



Protocol Page

A Phase 2 Study of E7070, Idarubicin and Cytarabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia and High-risk Myelodysplastic Syndromes  
2009-0570

---

**Core Protocol Information**

|                            |  |
|----------------------------|--|
| <b>Short Title</b>         | E7070, idarubicin and cytarabine in relapsed AML and HR MDS  |
| <b>Study Chair:</b>        | Gautam Borthakur   |
| <b>Additional Contact:</b> | Melodie S. England<br>Leukemia Protocol Review Group   |
| <b>Department:</b>         | Leukemia   |
| <b>Phone:</b>              | 713-563-1586   |
| <b>Unit:</b>               | 428  |
| <b>Full Title:</b>         | A Phase 2 Study of E7070, Idarubicin and Cytarabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia and High-risk Myelodysplastic Syndromes |
| <b>Protocol Type:</b>      | Standard Protocol  |
| <b>Protocol Phase:</b>     | Phase II   |
| <b>Version Status:</b>     | Terminated 06/08/2017  |
| <b>Version:</b>            | 10   |
| <b>Submitted by:</b>       | Melodie S. England--3/21/2014 12:20:05 PM  |
| <b>OPR Action:</b>         | Accepted by: Yolanda Shorte -- 4/7/2014 5:52:19 PM   |

|   |
|---|
| <b>Which Committee will review this protocol?</b><br><br><input checked="" type="radio"/> The Clinical Research Committee - (CRC) |
|---|

## Protocol Body



E7070 Amendment 6 Final 11-15-2013.doc

**Title: A Phase 2, Open-label Study of E7070, Idarubicin and Cytarabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndromes.**

**Principal Investigator:** Gautam Borthakur, MD

**Protocol Number:** 2009-0570

**Date of Protocol:** May 25, 2010

**Amendment #1:** February 9, 2011

**Amendment #2:** July 11, 2012

**Amendment #3:** October 3, 2012

**Amendment #4:** March 14, 2013

**Amendment #5:** June 21, 2013

**Amendment #6:** November 15, 2013

|                                       |   |
|---------------------------------------|---|
| <b>TITLE</b>                          | <b>A Phase 2, Open-label Study of E7070, Idarubicin and Cytarabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndromes.</b>  |
| <b>INVESTIGATORS / TRIAL LOCATION</b> | Gautam Borthakur, M.D.<br>University of Texas M.D. Anderson Cancer Center<br>Dept. of Leukemia,<br>1515 Holcombe Blvd., Unit 428<br>Houston TX 77030  |
| <b>SUPPORTER</b>                      | Eisai, Inc.   |
| <b>STUDY OBJECTIVES</b>               | <p><b>Primary objective:</b></p> <ol style="list-style-type: none"> <li>1. To assess the complete response (CR) and CR with incomplete platelet recovery (CRp) rates with combination therapy of E7070, idarubicin and cytarabine in patients with relapsed or refractory acute myeloid leukemia (AML) or high-risk myelodysplastic syndromes (HRMDS)</li> <li>2. To determine the safety and toxicity profile of combination therapy with combination therapy of E7070, idarubicin and cytarabine in patients with relapsed or refractory AML or HRMDS.</li> </ol> <p><b>Secondary objectives:</b><br/>To determine the:</p> <ol style="list-style-type: none"> <li>1. duration of response;</li> <li>2. disease-free survival; and</li> <li>3. overall survival</li> </ol>  |
| <b>STUDY DESIGN</b>                   | Phase 2   |
| <b>STUDY POPULATION</b>               | <p><b>Eligibility criteria:</b><br/> <b>Inclusion:</b></p> <ol style="list-style-type: none"> <li>1. All patients with histologically or cytologically confirmed relapsed or refractory AML [except acute promyelocytic leukemia], or HRMDS (Int-2 high risk by IPSS or &gt;10% blasts in marrow).</li> <li>2. Patients must be 18 years or older.</li> <li>3. Patients must have a performance status of 0-2 (Zubrod scale).</li> <li>4. Patients must have adequate renal function (serum creatinine <math>\leq</math> 1.3 mg/dL and/or creatinine clearance <math>&gt;</math> 40 mL/min). Patients with renal dysfunction due to organ infiltration by disease may be eligible after discussion with the P.I., (up to creatinine <math>\leq</math> 2.0) and appropriate dose adjustments will be considered.</li> <li>5. Patients must have adequate hepatic function (bilirubin <math>\leq</math> 2.0 mg/dl; SGOT or SGPT <math>\leq</math> 3X the ULN for the reference lab unless due to leukemia or congenital hemolytic disorder or bilirubin) excretion disorder. Patients with hepatic dysfunction (SGOT/SGPT up to <math>\leq</math> 5X ULN) due to organ infiltration by disease may be eligible after discussion with the P.I., and appropriate dose adjustments will be considered.</li> <li>6. Patients must have normal cardiac ejection fraction.</li> <li>7. QTc interval <math>\leq</math> 480 msec.</li> <li>8. Patients must sign an informed consent form indicating that they are aware of the investigational nature of this study, in</li> </ol> |

|  |   |
|--|---|
|  | <p>keeping with the policies of the hospital.</p> <p>9. Female patients must not be pregnant or lactating. Female patients of childbearing potential (including those &lt;1 year post-menopausal) and male patients must agree to use contraception.</p> <p><b>Exclusion:</b></p> <ol style="list-style-type: none"> <li>1. Patients must not have untreated or uncontrolled life-threatening infection.</li> <li>2. Patients must not have received chemotherapy and/or radiation therapy within 2 weeks. Hydroxyurea is allowed up to 48 hours prior to starting therapy in the setting of rapidly proliferating disease. For details of allowance of hydroxyurea use after the start of study drug, please refer to section VI.</li> <li>3. Patients must not have received an investigational anti-cancer drug within two weeks of E7070 administration.</li> <li>4. Any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent or cooperate and participate in the study or with the interpretation of the results.</li> </ol> |
| <b>TOTAL EXPECTED NUMBER OF PATIENTS</b> | Up to 40  |
| <b>STUDY DRUGS</b>                       | <p><b>E7070</b></p> <p><b>Idarubicin</b></p> <p><b>Cytarabine</b></p> <p><b>Dexamethasone</b></p>   |
| <b>ROUTE OF ADMINISTRATION</b>           | IV  |
| <b>DOSE REGIMEN</b>                      | <p>E7070 400 mg/m<sup>2</sup> intravenously (IV) approximately over 1 hour on day 1 and day 8:</p> <p>Idarubicin 8 mg/m<sup>2</sup> IV approximately over 1 hour daily x 3 (days 9-11)</p> <p>Cytarabine 1.0 g/m<sup>2</sup> IV approximately over 24 hours daily on day 9-12 (age &lt;60 years) or days 9-11 (age ≥ 60 years).</p> <p>Dexamethasone 10 mg IV daily for 3-4 days with cytarabine (Duration is approximately 28 days).</p>   |
| <b>EVALUATION CRITERIA</b>               | Toxicity will be evaluated using the National Cancer Institute (NCI) Version 4.0 criteria.  |
| <b>DURATION OF STUDY PERIOD</b>          | Patients will continue on study until death, disease progression, unacceptable toxicity, patient refusal, or withdrawal from study.   |

## Table of Contents

|        |  |    |
|--------|--|----|
| I.     | Objective  | 5  |
| II.    | Background   | 5  |
| III.   | Background Drug Information                          | 5  |
|        | A. E7070   | 5  |
|        | B. Cytarabine  | 7  |
|        | C. Idarubicin  | 7  |
| IV.    | Study Design   | 9  |
|        | A. Treatment Plan                                    | 9  |
|        | B. Dose Modifications                                | 10 |
| V.     | Patient Eligibility                                  | 10 |
| VI.    | Concomitant Medications                              | 11 |
| VII.   | Pretreatment Evaluation                              | 11 |
| VIII.  | Evaluation During Study                              | 12 |
| IX.    | End-of-Treatment Visit                               | 12 |
| X.     | Long Term Followup                                   | 12 |
| XI.    | Outside Physician Participation During Treatment     | 13 |
| XII.   | Schedule of Assessments                              | 14 |
| XIII.  | Criteria for Response for Acute Leukemias and MDS    | 15 |
| XIV.   | Criteria for Removal from Study                      | 16 |
| XV.    | Adverse Events, Serious Adverse Events and Reporting | 16 |
|        | A. Adverse Event                                     | 16 |
|        | B. Reporting of Adverse Event                        | 17 |
|        | C. Assessing Severity of Adverse Event               | 18 |
|        | D. Assessing Relationship to Study Treatment         | 18 |
|        | E. Classification of Causality                       | 19 |
|        | F. Reporting Requirements                            | 19 |
|        | G. Expedited Reporting                               | 21 |
|        | H. Unexpected Adverse Event                          | 21 |
| XVI.   | Drug Accountability                                  | 22 |
| XVII.  | Protocol Administration                              | 23 |
| XVIII. | Ethical and Regulatory Standards                     | 23 |
| XIX.   | Laboratory Tests                                     | 24 |
| XX.    | Statistical Considerations                           | 24 |
| XXI.   | References   | 25 |

## I. OBJECTIVES

### Primary Objectives

1. To assess the complete response (CR) and CR with incomplete platelet recovery (CRp) rates with combination therapy of E7070, idarubicin and cytarabine in patients with relapsed or refractory acute myeloid leukemia (AML) or high-risk myelodysplastic syndromes (HRMDS), and.
2. To determine the safety and toxicity profile of combination therapy with combination therapy of E7070, idarubicin and cytarabine in patients with relapsed or refractory AML or HRMDS.

### Secondary Objectives

Determine the duration of response, disease-free survival, and overall survival.

## II. BACKGROUND

### *The Disease*

The cure rates for patients with relapsed or refractory hematological malignancies are dismal. Therefore, new agents need to be identified, tested in clinical trials, and incorporated into effective regimens to improve the prognosis of these patients. This study is designed for patients with relapsed/refractory AML and HRMDS whose duration of first CR was less than 1 year. Once front-line therapy fails, patients' therapeutic options are limited. This population of patients with disease that has relapsed or is refractory to established frontline therapies has response rates of less than 10% to 20%.<sup>1</sup> Even if a small proportion of these patients achieve a remission, the remissions are short lasting.

### *Rationale for Proposed Therapy*

#### **Idarubicin and Cytarabine**

While a combination of an anthracycline (daunorubicin or idarubicin) and cytarabine is standard 'induction' regimen for patients with newly diagnosed AML, the 'best' salvage regimen for patients with relapsed disease is unclear. While patients with initial CR duration of over 1 year clearly benefit from high-dose cytarabine (HDAC) based regimens, the probability of achieving a second CR for patients with shorter first CR duration is very low. Cytogenetics, age, failure of prior salvage attempts add to the poor outcome of these patients. Investigational agents alone or in combination with traditional chemotherapy in clinical trials should be the most appropriate approach for these patients.

## III. BACKGROUND DRUG INFORMATION

### **A. E7070**

(Information detailed in Investigator's Brochure: all references in parentheses are Eisai reports outlined in Investigator's Brochure)

E7070 is a sulfonamide anticancer agent that was selected out by G1 cell-cycle arrest effect in murine leukemia P388 cells and antitumor effect in human tumor xenograft models in mice. E7070 induces G1 cell-cycle arrest and delay in G1/S transition in both P388 cells (P1&P2)

and the colorectal cancer CRC cell line HCT116 (P3). Cell cycle arrest in these cases is followed by induction of apoptosis at higher dose (P2). These effects of E7070 on cell cycle progression and apoptosis were found to be time-dependent (P2).

Gene expression analysis using high-density oligonucleotide microarrays has revealed that E7070 treatment causes characteristic repression of subsets of genes involved in redox metabolism, cell cycle control, immune response, and signal transduction (P5). A significant reduction in DNA topoisomerase II alpha and glutathione synthetase transcripts may provide a molecular basis for combination therapy with irinotecan (CPT-11) and platinum agents, respectively.

Proteomic studies using E7070-based affinity matrixes have identified cytosolic malate dehydrogenase (cMDH) as a specific binding protein of E7070. cMDH is a critical metabolic enzyme involved in the malate-aspartate shuttle, gluconeogenesis, and glycolysis. It catalyses the reversible conversion of oxaloacetate to malate using nicotinamide adenine dinucleotides (NAD and NADH) as cofactors. The core structure of E7070 competes with NADH in binding to cMDH at a physiologically relevant concentration (P6). It has yet to be demonstrated that this binding property is a prerequisite for the antitumor activity of E7070.

### **Potential interactions with other medications**

Human liver microsomal studies have shown that there is potential for CYP450 (CYP2C9, 2C19 and 3A4) inhibition by indisulam. As a consequence, there is a hypothetical chance of an interaction between indisulam and a number of drugs. Some drugs with which this interaction may be observed have a relatively narrow therapeutic index and so are of potential concern. The most important of these are listed below:

- oral anticoagulants
- terfenadine, cisapride, cyclosporin, tacrolimus
- theophylline
- diazepam
- sulphonylurea anti-diabetics
- phenytoin and carbamazepine.

There have been reports of drug interactions between E7070 and oral anticoagulants. Three patients from the Phase I program who were receiving chronic therapy with the oral anticoagulant acenocoumarol experienced bleeding and/or a further prolongation of the prothrombin time following treatment with E7070 at a dose of 700 mg/m<sup>2</sup> given as a 1-hour infusion. A pharmacokinetic study was performed to investigate this interaction further. The results indicate that E7070 may primarily interact with acenocoumarol by reducing its systemic clearance. Displacement of acenocoumarol's plasma protein binding by E7070 may also occur, but to a minor extent. In view of these findings, clinicians are advised to exercise caution during the introduction and after the withdrawal of E7070 therapy in patients stabilized on oral anticoagulation.

**Pre-clinical** work outlined below indicates synergy of E7070 with traditional chemotherapeutic agents.

### **E7070 Dosing**

Section 5.4.1 Table 34 in the Investigator's Brochure is the summary for recommended phase 2 doses for single agent E7070 and for the weekly schedule, 400 mg/m<sup>2</sup> weekly times four is



the recommended dose. In our proposed study, the dose of E7070 is scheduled at 400 mg/m<sup>2</sup> weekly times two to allow for the addition of chemotherapy and to avoid undue toxicity with the combination.

Moreover, in a phase 2 study (E7070-E044-214) combining E7070 with chemotherapy, the dose of E7070 was 400 mg/m<sup>2</sup> with irinotecan 125 mg/m<sup>2</sup> on days 1 and 8 in a 21 day cycle (Table 5.5.5 Page 93 of Investigator Brochure) and this was tolerated with acceptable level of toxicity (diarrhea, vomiting, cytopenias being most frequent toxicities).

These data has been used to arrive at the proposed doses in the current protocol.

The doses of idarubicin and cytarabine to be administered are lower than the usual 12mg and 1.5 gram per meter squared that is usually used, to avoid undue toxicity when combined with E7070.

## **B. Cytarabine**

Cytarabine (Ara-C, Cytosar) is commercially available from Pharmacia, ON, Canada L4W 5J5 or other manufacturers.

Cytarabine is an antimetabolite that is cell cycle specific. It is a pyrimidine analogue that affects rapidly dividing cells in the S phase and inhibits cell development from G<sub>1</sub> to S phase. Cytarabine is primarily metabolized in the liver, with a half-life of 1 to 3 hours. Eighty to ninety percent of the drug is excreted in the bile. Moderate amounts of the drug cross the blood-brain barrier, and cytarabine has been shown to cross the placental barrier.

How Supplied: Cytarabine is available in a freeze-dried preparation in multi-dose vials, 100 mg and 500 mg. The solution pH is 5.0 when reconstituted.

Solution preparation: Five ml of bacteriostatic H<sub>2</sub>O for injection (made with 5% dextrose or normal saline) should be added to 100 mg to get 50 mg cytarabine per ml. Diluents containing benzyl alcohol should not be used.

Stability and storage: Before mixing, cytarabine is stable at room temperature. After mixing, reconstituted solutions are chemically stable at room temperature for eight days.

Route of administration: Intravenous.

Overdosage: Doses up to 3 gm/m<sup>2</sup> for six doses have been used.

PRECAUTIONS: Dexamethasone 0.1% eye drops (1-2 drops every 6 hours for 2-7 days) should be administered to all patients to ameliorate conjunctivitis.

## **C. Idarubicin**

Idarubicin is commercially available and will not be supplied for this protocol. Please see package insert for further information.

Synonyms: 4-Demethoxydaunorubicin; 4-DMDR, Idarubicin Hydrochloride, IDR: IMI 30; NSC-256439, SC 33428, Idamycin

Use: Treatment of acute leukemias (AML, ANLL, ALL), accelerated phase or blast crisis of chronic myelogenous leukemia (CML), breast cancer

Contraindications: Hypersensitivity to idarubicin, other anthracyclines, or any component of the formulation; bilirubin >5 mg/dl; pregnancy

Warnings/Precautions: The U.S. FDA currently recommends that procedures for proper handling and disposal of antineoplastic agents be considered. Can cause myocardial toxicity and is more common in patients who have previously received anthracyclines or have preexisting cardiac disease; reduce dose in patients with impaired hepatic function.

Adverse Reactions: >10%: Cardiovascular: Transient EKG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. Congestive heart failure, dose-related. The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity at cumulative oral idarubicin doses up to 540 mg/m<sup>2</sup>; other reports suggest a maximum cumulative intravenous dose of 150 mg/m<sup>2</sup>. Other cardiovascular side effects include arrhythmias, chest pain, and myocardial infarction.

Central nervous system: Headache

Dermatologic: Alopecia (25% to 30%), radiation recall, skin rash (11%), urticaria

Oral: mucositis 10-20%

Gastrointestinal: Nausea, vomiting (30% to 60%); diarrhea (9% to 22%); stomatitis (11%); GI hemorrhage (30%)

Genitourinary: Discoloration of urine (darker yellow)

Hematologic: Myelosuppression, primarily leukopenia; thrombocytopenia and anemia. Nadir: 10-15 days Recovery: 21-28 days

Hepatic: Elevations of bilirubin and transaminases (44%) 1% to 10%:

Central nervous system: Seizures

Neuromuscular & skeletal: Peripheral neuropathy <1%: Hyperuricemia

Overdosage/Toxicology: Symptoms of overdose include severe myelosuppression and increased GI toxicity. Treatment is supportive. It is unlikely that therapeutic efficacy or toxicity would be altered by conventional peritoneal or hemodialysis.

Drug Interactions: Patients may experience impaired immune response to vaccines; possible infection after administration of live vaccines in patients receiving immunosuppressants

Stability: Store intact vials of solution under refrigeration (2°C to 8°C/36°F to 46°F); protect from light. Solutions diluted in D5W or NS for infusion are stable for 4 weeks at room temperature and 7 days under refrigeration.

Mechanism of Action: Similar to doxorubicin and daunorubicin; inhibition of DNA and RNA synthesis by intercalation between DNA base pairs

Pharmacodynamics/Kinetics: Absorption: Oral: Variable (4% to 77%; mean: ~30%)

Distribution: Vd: 64 L/kg (some reports indicate 2250 L)

Metabolism: Hepatic to idarubicinol (pharmacologically active)

Half-life elimination: Oral: 14-35 hours; I.V.: 12-27 hours Time to peak, serum: 1-5 hours

Excretion: Oral: Urine (~5% of dose; 0.5% to 0.7% as unchanged drug, 4% as idarubicinol); hepatic (8%)

I.V.: Urine (13% as idarubicinol, 3% as unchanged drug); hepatic (17%)

Dosage: Refer to individual protocols.

I.V.: Leukemia induction: 12 mg/m<sup>2</sup>/day for 3 days  
Leukemia consolidation: 4-8 mg<sup>2</sup>/m/day for 2 days

Extravasation management: Topical cooling may be achieved using ice packs or cooling with circulating ice water. Cooling of site for 24 hours as tolerated by the patient. Elevate and rest extremity 24-48 hours, then resume normal activity as tolerated. Application of cold inhibits vesicant's cytotoxicity. Application of heat can be harmful and is contraindicated. If pain, erythema, and/or swelling persist beyond 48 hours, refer patient immediately to plastic surgeon for consultation and possible debridement.

#### IV. STUDY DESIGN

This is a phase 2 study of E7070 in combination with idarubicin and cytarabine in patients with relapsed/refractory AML with a particular focus towards patients with primary refractory disease or who are receiving first salvage therapy or beyond. Patients with newly diagnosed AML who do not qualify for front-line induction studies will also be eligible. HRMDS patients will also be eligible. Patients will be treated according to the schedule below:

##### A. Treatment Plan

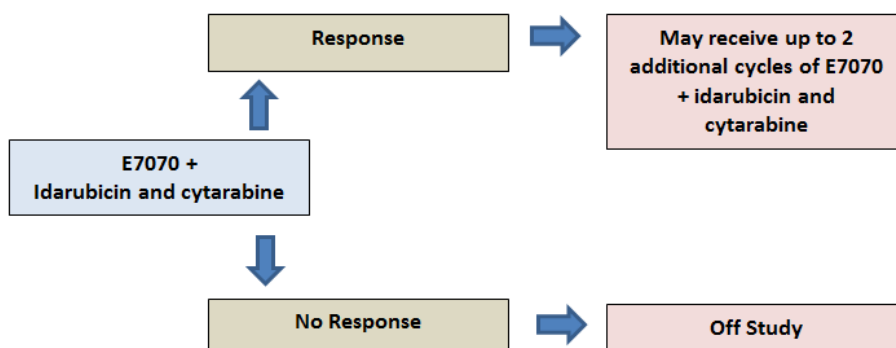
E7070 400 mg/m<sup>2</sup> intravenously (IV) approximately over 1 hour on day 1 and day 8 (± 2 days on Day 8 only) followed by:

- Idarubicin 8 mg/m<sup>2</sup> IV approximately over 1 hour daily x 3 (days 9-11) and
- Cytarabine 1.0 g/m<sup>2</sup> IV approximately over 24 hours daily on day 9-12 (age <60 years) or days 9-11 (age ≥ 60 years).
- Dexamethasone 10 mg IV daily for 3-4 days with cytarabine

Variations in infusion times due to minor differences in IV bag overfill/underfill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation.

Patient will undergo disease assessment on day 28 ± 3 days at the discretion of treating physician. This assessment can be repeated or delayed at the discretion of treating physician if there is ground to believe that the patient is benefiting from study drug. Patients who derive clinical benefit e.g. CR, CRp, PR or marrow clearance of blasts may receive up to two additional cycles of E7070 in combination with chemotherapy at the above doses. Each cycle will be approximately 28 days (+/- 2 days). Dose modifications and delays are allowed for persistent cytopenias or non-hematological toxicities.

Patients not achieving less than an objective response after cycle 1 may receive another cycle of therapy if considered to be in best interest by investigator. If such a patient achieves an objective response as defined in response criteria after the second cycle may receive one more cycle of therapy on study. If a patient does not achieve an objective response after two cycles of therapy, the patient will be removed from study for lack of response.



**B. Dose modification** will be according to Table 1:

**Table 1**

|            | <b>Dose level 0</b>   | <b>Dose level -1</b>   | <b>Dose level -2</b>  |
|------------|-----------------------|------------------------|-----------------------|
| E7070      | 400 mg/m <sup>2</sup> | 25% reduction          | 50% reduction         |
| Cytarabine | 1 gm/m <sup>2</sup>   | 0.75 gm/m <sup>2</sup> | 0.5 gm/m <sup>2</sup> |
| Idarubicin | 8 mg/m <sup>2</sup>   | 6 mg/m <sup>2</sup>    | 4 mg/m <sup>2</sup>   |

**V. PATIENT ELIGIBILITY:**

**INCLUSION:**

1. All patients with histologically or cytologically confirmed relapsed or refractory AML [except acute promyelocytic leukemia], or HRMDS (Int-2 high risk by IPSS<sup>2</sup> or >10% blasts in marrow).
2. Patients must be 18 years or older.
3. Patients must have a performance status of 0-2 (Zubrod scale).
4. Patients must have adequate renal function (serum creatinine ≤ 1.3 mg/dL and/or creatinine clearance > 40 mL/min). Patients with renal dysfunction due to organ infiltration by disease may be eligible after discussion with the P.I., (up to creatinine ≤ 2.0) and appropriate dose adjustments will be considered.
5. Patients must have adequate hepatic function (bilirubin ≤ 2.0 mg/dl; SGOT or SGPT ≤ 3X the ULN for the reference lab unless due to leukemia or congenital hemolytic disorder or bilirubin). Patients with hepatic dysfunction (SGOT/SGPT up to ≤ 5X ULN) due to organ infiltration by disease may be eligible after discussion with the P.I., and appropriate dose adjustments will be considered.
6. Patients must have normal cardiac ejection fraction.
7. QTc interval ≤ 480 msec.

8. Patients must sign an informed consent form indicating that they are aware of the investigational nature of this study, in keeping with the policies of the hospital.
9. Female patients must not be pregnant or lactating. Female patients of childbearing potential (including those <1 year post-menopausal) and male patients must agree to use contraception.

**EXCLUSION:**

1. Patients must not have untreated or uncontrolled life-threatening infection.
2. Patients must not have received chemotherapy and/or radiation therapy within 2 weeks. Hydroxyurea is allowed up to 48 hours prior to starting therapy in the setting of rapidly proliferating disease. (For details of allowance of hydroxyurea use after the start of study drug please refer to section VI)
3. Patients must not have received an investigational anti-cancer drug within two weeks of E7070 administration.
4. Any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent or cooperate and participate in the study or with the interpretation of the results.

**VI. CONCOMITANT MEDICATIONS:**

Use of hydroxyurea to control proliferative disease will be allowed starting from day 2 until day 7 Cycle 1. Maximum dose of hydroxyurea allowed daily is 5 gram and hydroxyurea must be discontinued once administration of idarubicin and cytarabine is started.

**VII PRETREATMENT EVALUATION (within 7 days of start of study drug except where noted)**

- History and Physical Examination to include vital signs and weight.
- CBC with differential platelets, glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, CO<sub>2</sub>], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen.
- Record all concomitant medications and baseline adverse events.
- Bone marrow aspirate and/or biopsy (within one month), and cytogenetics, unless these tests were done within 3 months.
- Chest x-ray (PA and lateral) [at or within one month of screening].
- Electrocardiogram [at or within 1 month of screening].
- Evaluation of cardiac ejection fraction (MUGA or ECHO) (at or within 1 month of screening).

- Urine or blood pregnancy test for women of childbearing potential (within 7 days prior to day 1).
- ECOG assessment.

## **VIII. EVALUATION DURING STUDY**

- CBC, differential (if WBC >  $10^9/L$ ), every 4-7 days during Cycle 1 and every 1 to 4 weeks during Cycle 2.
- Record all concomitant medications and adverse events: continuously during study.
- Disease assessment: Cycle 1, Day 28 (+/- 3 days)
- Electrocardiogram on Day 2 (+/- 1 day) and Day 8 (+/- 2 days) of Cycle 1 done at least 1 hour after completion of E7070 infusion.
- Bone marrow aspiration on day 28 (+/- 3 days) and as indicated at the discretion of the treating physician until documentation of response. Bone marrow examinations may be omitted in patients where there is clear evidence of active disease (e.g., increasing blasts in peripheral blood).
- Creatinine, total bilirubin, electrolytes, AST and/or ALT once every week during induction Cycle 1, then every 2-4 weeks during Cycle 2.
- Safety lab assessments (CBC, differential, platelets, creatinine, total bilirubin, electrolytes, AST and/or ALT) can be performed by local physician, see Section X.

## **IX. END-OF-TREATMENT VISIT (30 days [+/- 5 days] after the last dose of study drug), unless the patient has started on alternative therapy**

- CBC, platelet count, differential
- Serum chemistries (creatinine, total bilirubin, electrolytes, AST and/or ALT)
- Record adverse events

## **X. LONG TERM FOLLOW-UP (unless the patient has started on alternative therapy)**

Patients will have blood counts and chemistry studies every 2-3 months for up to 2 years. These can be done by a local physician. If the counts are abnormal and relapse is suspected, patients will return to M. D. Anderson for additional evaluation of their disease. See Section X.

## **XI. OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT AND LONG-TERM FOLLOW-UP**

- MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
- A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix H)
- Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
- Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
- A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
- Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
- The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
- Patients will return to MDACC every month for evaluation prior to subsequent cycles.

## XII. SCHEDULE OF ASSESSMENTS

| Procedure  | Pre treatment<br>(Within 7 days of start of study drug except where noted) | Cycle 1   | Cycle 2-3                    | End-of-Treatment<br>(30 days [+/- 5 days] after the last dose of study drug) | Long Term Follow-up<br>(unless the patient has started on alternative therapy) |
|--|--|---|------------------------------|--|--|
| Medical History  | X  |   |                              |  |  |
| Physical examination <sup>11</sup>                     | X  |   |                              |  |  |
| ECOG assessment  | X  |   |                              |  |  |
| Hematology <sup>1</sup>                                | X  | Every 4-7 days                                      | Every 1-4 weeks              | X  | Every 2-3 months for up to 2 years <sup>2</sup>                                |
| Serum Chemistry  | X <sup>3</sup>   | Once each week <sup>4</sup>                         | X <sup>4</sup>               | X  | Every 2-3 months for up to 2 years <sup>2,4</sup>                              |
| Bone Marrow aspirate and/or biopsy                     | X <sup>5</sup>   | Day 28 (+/- 3 days) <sup>6</sup>                    |                              |  |  |
| Chest x-ray  | X <sup>7</sup>   |   |                              |  |  |
| Electrocardiogram                                      | X <sup>7</sup>   | Day 2 (+/-1 day) and Day 8 (+/-2 days) <sup>8</sup> |                              |  |  |
| Evaluation of cardiac ejection fraction (MUGA or ECHO) | X <sup>7</sup>   |   |                              |  |  |
| Urine or blood pregnancy test                          | X <sup>9</sup>   |   |                              |  |  |
| Dosing (see Study Design)                              |  | Day 1 and Day 8 <sup>12</sup> (+/- 2 days)          | Day 1 and Day 8 (+/- 2 days) |  |  |
| Disease Assessment                                     |  | Day 28 (+/- 3 days) <sup>10</sup>                   |                              |  |  |
| Adverse Events   | X  | Continuous  |                              |  |  |
| Concomitant Medications                                | X  | Continuous  |                              |  |  |

<sup>1</sup> To include CBC with differential platelets

<sup>2</sup> Tests can be performed by local physician.

<sup>3</sup> To include glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, CO<sub>2</sub>], calcium, phosphorus, magnesium, uric acid, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen will be performed at least weekly.

<sup>4</sup> Creatinine, total bilirubin, electrolytes, AST and/or ALT once every week during Cycle 1, then every 2-4 weeks during Cycles 2-3.

<sup>5</sup> Within one month, to include cytogenetics, unless these tests were done within 3 months.

<sup>6</sup> And as indicated until documentation of response. Bone marrow examinations may be omitted in patients where there is clear evidence of active disease (e.g., increasing blasts in peripheral blood)

<sup>7</sup> At or within 1 month of screening

<sup>8</sup> Done at least 1 hour after completion of E7070 infusion if EKG is done on the day of the E7070 infusion day

<sup>9</sup> For women of childbearing potential within 7 days prior to day 1



<sup>10</sup> If patient is found to be CR, CRp, PR or marrow clearance of blasts, may receive up to 2 additional cycles of E7070 in combination with chemotherapy

<sup>11</sup> To include vital signs and weight

<sup>12</sup> Approximately every 28 days to 2 additional cycles

### XIII. CRITERIA FOR RESPONSE FOR ACUTE LEUKEMIAS AND MDS

International Working Group Criteria<sup>3,4</sup> will be used to define response.

1. Complete remission (CR): The patient must be free of all symptoms related to leukemia and have an absolute neutrophil count  $\geq 1.0 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and normal bone marrow differential ( $\leq 5\%$  blasts).
2. Complete remission without platelet recovery (CRp): As per CR but platelet count  $< 100 \times 10^9/L$ .
3. Partial remission (PR): CR with 6 to 25% abnormal cells in the marrow or 50% decrease in bone marrow blasts.
4. Marrow CR: Bone marrow:  $\leq 5\%$  myeloblasts and decrease by  $\geq 50\%$  over pre-treatment (MDS only)
5. Morphologic leukemia-free state: Normal marrow differential ( $< 5\%$  blasts); neutrophil and platelet counts are not considered. (AML only)
6. Hematologic Improvement (HI): HI should be described by the number of individual, positively affected cell lines (e.g. HI-E; HI-E + HI-N; HI-E + HI-P + HI-N)
  - a) Erythroid response (HI-E):
    - Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent subjects, transfusion independence.
    - Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.
  - b) Platelet response (HI-P):
    - Major response: For patients with a pretreatment platelet count less than  $100 \times 10^9/L$ , an absolute increase of  $30 \times 10^9/L$  or more; for platelet transfusion-dependent patients, stabilization of platelet transfusion independence.
    - Minor response: For patients with a pretreatment platelet count less than  $100 \times 10^9/L$ , a 50% or more increase in platelet count with a net increase greater than  $10 \times 10^9/L$  but less than  $30 \times 10^9/L$ .
  - c) Neutrophil response (HI-N):
    - Major response: For absolute neutrophil count (ANC) less than  $1.5 \times 10^9/L$  before therapy, at least a 100% increase, or an absolute increase of more than  $0.5 \times 10^9/L$ , whichever is greater.
    - Minor response: For ANC less than  $1.5 \times 10^9/L$  before therapy, ANC increase of at least 100%, but absolute increase less than  $0.5 \times 10^9/L$ .

7. Progression/relapse after HI: One or more of the following: a 50% or greater decrement from maximum response levels in granulocytes or platelets, a reduction in hemoglobin concentration by at least 2 g/dL, or transfusion.

#### **XIV. CRITERIA FOR REMOVAL FROM THE STUDY**

The investigator may remove patients from the study for any of the following reasons:

- Clinically significant progressive disease
- Failure to achieve any clinically significant response after two cycles of therapy
- Unacceptable adverse events/toxicities
- Investigator thinks a change of therapy would be in the best interest of the patient (e.g. potential for worsening of existing infection or other toxicities)
- The patient has an intercurrent, non-leukemia-related illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy
- Patient request
- Patient is non-compliant with protocol requirements

#### **XV. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING**

**A. Adverse Event (AE):** Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the medicinal product is E7070.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test (e.g., ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- Recurrence of an intermittent medical condition (e.g. headache) not present at Baseline.

An abnormal laboratory test result may be considered as an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not.

A laboratory result should be considered by the Investigator to be an adverse event if it:

- results in the withdrawal of study treatment
- results in withholding of study treatment pending some investigational outcome
- medical evaluation, results in the initiation of an intervention (e.g. potassium supplement for hypokalemia)
- Any out of range laboratory value that in the Investigator's judgment, fulfills the definitions of an AE with regards to subject's medical profile
- Increases in severity compared to Baseline by  $\geq 2$  NCI grades (see Appendix A for NCI CTCAE Ver 4.0 criteria), with the exception of lymphocytes, albumin, cholesterol, glucose and phosphate. For these tests, a change of  $\geq 2$  grades will be evaluated by the Investigator to determine if they are of clinical significance and if so, will be considered an adverse event.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an adverse event should be reported on the Adverse Event Case Report Form (CRF).

It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an adverse event. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

## **B. Reporting of Adverse Events**

Adverse events will be recorded by the research personnel on a MDACC Adverse Event log. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Adverse event logs will be scanned into Clinic Station when a patient is removed from study or approximately every 6 months.

For this protocol, adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

All AEs encountered during the clinical study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent. Adverse events in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.

Subjects with AEs that are ongoing at the subject's last study visit must be followed until resolution or for 30 days after the subject's last study visit, whichever comes

first. Adverse events that are reported during the Follow-up Period will be recorded on the Adverse Events CRF and followed until resolution or for up to the 30 days after the subject's last study visit, whichever comes first, with the exception that SAEs will be followed until the event resolves or the event or sequelae stabilize.

**Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study treatment.**

### **C. Assessing Severity of Adverse Events**

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Ver 4.0) is used to assign severity scales to AEs (Appendix A). They are:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life Threatening

Grade 5 = Death

AEs that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

In addition, all AEs reported using the NCI CTCAE classification and graded as 4 or 5 are to be considered serious.

The criteria for assessing severity are different than those used for seriousness.

### **D. Assessing Relationship to Study Treatment**

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment, or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event

- The presence of non-study treatment related factors which are known to be associated with the occurrence of the event

## **E. Classification of Causality**

**Not Related:** A causal relationship between the study treatment and the AE is not a reasonable possibility.

**Related:** A causal relationship between the study treatment and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty as “**possible**” or “**probable**.”

## **F. REPORTING REQUIREMENTS**

Reporting requirements will be as per institutional guidelines.

### **Adverse events (AE) related to study conditions**

The serious adverse event (SAE) reporting period will begin with the signing of the informed consent.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate.

### **Serious Adverse Event Reporting (SAE)**

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it 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 incapacity or substantial disruption of the 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).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- 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 “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

#### **Reporting to FDA:**

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

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

#### **G. Expedited Reporting**

Eisai, Inc. must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

- H. An Unexpected Adverse Event** is one that is not listed in the current Clinical Investigator’s Brochure (CIB) / Package Insert or that differs from the event mentioned in the CIB / Package Insert because of greater severity or specificity.

**Causality** is a determination of whether there is a reasonable possibility that the drug may have caused or contributed to an adverse event. It includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of

association) with underlying diseases, and the presence (or absence) of one or more likely causes.

The investigator must attempt to determine whether an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

**Unlikely:** The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, or a new condition that, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

**Possible:** The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug, *but* the event could have been produced by a concomitant medication or an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

**Probable:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug and the event cannot be reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.

**Definite:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug, and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

**Unknown:** Based on the evidence available, causality cannot be ascribed.

Please see Appendix G regarding data capturing of adverse events and adverse events source documentation.

## **XVI. DRUG ACCOUNTABILITY**

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following Eisai, Inc. instructions and adhere to GCP guidelines as well as local and / or regional requirements.

Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be administered to any individual who is not enrolled in the study.

An accurate and timely record of the receipt of all clinical supplies, administration of study drug to the subject, and subsequent destruction of all used and unused study

drug must be maintained. This includes, but may not be limited to: (a) documentation of receipt of clinical supplies, (b) study drug dispensing/return reconciliation log, (unused vials will be shipped back, all used vials should be destroyed on-site per MDACC institutional policy) (c) study drug accountability log, and (d) all shipping service receipts. All forms will be provided by Eisai, Inc. Any comparable forms that the investigational site wishes to use must be approved by Eisai, Inc.

The supplies and inventory records must be made available, upon request, for inspection by the designated representative of Eisai, Inc., a representative of the Food and Drug Administration, or a representative of a non-U.S. health authority. All used and unused study drug, including empty containers, are to be accounted for and destroyed according to site policy and procedure throughout the course of the trial.

The CRAs will review drug accountability during investigational site visits and at the completion of the study.

## **XVII. PROTOCOL ADMINISTRATION**

### **Study Organization**

**Institution:** The University of Texas M. D. Anderson Cancer Center  
**Address:** Department of Leukemia  
1515 Holcombe Blvd, Unit 428  
Houston, TX 77030

**Principal Investigator:** Gautam Borthakur, M.D.  
Phone: (713) 563-1586  
Fax: (713) 794-4297  
Email: [gborthak@mdanderson.org](mailto:gborthak@mdanderson.org)

## **XVIII. ETHICAL AND REGULATORY STANDARDS**

### **Ethical Principles**

The study will be conducted according to the principles outlined by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments; the International Conference on Harmonization Guidelines for Good Clinical Practice; and FDA regulations regarding the conduct of clinical trials and the protection of human subjects.

### **Informed Consent**

It is the responsibility of the Investigator to obtain written informed consent from a patient or a patient's legal representative before any study-related procedures are performed. The Investigator will provide an informed consent in compliance with ICH, GCP, and U.S. FDA guidelines (21 CFR 50). The informed consent document must clearly describe the potential



risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. The informed consent must be approved by the IRB prior to being presented to a potential patient.

One copy of the patient's signed, dated, and witnessed written consent will be kept in the patient's medical record, and one copy will be given to the patient or the patient's legal representative.

### **Institutional Review Board (IRB) Approval**

The Investigator must obtain approval of the protocol, the informed consent document, and any other material used to inform the patient about the nature of the trial from the local IRB in the form of a written letter. In the approval letter, which must be signed by the Chairperson of the IRB or the Chairperson's designee, the following items should be clearly stated: trial title, protocol number and version, study-related documents (protocol, informed consent material, advertisement when applicable), IRB review date, and IRB decision. The trial should not start until a copy of this written approval has been received by the Investigator.

If the Investigator is a member of the IRB, the Investigator may participate in any discussion of the study but may not participate in the final vote deciding whether to approve the study.

Annually, or more often if stipulated by the IRB, and at the completion or termination of the study, the Investigator will report the progress of the trial to the IRB.

### **Additional Responsibilities of the Investigator**

The Investigator(s) agrees to perform the study in accordance with ICH Good Clinical Practice and FDA regulations. The Investigator is required to ensure compliance with respect to the investigational drug schedule, visit schedule, and procedures required by the protocol.

The Investigator should be able to recruit the required number of suitable patients and should have sufficient time to properly conduct and complete the trial. The Investigator should have available an adequate number of qualified staff and adequate facilities for the duration of the trial and should ensure that all persons assisting with the trial are adequately informed about the protocol, the protocol-defined procedures, protocol therapy, and trial-related duties and functions.

The Investigator should be responsible for all trial-related medical decisions. During and following a patient's participation in a trial, the investigator should ensure that adequate medical care is provided to a patient for any adverse events related to the trial.

### **Confidentiality**

It is the responsibility of the Investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms must never contain the name of a trial patient. All case report forms and any identifying information must be kept in a secure location, with access limited to the study staff directly participating in the trial. Personal medical information may be reviewed by a representative of Eisai, Inc., of the IRB, or of regulatory authorities in the course of auditing the trial. Every reasonable effort will be made to maintain such information as confidential.

## **XIX. LABORATORY TESTS**

All labs for eligibility determination and bone marrow aspirations and/or biopsy for disease evaluation will be done at MD Anderson Cancer Center. Safety labs and Long Term Follow-up labs may be done with patients' local physician. See Section XI.

## **XX. STATISTICAL CONSIDERATIONS**

The objective of this study is to assess the efficacy and safety of treatment of E7070 with chemotherapy in Leukemia patients. The efficacy will be measured by the overall response (CR + CRp + PR+ marrow clearance of blast) during Cycle 1. The sample size and stopping rules will be determined according to Simon's two-stage design.

The efficacy will be assessed based on the Simon's two-stage Minmax design. The new treatment will be considered promising if the response rate is 25% or higher, and will be considered unworthy of further investigation if response rate is 10% or less. The maximum sample size of 40 patients is chosen to differentiate between response rates of 10% and 25% with 90% power at a significance level of 0.1. In particular, 27 patients will be enrolled at the first stage. If there are two or fewer patients with response, the trial will be terminated; otherwise another 13 patients will be treated for a total of 40 patients. If, among 40 patients, there are 6 or fewer patients with response, the treatment will be concluded ineffective. The probability of early termination due to futility is 0.48.

A Bayesian sequential monitoring method<sup>5</sup> will be used to monitor the toxicity. We stop the trial if the toxicity is likely to be greater than 33%. That is, stop the trial if

$$\text{Prob \{toxicity rate > 33\% | data\}} > 0.80.$$

The prior distribution of toxicity rate is assumed to be beta (0.67, 1.33). Following this rule, the trial will be terminated due to toxicity if  $[\# \text{ toxicity}]/[\# \text{ patients evaluated}] \geq 2/3, 3/5, 4/7, 5/10, 6/13, 7/15, 8/18, 9/20, 10/23, 11/26, 12/28, 13/31, 14/34, 15/37, \text{ or } 16/40$ .

A toxic event will be defined as death or a CTCAE 4.0 grade 3/4 non-hematological toxicity related to study drug lasting or 7 days or more.

Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. Fisher's exact test and Wilcoxon rank test will be used in univariate analyses of categorical and continuous variables, respectively. Overall response (CR + CRp + PR) rate and its 95% confidence interval will be estimated using a binomial distribution. Overall survival and progression free survival functions will be estimated using the Kaplan-Meier method. The two-sided log-rank test will be used to examine the difference of survival functions among different groups. Toxicity will be reported by type, frequency and severity. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements.

## XXI. REFERENCES

1. Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia* 2000;14(3): 476-9.
2. van den Bongard HJ, Sparidans RW, Critchley DJ, Beijnen JH, Schellens JH. Pharmacokinetic drug-drug interaction of the novel anticancer agent E7070 and acenocoumarol. *Invest New Drugs* 2004;22(2):151-8. Available from [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14739663](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14739663).
3. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89(6): 2079-88.
4. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003;21(24): 4642-9.
5. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006;108(2): 419-25.
6. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med* 1995;14(4): 357-79.