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MD Anderson Cancer Center

Protocol Page

Clofarabine plus Low-Dose Cytarabine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome (MDS) who have been Relapsing after, or are Refractory to, Hypomethylator Therapy
2011-0660

Core Protocol Information

Short Title	Clofarabine plus Low-Dose Cytarabine for Patients with Higher-Risk MDS
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Full Title:	Clofarabine plus Low-Dose Cytarabine for the Treatment of Patients with Higher-Risk Myelodysplastic Syndrome (MDS) who have been Relapsing after, or are Refractory to, Hypomethylator Therapy
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Pimary objectives

The primary objective is to assess complete response (CR) rate and overall survival

Secondary objectives

The secondary objectives are to assess duration of response, relapse-free survival, and the safety profile

2.0 Background

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders charaterized by progressive pancytopenia due to impaired cellular differentiation and increased apoptosis, with a tendency to convert to acute leukemia [1]. The disease typically affects individuals over 65 years of age, and it is thought to result from multiple mutations affecting the hematopoietic stem cell. There is a wide clinical spectrum of MDS ranging from moderate anemia with normal neutrophil and platelet counts, to frank leukemia with a clinical course that can range from a few months to many years. Treatment options are limited. Only bone marrow transplantation offers a cure although there are significant treatment-related adverse events that can result from this procedure [2].

In the U.S. there are currently 2 drugs approved for the treatment of (non 5q-) MDS: azacitidine and decitabine (referred to collectively as hypomethylating agents). Both drugs are active although the objective response rates they produce are low [3]. In the case of azacitidine a recent large randomized study demonstrated a survival benefit for azacitidine-treated patients compared to those who received conventional care (including best supportive care) [4]. Although either of these drugs are among the best availabe outside clinical trials, they are not curative and typically patients relapse either on therapy or shortly after completion of therapy. SGI-110 is a second generation hypomethylating agent with significantly increased activity than azacitidine or decitabine and is being investigated at MD Anderson Cancer Center (MDACC Protocol # 2010-0615).

These patients who have either not responded to or relapsed from treatment with hypomethylating agents carry a dismal prognosis with a median survival of less than 6 months, a 1-year survival probability of less than 30% and a likelihood of response to conventional therapies (e.g. cytarabine of around 20%) [5]. Hence, new approaches are needed for patients in this situation.

Clofarabine is a second generation purine nucleoside analog that incorporates two halogen atoms, chlorine and fluorine, resulting in resistance to both adenosine deaminase degradation and phosphorolysis [6]. Studies of clofarabine (both i.v. and p.o.) have demonstrated activity in patients with higher risk MDS [7]. In addition, we have previously shown the feasibility and efficacy of the combination of lower dose clofarabine (30 mg/m^2/day) with low-dose cytarabine in patients with high-risk MDS and acute myeloid leukemia (AML), which was more active than single agent clofarabine [8].

Here we propose to take this approach of the combination of clofarabine with low-dose cytarabine and use this combination to treat patients with higher-risk MDS who have failed to respond to hypomethylating agents.These patients are facing a huge unmet medical need.

3.0 Background Drug Information

3.1 Clofarabine

Clofarabine is FDA approved for children with relapsed/refractory acute lymphoblastic leukemia and

therefore commercially available.

Clofarabine is formulated at a concentration of 1mg/mL in sodium chloride (9mg/mL), United States Pharmacopeia (USP) or European Pharmacopeia (EP) and water for injection, USP or EP, quantity sufficient (qs) to 1 mL. Clofarabine is supplied in 20-mL flint vials contain 20 mL (20 mg) of solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and practically colorless, is preservative free, and is free from foreign matter.

Vials containing undiluted clofarabine should be stored at room temperature (15° to 25° C; 59° to 77° F). Ongoing shelf-life stability studies indicate that clofarabine is stable for 36 months at 25°C and 60% relative humidity and for 6 months at 40°C (+/- 2°C) and 75% (+/- 5%) relative humidity.

Clofarabine for injection should be filtered through a sterile 0.2 microM syringe and then further diluted with 0.9% sodium chloride injection USP or EP for a final concentration of 0.15 to 0.4 mg/mL prior to IV infusion. The resulting admixture may be stored at room temperature, but must be used within 24 hours of preparation. Clofarabine will be administered as a 1- to 2-hour IV infusion as tolerated. To prevent drug incompatibilities, no other medications should be infused concurrently throught he same IV lines as clofarabine. Also, no blood products should be administered at the same time as clofarabine.

3.2 Cytarabine (Ara-C)

Cytarabine is available commercially.

Cytarabine is a deoxycytidine analog that is metabolized to cytarabine triphosphate, a substance that inhibits DNA polymerase. It is S phase specific, and thus affects DNA synthesis. It has an initial plasma half-life of about 15 minutes, with a secondary phase of about 2 hours, and is rapidly catabolized by hepatic cytidine deaminases to Ara-U.

Cytarabine injection, an antineoplastic is a sterile solution of cytarabine for intravenous administration. Each mL contains 20 mg cytarabine in 100 mg (20 mg/mL) single dose vials and 100 mg cytarabine in 2 g (100 mg/mL) single dose vial.

Cytarabine comes as 20 mg/mL (5, 25 and 50 mL vials) and 100 mg/ml solutions (20 mL vial), in addition to several vial sizes of powder for solution (100 mg, 500 mg, 1 g, 2 g).

Cytarabine to be prepared as per institutional standards based on product availability.

3.3 Expected Toxicities

Myelosuppression, nausea/vomiting, diarrhea, mucositis, skin rash with blisters (particularly hand-foot syndrome), Steven-Johnson's syndrome, fatigue, mental status changes/coma, allergic reactions (including fever, muscle aches, edema, dyspnea), congestive heart failure, conjunctivitis, and anorexia. Pancreatitis, liver failure, kidney failure. Infections.

Autoimmune reactions (antiplatelet antibodies, erythema nodosum) and/or chemical imbalances in the blood, lethargy, malaise, asthenia, alopecia, peritonitis, anorexia, stomatitis/pharyngitis, hyperbilirubinemia, increase of SGPT and/or SGOT, abdominal pain or cramping.

3.4 Drug Supply

Clofarabine is approved by the FDA for use in pediatric acute lymphoblastic leukemia and will be used off label in higher-risk MDS in this study. Ara-C (cytarabine) is approved for use in patients with AML but will

be used for patients with higher-risk MDS in this study. Neither clofarabine nor cytarabine will be provided free of charge during the study.

4.0 Patient Eligibility

Inclusion:

1) Age >/= 18 years.

2) Diagnosis of MDS confirmed within 10 weeks prior to study entry according to WHO or FAB 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-2 and high risk patients.

4) No response, progression, or relapse (according to 2006 IWG criteria; see section 8 for details) following at least 4 cycles of either azactidine or decitabine, or following at least 2 cycles of SGI-110, which were completed within the last 2 years - AND/OR - intolerance to azacitidine, decitabine, or SGI-110 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 proecdures required for the study and is willing to participate in the study.

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 devies [IUD], double-barrier method [spermidical jelly or foam with condoms or diaphragm], contraceptive patch, or surgial 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) No prior treatment with cytarabine or clofarabine. 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 Study Treatment

Patients may receive up to 3 cycles of induction therapy and up to 12 cycles of consolidation. Treatment will be terminated if patients exhibit evidence of treatment failure, disease progression, experience clinically significant 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 BSA. Body surface area (BSA) will be calculated before each cycle and will be based on the patient's height (measured at baseline) and weight (measured each cycle).

Patients will be instructed to self-administer cytarabine at home and return unused drug to be handled and processed by the dispensing pharmacy.

In order to lower the risk of pregnancy, patients of child bearing potential must agree to use acceptable forms of birth control until at least 8 weeks after the last dose of therapy is administered. If patients are already using birth control, they must check with the study doctor or a member of the study staff to make sure that it is considered one of the acceptable forms to use in this study. Examples of effective birth control include condoms or diaphragms with spermicidal jelly, and birth control methods that are taken by mouth, injected, or implanted.

Exepct for the first cycle, treatment can be administered at MDACC or through the supervision of the home physician.

5.1.1 Induction

Clofarabine 10 mg/m2 as a 1-2 hours i.v. infusion. daily for 5 days (days 1-5)
Cytarabine 20 mg s.c. twice daily for 7 days (days 1-7)

Cytarabine should be administered 3 to 6 hours following the start of the clofarabine infusions.

Cycles are repeated every 4 to 8 weeks depending on resolution of toxicities. No dose reductions, delays, or modifications are required for hematologic toxicities during the induction cycles. It is assumed that low counts at diagnosis are due to involvement by the disease process and require therapy for improvement. Patients who receive repeated induction cycles have persistent disease and thus no recovery of hematologic parameters can be expected.

Patients can receive up to a maximum of 3 induction cycles as long as they have stable disease and do not progress. If patients have not achieved at least a hematologic improvement after three cycles, they should be taken off study. Patients with at least hematologic improvement can continue the consolidation. Patients with any response less than CR or CRp before completion of three induction cycles can complete all three induction cycles in an effort to maximize their response prior to moving on with the consolidation if this is considered in the best interest of a particular patient.

5.1.2 Consolidation

Clofarabine 10 mg/m2 as a 1-2 hours i.v. infusion daily for 3 days (days 1-3)
Cytarabine 20 mg s.c. twice daily for 5 days (days 1-5)

Cytarabine should be administered 3 to 6 hours following the start of the clofarabine infusions.

Cycles are repeated every 4 to 8 weeks depending on hematopoietic recovery and resolution of toxicities. The maximum number of consolidation cycles is 12. Patients who continue with treatment after a delay for any reason other than toxicity or adverse event must restart treatment by Day 84 after Day 1 of the previous cycle. Patients can start after day 84 if discussed with and approved by the Principal Investigator.

5.1.3. Supportive Measures During Treatment

Necessary supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the patient's medical need and by the institutional guidelines. Administration of antiemetics during drug administration is strongly recommended.

It is recommended that the patient's fluid status and hepatic and renal function be carefully monitored daily during the drug administration period.

Management of Capillary Leak Syndrome

In pediatric studies, during or shortly after IV clofarabine administration a few patients developed signs and symptoms consistent with capillary leak syndrome. In these heavily pretreated patients, it has been difficult to separate potential drug-related cases of capillary leak syndrome from concurrent medical conditions such as infections/sepsis, progressive disease, or other underlying problems resulting from prior antileukemic therapies.

For these reasons, during and after each dose of clofarabine investigators should assess patients for the onset of the following signs or symptoms >/= grade 2:

- Tachypnea or other evidence of respiratory distress;
- Unexplained hypotension; and/or
- Unexplained tachycardia

If one or more of these signs or symptoms occurs during study drug infusion, clofarabine administration is to be interrupted or held as clinically indicated. It is recognized that the total infusion time for this clofarabine dose in this circumstance may exceed 1 hour. Thus, if the patient's condition stabilizes or improves, clofarabine administration may resume. Pretreatment with steroids (e.g. hydrocortisone 100 mg/day or its equivalent or dexamethasone 20 mg/day as part of an anti-emetic regimen) is recommended for all subsequent doses during the remainder of that treatment cycle and for all subsequent treatment cycles.

5.2 Dose Modifications

Dose modifications can be made for one drug only if the investigator is reasonably confident that the toxicity relates to that particular drug. If that distinction cannot be made, the doses of both drugs should be modified.

Missed doses of clofarabine and/or cytarabine can be made up on subsequent days if felt to be in the best interest of the patient.

5.2.1 Hematologic (Blood/Bone Marrow) Toxicity

No dose reductions, delays, or modifications are required for hematologic toxicities during the induction cycles. It is assumed that low counts at diagnosis are due to involvement by the disease process and require therapy for improvement. Patients who are considered for reinduction have persistent disease and thus no recovery of hematologic parameters can be expected in the absence of further therapy.

Patients who achieve a CR/CRp should receive the consolidation cycles no sooner than 28 days from Day 1 of the previous cycle, provided the ANC has recovered to >/= 1.0 x 10^9/L and the platelet count >/= 50 x 10^9/L (in case of CR). For patients in CRp where the platelet count by definition has not recovered, no limits are set to continue. If the peripheral count recovery is delayed beyond 42 days from Day 1 of the prior cycle and the delay is presumed to be secondary to the therapy, the study drug doses for the next cycle should be reduced by 25%.

5.2.2 Non-Hematologic Toxicity

Patients who experience a > grade 1 drug-related non-hematologic toxicity or drug-related asymptomatic grade 2 elevations of creatinine, bilirubin, amylase, lipase during any week of treatment should have clofarabine held until recovery to grade 1 before starting treatment. Grade 3 drug-related toxicities that result in delays or omissions must resolve to grade 1 before starting treatment. Dose omissions due to toxicities that occur during the treatment can be made up as per the treating physician's discretion and if this is felt to be in the best interest of the patient.

5.2.2.1 Infections

If a patient develops a clinically significant infection of any grade, initiation of treatment cycles will be delayed or withheld until the infection is clinically controlled (e.g., the patient is afebrile and with improving signs/symptoms). Treatment (i.e., subsequent cycles) may then resume at the full dose. At the discretion of the investigator, prophylactic therapy to prevent recurrence of infection can be instituted as clinically indicated.

5.2.2.2 Non-infectious, drug-related

a) First or second occurrence of a drug-related >/= grade 3 toxicity:

<u>If toxicity recovers to Grade 1 within 35 days from the onset of the toxicity</u>: study therapy is to be restarted at 25% reduction with no alteration in schedule from the previous doses for all subsequent cycles.*

<u>If toxicity **does not** recover to Grade 1 within 35 days from the onset of toxicity</u>: the patient should not receive additional study drug.*

* Excludes NCI CTC grade 2 alopecia and >/= grade 3 anorexia, transient elevations in hepatic transaminases or alkaline phosphatase based on institutional normals without clinical significance, and nausea/vomiting, diarrhea or mucositis that resolves (with or without supportive care) to < grade 2 within 72 hours of onset to grade 3.

b) 3rd Occurrence of a drug-related non-infectious event(s): Grade 3 toxicity:

The patient should not receive any additional treatment.

5.3 Supportive Care

5.3.1 Blood Products

All blood products are to be irradiated and leukocyte-reduced according to institutional guidelines.

5.3.2 Infection Prophylaxis

The use of prophylactic antibacterial, antifungals, and antiviral agents is recommended according to standard of care.

5.3.3 Colony Stimulating Factors

Hematopoietic growth factors (e.g., granulocyte colony stimulating factor [G-CSF]) can be administered at the treating physician's discretion and judgment.

5.3.4 Concomitant Therapy

No systemic concomitant cytotoxic therapy or investigational therapy is allowed during the study.

To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B, etc) and hepatotoxic (e.g., voriconazole, cyclosporine, etc) agents is strongly discouraged and is to be avoided during clofarabine administration for all treatment cycles unless there are compelling reasons to do so.

6.0 Pretreatment evaluation

History and physical.

CBC with differential and platelets, chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT, uric acid, LDH, potassium, magnesium) within 14 days of therapy start.

Bone marrow aspirate and/or biopsy within 28 days of therapy start. The bone marrow evaluation must include cytogenetic studies except for situations where cytogenetic analysis was not added to a bone marrow aspirate and/or biopsy and the stage/prognostic group of the MDS can be ascertained as higher risk based on the available information (eg, blasts and/or degree of cytopenias).

Pregnancy (urine or blood) test for women of childbearing potential within two weeks of start of therapy. Child bearing potential is defined as not post-menopausal for 12 months or no previous surgical sterilization.

7.0 Evaluation During Study

CBC with differential and platelet counts at least weekly while on therapy and every 4 to 8 weeks thereafter as long as on study. No differential is needed if the WBC is $< 1.0 \times 10^9$/L.

Chemistry profile (at least creatinine, SGOT or SGPT, total bilirubin, potassium, magnesium) every two weeks while on therapy, then every 4 to 8 weeks as long as on study.

Bone marrow aspirate and/or biopsy at the end of course 1 (day 28 +/- 7 days). If a patient is not in remission at this point, further bone marrow aspirate and/or biopsy can be scheduled as per the investigator's discretion and mandated by the development of the peripheral blood counts.

No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests, or, in patients with a WBC $\leq$ 0.3 if the bone marrow test is considered non-contributory by the investigator at any time point.

Follow up marrow tests should include cytogenetic analysis for those patients who had abnormalities prior to therapy start.

Repeat physical examination (problem focused) prior to administration of each course

After completion of therapy and as long as still on study, patients will return to MD Anderson Cancer Center for repeat physical examination (problem focused), repeat CBC with differential and platelet count, and chemistry profile (at least creatinine, SGOT or SGPT, total bilirubin, potassium, magnesium) every 6 months (+/- 2 months). A CBC with differential and platelet count should be checked every one to two months, but these blood tests may be done locally.

8.0 Criteria for Response

Category	Response Criteria (responses must last for at least 4 weeks)
Complete remission (CR(	**Marrow**: </= 5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia will be noted (dysplastic changes should consider the normal range of dysplastic changes.) **Blood:** - Hemoglobin (Hb) >/= 11 g/dL (untransfused, patient not on EPO) - Neutrophils >/= 1x109/L (not on myeloid growth factor) - Platelets >/= 100 x 109/L (not on thrombopoietic agent) - No blasts
Partial remission (PR)	All CR criteria (if abnormal prior to treatment), except: Marrow blasts decreased by >/= 50% compared with pretreatment but still > 5%. Cellularity and morphology not relevant
Marrow CR	Marrow: </= 5% myeloblasts and decrease by >/= 50% over pretreatment Blood: if hematologic improvement (HI) responses, they will be noted in addition to the marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks.
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment.
Relapse after CR or PR	At least one of the following: - Return to pretreatment bone marrow blast percentage - Decrement of >/= 50% from maximum remission/response levels in granulocytes or platelets - Reduction in Hb concentration by >/= 1.5 g/dL or transfusion dependence (in the absence of another explanation, such as acute infection, GI bleeding, hemolysis, etc.)
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality

Disease progression	For patients with < 5% blasts: >/= 50% increase in blasts to > 5% blasts 5%-10% blasts: >/= 50% increase in blasts to > 10% blasts 10%-20% blasts: >/= 50% increase in blasts to > 20% blasts 20%-30% blasts: >/= 50% increase in blasts to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response levels in granulocytes or platelets. Reduction in Hb concentration by >/= 2 g/dL. Transfusion dependence (in the absence of another explanation, such as acute infection, GI bleeding, hemolysis, etc.)
Hematologic Improvement	**Response Criteria (responses must last at least 8 weeks)**
Erythroid response (pretreatment, < 11 g/dL)	Hb increase by >/= 1.g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hb of </= 9 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, < 100x109/L)	Absolute increase of >/= 30 x 109/L for patients starting with > 20 x 109/L Increase from < 20 x 109/L to > 20 x 109/L and by at least 100%
Neutrophil response (pretreatment, < 1 x 109/L)	At least 100% increase an an absolute increase > 0.5 x 109/L
Progression or relapse after HI	At least 1 of the following: At least 50% decrement from maximum respnose levels in granulocyte or platelets Reduction in Hb by >/= 1.5 g/dL Transfusion dependence (in the absence of another explanation, such as acute infection, GI bleeding, hemolysis, etc.)

Reference: Cheson et al. 2006

9.0 Criteria for Removal from the Study

Reason to take patients off study include (but are not limited to) the following:

- Progressive disease
- Patient refusal
- Patient non-compliance
- Physician judgment
- Pattern of patient non-compliance

10.0 Data Monitoring Plan

This is a single arm phase II study in patients with MDS who have failed therapy with or are intolerant of hypomethylating agents.

Primary objective: complete response (CR); overall survival.
Secondary objective: duration of response; relapse-free survival; safety.

It will be postulated that the treatment can achieve a CR rate of 20% and a median overall survival time of 6 months.

A maximum of 80 patient will be accrued at a rate of 2 to 5 patients per month (maximum accrual period 3.33 yrs). 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. The study will be stopped for toxicity and futility based on the following stopping rules.

Efficacy monitoring

Complete response and overall survival will be monitored separately. The method of Thall, Simon, and Estey [9] will be used to monitor response and Bayesian time-to-event model [10] will be used to monitor overall survival.

a. CR

CR will be monitored in all pts using the method of Thall et al.[9] Denote the probability of CR by PE. We assume PE ~ beta (0.4, 1.6). We will stop the trial if at any point that there is < 1% chance that the CR rate is > 20%. Stopping boundaries corresponding to this stopping rule and operating characteristics are listed in tables 1a and 1b. CR in the 4 months after the treatment will be included in the primary analysis.

Table 1a. Stop accrual if the number of response is equal to or less than indicated (i.e., # response) among number of patients accrued (i.e., # Patients). (PL=0.01)

# CR	0	1	2	3	4	5	6	7	8
# Pts	15	24	33	41	49	56	64	71	78

Table 1b: Operating characteristics of response (based on 10000 simulations) (PL=0.01)

True Probability	**Stop Probability**	**Trial Sample Size Percentile**		
		25%	**50%**	**75%**
0.05	0.992	15	24	33
0.1	0.735	24	41	80
0.15	0.301	64	80	80
0.2	0.086	80	80	80

b. Overall survival

Bayesian time-to-event model will be used to monitor the overall survival [10]. Let Te and Ts represent the overall survival time for the study and the historical treatment, respectively. We assume Te|Me and Ts|Ms follow an exponential distribution with median Me and Ms, respectively. We further assume that the prior for Ms follows Inverse Gamma (IG) (35, 204) to reflect our knowledge of overall survival from the historical data, which has a mean of 6 months and a variance of 1.09. The prior for Me is assumed to be IG (3,12), which has the same mean as Ms but with a much larger variance (36) to reflect much greater uncertainty about the median time to progression of the study treatment.

The study will be monitored after the first 14 pts have been enrolled and then be repeated every month. The study will be stopped early if, based on the available data, we have little reason to believe that the median OS is 6 months or more. Formally, we'll stop the study early if there is < 5% chance that the median OS is 6 months or more. The operating characteristics of this decision rule are shown in the following table:

Table 2: Operating characteristics of Efficacy Monitoring(PL=0.05)

True Median OS (Mos)	P(Stop)	Mean Number of Pts (25%, 75%)
2	1	18 (15,20)
4	0.835	42 (21,63)
6	0.079	76 (80,80)
7	0.024	79 (80,80)

Toxicity Monitoring

Toxicity will be monitored in all pts using the method of Thall et al 1995 [9]. Toxicity is defined as non-hematologic grade 3 or 4 toxicities during the treatment course. Denote the probability of toxicity by E, where study drug related toxicity is defined as any Grade 3 or greater non-hematological toxicities. We assume E ~ beta (0.6, 1.4). We will stop the trail if at any point Pr(E > 0.30 | data) >0.95, i.e. if at any time during the study, we determine that there is > 95% chance that the study drug related toxicity rate is > 30%. Toxicity monitoring will be done in cohorts and the trial will be stopped if (number of toxicity observed / among number of patients) >/= 6/10, 8/15, 10/20, 12/25, 14/30, 16/35, 18/40, 19/45, 21/50, 23/55, 25/60, 26/65, 28/70, 30/75, and 31/80.

Table 3: The operating characteristics for toxicity monitoring are summarized in the following table

True toxicity probability	Probability of early stop	Sample size percentiles (10, 25, 50, 75, 90)
0.1	0	80 80 80 80 80
0.2	0.012	80 80 80 80 80
0.3	0.188	23 80 80 80 80
0.4	0.755	10 15 36 79 80
0.5	0.99	10 10 15 25 41

Early termination of the study can be caused by either lack of efficacy or too much toxicity. If the efficacy and toxicity are considered jointly, the stopping probabilities will be higher than the probabilities shown in Tables 1 to 3.

Table 4 shows several scenarios of the joint stopping probabilities assuming that efficacy and toxicity are independent.

Table 4: Operating characteristics considering efficacy and toxicity jointly

True probability of CR	True Median OS (mos)	True Probabilty of Toxicity	Early Stop Probability
0.25	7	0.2	0.06
0.25	4	0.2	0.84
0.25	7	0.5	0.99
0.2	6	0.3	0.316
0.1	4	0.4	0.989
0.1	6	0.2	0.759
0.1	7	0.4	0.937

All calculations were performed using OnearmTTE and Multc99.

Trial Conduct

The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct") for monitoring of the overall survival. The Clincal Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology.

Personnel responsible for enrolling patients on trials will be trained in the use of the trial website, with emphasis on the importance of timely updating of follow-up times and recording of events. The monitoring rules for the overall survival will be automatically evaluated each time patient data are updated on the trial website. If the stopping rule is met, the study statistician, research nurse, and principal investigator will each receive an email notification that the stopping boundary has been met.

Analysis Plan

For discrete or categorical data, descriptive statistics will include tabluations of frequencies. For continuous data, summary statistics including n, mean, standard deviation, median, minimum and maximum will be computed. The posterior CR rate and its 95% credible intervals will be estimated. The Kaplan-Meier method will be used to estimate the probability of the overall survival.

11.0 Reporting Requirements

Please refer to Appendix D (Leukemia-specific adverse event recording guidelines) and Appendix E (Expected adverse events in leukemia).

Serious Adverse Event Reporting (SAE)

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

· Death
· A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
· Inpatient hospitalization or prolongation of existing hospitalization
· A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
· A congenital anomaly/birth defect.

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

· All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events".

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

Recommended Adverse Event Recording (PDMS) Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

12.0 References

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