRR to 20% with acceptable toxicity. A toxicity rate greater than 30% is considered unacceptable. Thus, a beta (20, 80) and beta (0.4, 1.6) priors were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a beta (30, 70) and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity rate and experimental treatment toxicity prior distribution, respectively. Interim monitoring rules, assuming the prior distributions, were constructed that meet the following two conditions,

1) $Pr(\theta_{S,\,Toxicity} < \theta_{E,\,Toxicity} \mid data) > 0.975$ and,

2) $Pr(\theta_{E,\,CR} > \theta_{S,\,CR} \mid data) < 0.025$

Where $\theta_{E,\,Toxicity}$ and $\theta_{E,\,CRR}$ are the toxicity and response rates for the experimental treatment, and $\theta_{S,\,Toxicity}$ and $\theta_{S,\,CRR}$ are the toxicity and response rates for the standard treatment respectively. The first rule provides for stopping the study if excessive toxicity is highly probable (i.e., probability >97.5%) for the experimental treatment. The second condition will stop the study early if the data suggest that it is unlikely (i.e., probability < 2.5%) that CR rate of the experimental treatment is 20%. Assuming the minimum number of patients is 5, the maximum number of patients is 80 and the cohort size is 5. Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 4).The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is in Table 2. Toxicity is defined as grade 3 or higher drug-related non-hematologic toxicity during the first cycle. For example, accrual will cease if 5 patients experience toxicities among the first 5 patients treated or if 7 or more patients experience toxicities among the first 10 patients.

Table 2. Stop accrual if the number of toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated

# patients evaluated	# patients with toxicities		# patients evaluated	# patients with toxicities
5	5		45	22-45
10	7-10		50	24-50
15	9-15		55	26-55
20	11-20		60	28-60
25	14-25		65	30-65
30	16-30		70	32-70
35	18-35		75	34-78
40	20-40		80	Always stop with his many patients

Monitoring the response rate, based on the above assumptions will begin after 5 patients are treated, on an intent-to-treat basis (Table 3). For example, accrual will cease if 0 patients experience a response in the first 10 patients treated.

Table 3. Stop accrual if the number with CR is less than or equal to indicated (i.e., # patients with CR) among the number of patients evaluated

# patients evaluated	10-20	25-30	35-40	45	50-55	60-65	70	75
# patients with CR	0	0-1	0-2	0-3	0-4	0-5	0-6	0-7

The probability of stopping the study early for low CRRs (i.e., 10%) was higher than 0.70 when toxicity rates were ranged from 20% to 40%. Probabilities of stopping early for high true toxicity rates (i.e., 40%) were 81% when the true CR rate was 10% and 45% when true CRR was 20%.

Table 4. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated

True CRR	True Toxicity Rate	True Probability Vector (CRR/Tox, CRR/NoTox, NoCRR/Tox, NoCRR/NoTox)	Probability of Stopping	Average number of patients treated
10%	20%	(0.02, 0.08, 0.18, 0.72)	0.6960	44
10%	30%	(0.03, 0.07, 0.27, 0.63)	0.7076	43
10%	40%	(0.04, 0.06, 0.36, 0.54)	0.8054	36
20%	20%	(0.04, 0.16, 0.16, 0.64)	0.1346	71
20%	30%	(0.06, 0.14, 0.24, 0.56)	0.1676	69
20%	40%	(0.08, 0.12, 0.32, 0.48)	0.4462	57

30%	20%	(0.06, 0.24, 0.14, 0.56)	0.0309	78
30%	30%	(0.09, 0.21, 0.21, 0.49)	0.0679	76
30%	40%	(0.12, 0.18, 0.28, 0.42)	0.3798	61

11.3 Analysis method

Safety data will be summarized using frequency and percentage. Complete response rates will be estimated along with the 95% credible intervals. Kaplan--Meier method will be used to analyze survival data including overall survival time, response duration and relapse free survival time. The survival medians will be estimated with 95% confidence intervals.

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