University of Illinois Cancer Center **Confidential**

AML-02: Study of the Activity and Safety of the Addition of Omacetaxine to the Standard-of-Care Induction Therapy Regimen of Cytarabine and Idarubicin in Newly-Diagnosed AML patients

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NOTE: Omacetaxine is supplied by TEVA Pharmaceuticals

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REVISION HISTORY

Revision #	Date	Details of changes	Consent change?
1.1	9/15/2014	Principal Investigator: John Quigley, MD In response to UIC PRC queries, the study background has been revised to discuss determination of complete response rate. Clarifications were made to the following sections: Primary Endpoint, the Dose Finding Component, Treatment Success, Eligibility Criteria, Omacetaxine Adminstration & Precautions, the Study Schedule of Events, and Adverse Event Documentation & Reporting.	No
1.2	3/17/2015	Revised protocol to clarify Eligibility (remove duplicate criteria and clarified exclusion criteria) and Schedule of Events (clarified timing of post-induction bone marrow on Day 14-17). Other minor revisions and corrections to references.	Yes
1.3	4/09/2015	Per IRB request, removed "No" from Exclusion Criteria #3, #8, #9, & #10.	Yes
2.0	5/07/2015	Removed specific timeframe from Lost to Follow-up and reference to the DSMC. Removal of duplicate inclusion/exclusion criteria regarding hepatic and renal function. Clarifications to Dose Modifications section to allow treatment to be stopped per PI discretion.	Yes
3.0	7/01/2015	Eligibility criteria revised to allow for subjects up to age 70. Allow MUGA scans to be completed in place of echocardiogram.	Yes
4.0	8/18/2015	Eligibility criteria modified to remove ≥20% blasts in peripheral blood or bone marrow as a requirement, in order to allow for patients with atypical presentation of AML like myeloid sarcoma	No
5.0	11.29.2015	Modified definition of hematologic toxicity as more than 30% of the patients having CRi or CRp by day 50 and modified the wording for BM examination will be performed at recovery usually 3-4 weeks	No
6.0	2.22.2016	Addition of Bi-weekly BMP procedure, removal of daily BMP monitoring, removal of long-term follow up every 2 months for 6 months for symptom and toxicity checks, addition of HbA1c follow up for diabetic patients, update to analysis plan for primary objective, and process for collection of adverse event documentation updated.	No
7.0	5.19.2016	Modify the definition of CR to include CRc (complete cytogenetic remission), update Teva contact personnel, and references	No
8.0	7.11.2016	Add insulin sliding scale and hyperglycemia management guidelines	No
9.0	1.25.2017	Changes to Sub-investigator personnel and of biostatistician	No
10.0	4.20.2017	Changes to consent form (i) allow potential for taking deidentified photographs of patients who develop skin changes and (ii) add risk for arrhythmias (predominantly atrial fibrillation). Changes to definitions of non-hematological toxicities, efficacy, and clarification of the Stopping Rules.	Yes

Synopsis

Primary Objective:

The primary objective of this study is to assess the activity and safety of Omacetaxine when it is administered with the standard acute myelogenous leukemia (AML) induction therapy of cytarabine and Idarubicin to patients under 65 years old with newly diagnosed AML.

Patient Population:

- Newly diagnosed, untreated male or female patients, 18-70 years of age, with AML according to the WHO classification for AML
- Previously untreated AML (≥20% blasts). Prior short-term therapy (≤7 days) with hydroxyurea, steroids, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors, azacitidine, ATRA), or hematopoietic growth factors is allowed. A single or two-day dose of cytarabine (up to 3 g/m2) for emergency use is also allowed as prior therapy.
- ECOG status 0-3 (Appendix III)
- Adequate hepatic and renal function as defined in section 5.1 (inclusion criterion #6)

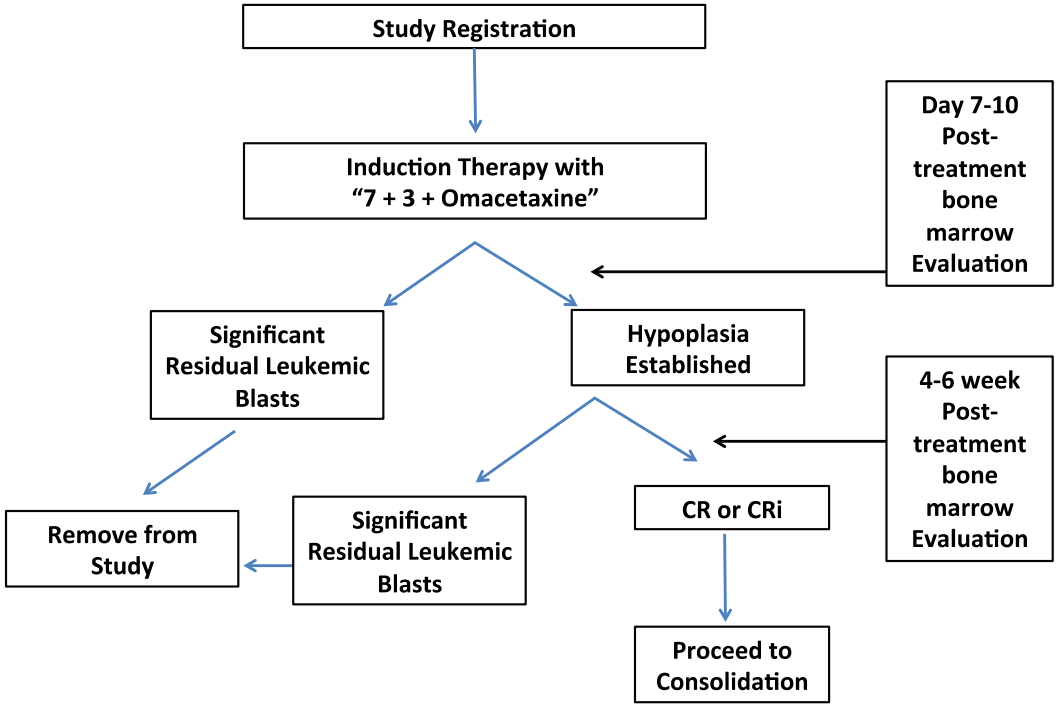
Study Design:

This is a dose escalation study to evaluate Omacetaxine when given in combination with a standard induction regimen of "7+3" (cytarabine for Days 1-7 and Idarubicin for Days 1-3) in patients with newly diagnosed acute myelogenous leukemia (AML). Omacetaxine will be given subcutaneously Q12 hours on Days 1-7. The optimally safe and active dose (OD) will be determined using the EffTox design. EffTox is a Bayesian adaptive design that seeks to determine the optimal dose for further study in Phase II by considering a trade-off between efficacy and toxicity. The EffTox design begins by treating a cohort of three patients at dose level 1. These patients' efficacy and toxicity outcomes are used to update the posterior distributions for the probability of efficacy and toxicity and identify acceptable dose levels. The study terminates if no dose levels are acceptable. Otherwise, the acceptable doses are ranked using the Euclidean distance from (1.0, 0.0) and the next cohort is treated at the dose with the minimum distance under the restriction that we may only escalate or deescalate by one dose level at a time (e.g., the second cohort can only escalate to dose level 2 or deescalate to dose level -1). The second cohort is treated at the dose with the minimum distance and posterior distributions, and the list of acceptable doses and distances are updated as before. This process continues until at least 20 subjects are enrolled in the study. The dose with the minimum distance at study completion is considered the optimal dose for further investigation. If none of the dose levels are acceptable at study completion, an optimal dose level will not be identified and the drug does not warrant further investigation.
Post induction therapy will consist of standard cytarabine consolidation chemotherapy or allogeneic stem cell transplantation based on pretreatment risk assessment.

Treatment Plan:

Omacetaxine (assigned dose) administered subcutaneously Q12 hours Days 1 to 7; Cytarabine (100mg/m2/day) in 1000ml NS as a continuous IV infusion over 24 hours x 7 days; and Idarubicin (12 mg/m2/day) IVPB in 100 mL NS over 15 minutes daily from Days 1 to 3.

Study Schema



Induction Chemotherapy Regimen							
Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cytarabine	100mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI
Idarubicin	12mg/m2 IV	12mg/m2 IV	12mg/m2 IV				
Omacetaxine	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h

Phase I Dose Levels

Dose Level	**Omacetaxine** mg/m^2
-1	0.5
1	0.625
2	1.25
3	2.0
4	3.0
5	4.2

Abbreviations

Abbreviation	Definition
4'-DMHHT	4'desoxyhomoharringtonine
AD	cytarabine and daunorubicin
AE	adverse event
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCL-2	B-Cell lymphoma 2 protein
β-HCG	β-human chorionic gonadotropin
CML	chronic myelogenous leukemia
CTO	clinical trial office
CR	complete response
CRc	complete cytogenetic response
CRi	complete response with incomplete hematologic recovery
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CI	continuous infusion
CTEP	cancer therapy evaluation program
D	day
dL	deciliter
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
FDA	Food and Drug Administration
FLT3	Fms-like tyrosine kinase 3
G-CSF	granulocyte colony-stimulating factor
HT	Hematologic Toxicity
HAA	homoharringtonine, cytarabine and aclarubicin
HAD	homoharringtonine, cytarabine and daunorubicin
IND	investigational new drug
IRB	institutional review board
IV	intravenous
kg	kilogram
MCL-1	myeloid cell leukemia-1 protein
mg	milligram

Abbreviation	Definition
Min	minute
µL	microliter
mL	milliliter
mm^3	cubic millimeters
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
OD	optimally safe and active dose
PARP	Poly [ADP-ribose] polymerase
SAE	serious adverse event
subQ	subcutaneous
US	United States
Wt	weight
WHO	World Health Organization

1 Background/Rationale

1.1. Background

Acute myelogenous leukemia (AML) has been treated with standard "7+3" induction chemotherapy comprising cytarabine (days 1-7) and an anthracycline (such as daunorubicin, mitoxantrone or Idarubicin for days 1-3) since the regimen was first introduced more than 30 years ago.[1] Few modifications have been made to this induction regimen over the years despite complete response rates that remain in the range of 60-80% for adults less than 60 years old and 30-50% for adults over age 60.[2-6] In the United States in 2009, there were about 13,000 new cases of AML and more than 9,000 deaths, demonstrating the continued overall poor outcome associated with this disease.

With this regimen a bone marrow is normally performed 7 days after completion of induction chemotherapy; patients then receiving a second induction chemotherapy if this day 14 bone marrow examination shows residual leukemia. Note that the CR rate is dependent on the number of induction cycles given; for example, in a retrospective analysis of almost 2000 adult patients treated with 1 or 2 inductions (from 1983-1997)[6], the overall CR rate at the end of the induction was 64%, with 75% (48%) of the total attaining CR after the first, and 25% (16%) after the second induction cycle.[6] With the improvement in CR rates in recent years[2-5], the CR rate with one induction is likely 60%. The median duration of neutropenia and thrombocytopenia in large recent trials of "7+3" is 29-30 days, with ~30% of patients having more prolonged cytopenias (>30 days).[2]

Homoharringtonine:

Homoharringtonine is a naturally occurring cephalotaxine alkaloid, extracted from the bark of the Cephalotaxus species, trees indigenous to China and parts of Japan. The bark has been used in traditional Chinese medicine for the treatment of cancers for over 30 years. In early studies, the cephalotaxine esters (harringtonine, isoharringtonine, homoharringtonine and deoxyhomoharringtonine) were used, for example, to successfully treat mice harboring leukemia cell lines, demonstrating promising results.[7,8]

Omacetaxine:

Further investigations were hindered by both a lack of purity of the drug and drug availability until a purified semisynthetic form of homoharringtonine, now termed Omacetaxine mepesuccinate, was developed. [9,10] Omacetaxine can be administered either subcutaneously or as a continuous infusion.

Cortes *et al.* conducted a phase II trial of Omacetaxine in chronic phase chronic myeloid leukemia (CML) patients with the BCR-ABL protein T315I mutation who had failed imatinib. Hematologic responses were observed in 77% of subjects and the duration of response was 9.1 months. A major cytogenetic response was seen in 23% of subjects.[11] These study results led to FDA approval of Omacetaxine mepesuccinate for the treatment of CML in October 2012.

Omacetaxine mepesuccinate clearly has efficacy in the treatment of CML, however its role in AML is unclear. Omacetaxine mepesuccinate induces apoptosis in cell lines by inhibiting protein synthesis. It acts by inhibiting aminoacyl-tRNA binding to the ribosomal acceptor site, thus preventing peptide bond formation.[9,11] Other studies indicate it significantly down regulates myeloid cell leukemia-1 protein (MCL-1), an important anti-apoptotic regulator in AML, which is part of the BCL-2 superfamily.[13] Homoharringtonine was also found to mediate apoptosis *in vitro* through the Poly [ADP-ribose] polymerase (PARP) pathway.[14] Of interest, a synergistic *in vitro* effect was observed against a myeloid leukemia cell line when homoharringtonine was combined with cytarabine.[7]

Trials in AML:

Both homoharringtonine and semisynthetic homoharringtonine have been used as single agents in early clinical trials of the drug in patients with AML. The complete remission (CR) rates in Chinese and US trials

ranged from 0-25%, similar to the responses observed with other single agent treatments in patients with AML.[15] Jin *et al.* demonstrated that homoharringtonine in combination with cytarabine and aclarubicin can be administered safely to patients with *de novo* AML. The overall CR rate in this phase II trial was 79%[16], suggesting that combining homoharringtonine (or semisynthetic homoharringtonine) with standard induction therapy would improve CR rates.

In 2013 Jin *et al.* reported on a phase III, multicenter randomized controlled trial in China that involved 620 patients with *de novo* AML.[17] The three comparison arms included: homoharringtonine, cytarabine and aclarubicin (HAA), homoharringtonine, cytarabine and daunorubicin (HAD), and cytarabine and daunorubicin (AD). The CR rate for the HAA arm was significantly higher than for the AD arm, 73% vs 61% (p=0.0108). All three groups had similar event free and overall survival rates. However, subgroup analysis of patients with favorable and intermediate cytogenetic profiles demonstrated that the HAA arm had significantly better event free and overall survival compared to the standard therapy (AD) group.

In previous studies, the maximum tolerated dose (MTD) of semisynthetic homoharringtonine as a single agent was determined to be 5 mg/m^2/day subcutaneously for 9 days, in a phase I trial of the drug in patients with acute leukemia.[15] Myelosuppression was a dose limiting toxicity (DLT) and the median duration of myelosuppression was 31 days. Grade III hyperglycemia and pulmonary aspergillosis were also observed in this heavily pretreated group. Conversely, in the treatment of patients with CML, the MTD was determined to be 1.25 mg/m^2 when given subcutaneously for 14 days every 28 days.[18] The incorporation of Omacetaxine mepesuccinate into a standard AML induction regimen of cytarabine and an anthracycline (such as Idarubicin), however, has not been performed and the optimally active and safe dose (OD) of Omacetaxine mepesuccinate in combination with cytarabine and Idarubicin is unknown.

Definition of CR in AML:

The International Working Group originally developed the diagnostic and response criteria for AML in 1990. Due to major advances in the understanding of AML, revised recommendation were published in 2003. They acknowledged that cytogenetics confer one of the most important prognostic information in AML, and recommended that cytogenetic complete remission (CRc) be reported as part of the response criteria[19].

Marcucci et al evaluated the usefulness of cytogenetic analysis performed on the first day of complete response (CR) as a predictor for clinic outcome in a retrospective study. They found that patients with abnormal cytogenetics at CR had significantly shorter overall survival (OS) (1.1 vs 2.1 years, p=0.006) and disease free survival (0.6 vs 1.0 years, p=0.001), and higher cumulative incidence of relapse (CIR) (1.2 vs 0.6, p=0.0001) compared to patients with normal cytogenetics at CR (all patients had abnormal cytogenetics at diagnosis)[20]. Chen et al also investigated the prognostic impact of persistent cytogenetic abnormalities at CR on relapse-free survival (RFS) and OS. Patients with persistent cells with abnormal karyotype at CR had significantly shorter RFS (6 months vs 21 months, p=0.001) and OS (11 months vs 46 months, p<0.001) compared to patients who had normal cytogenetics at CR[21].

Based on these studies, recent NCCN guidelines, and recommendations from the expert panel on behalf of European LeukemiaNet, we will like to include cCR in the definition of CR in our study in patients with abnormal karyotype at the time of diagnosis. cCR will be defined as normal karyotype as evaluated in a minimum of 20 metaphase cells analyzed from bone marrow to establish the diagnosis of a normal karyotype[22,23].

1.2. Rationale

Based on previous studies, *we propose that combining this drug with the standard AML induction regimen of "7+3" will result in a significant increase in the CR rate among newly diagnosed patients with AML*. We propose a dose-finding study to determine the activity and safety of Omacetaxine mepesuccinate in combination with standard induction chemotherapy in newly diagnosed AML patients.

2 Objectives

2.1. Primary Objective

The primary objective of this component of the study is to determine the activity and safety of Omacetaxine when it is administered with the standard AML induction therapy of cytarabine and Idarubicin to patients under 65 years old with newly diagnosed AML.

2.2. Secondary Objectives

2.2.1. Describe the adverse events associated with Omacetaxine when administered in combination with cytarabine and Idarubicin as induction therapy for AML, using CTCAE grading and the time to hematologic recovery.

2.2.2. Determine the overall survival of patients treated with Omacetaxine when administered in combination with cytarabine and Idarubicin as induction therapy for AML.

2.2.3. Determine the relapse-free survival in patients who achieve CR or CRi (complete remission with incomplete blood count recovery) following treatment with Omacetaxine in combination with cytarabine and Idarubicin as induction therapy for AML.

2.2.4. Determine the event-free survival in patients who achieve CR or CRi following treatment with Omacetaxine in combination with cytarabine and Idarubicin as induction therapy for AML.

3 Endpoints

3.1. Primary Endpoint

The primary endpoint is determination of the optimally active and safe dose (OD) of Omacetaxine when added to the standard-of-care induction chemotherapy for AML and the estimation of the efficacy and response rate. OD will be defined as a dose level at which fewer than 30% of patients experience hematologic toxicity and greater than 60% of patients achieve a CR (as a second induction is not being given in this study).[2-6]

3.2. Secondary Endpoints

3.2.1. Adverse effects (AE) as defined by CTCAE v4.1 [24]

3.2.2. Overall survival of patients

3.2.3. Relapse-free survival of patients

3.2.4. Event-free survival in patients

4 Overall Design and Study Plan

This is a dose escalation study to evaluate Omacetaxine when given in combination with cytarabine and Idarubicin. The study will evaluate Omacetaxine dose escalation using an EffTox design (see Section 11 for statistical considerations). Post induction therapy will consist of standard high dose cytarabine consolidation chemotherapy or allogeneic stem cell transplantation based on pretreatment cytogenetic risk assessment.

4.1 Dose Finding Component:
Up to 5 dose levels of Omacetaxine will be tested (refer to Omacetaxine dosing in Section 7). The OD of Omacetaxine in combination with cytarabine and Idarubicin will be determined using the EffTox design (as described in Section 12.1), and will follow the standard rules for evaluation of hematologic toxicity (HT).

If none of the dose levels are acceptable at study completion, an optimal dose level will not be identified and the drug does not warrant further investigation.

Note however that if, for example, addition of a lower dose of Omacetaxine (e.g., dose level 1 (0.625mg/m2) to "7+3" results in a lack of efficacy and no toxicity and the next higher dose used (i.e., level 2 (1.25mg/m2)) results in unacceptable toxicity **we may seek to modify the protocol** to allow use of a dose of Omacetaxine intermediate to the current dose increments (in this example we would use 1mg/m2).

4.1.1 Hematologic toxicity

Hematologic toxicity is defined as the following event occurring during induction:
Treatment-related hematologic toxicity, defined as bone marrow hypoplasia present for more than 6 weeks duration from the last day of treatment; specifically, failure to recover peripheral ANC > 1000/μL and platelets > 100,000/μL *with the* bone marrow documented to be free of leukemic infiltration.

4.1.2 Evaluation of Activity

Activity evaluation will be performed by looking at treatment failure and CR rates.

Treatment Failure:
If hypoplasia is not established on the Day 7-10 post-induction treatment bone marrow biopsy/aspirate–defined as cellularity <10%-20% with residual blasts comprising <5%-10% of these cells–and a second induction is required, then the subject will be removed from the study and this dose will be considered a treatment failure.
If the Day 7-10 bone marrow biopsy/aspirate is ambiguous for residual leukemic blasts, then a repeat bone marrow biopsy will be performed 1-2 weeks later. If persistent leukemia is present at that time, then this will be defined as treatment failure.

Treatment Success: Defined as a complete remission (CR) per the European LeukemiaNet criteria (i.e., BM blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L (1000/μL); platelet count > 100 x 10^9/L (100,000/μL); independent of red cell transfusions; see appendix I) or CRi (all CR criteria present except for residual neutropenia < 1.0 x 10^9/L (1000/μL) **or** thrombocytopenia < 100 x 10^9/L (100 000/μL); see appendix I).

In patients with abnormal cytogenetics at diagnosis, CR (or CRi) will be delineated as above plus evidence of complete cytogenetic response (also known as CRc)—defined as a finding of normal cytogenetics at the time of the BM examination performed at day 7-10 and at 3-4 weeks after induction therapy.
If subjects obtain a CR or CRi rate that is equal or better than 60% after treatment, then this will be considered active treatment. BM examination(s) will be performed at recovery (usually 3-4 weeks) and may be repeated at 6 weeks (and later if necessary) if BM recovery has not occurred.

The rules for dose (de) escalating are described in Section 12.1
The EffTox design begins by treating a cohort of three patients at dose level 1. The efficacy and toxicity outcomes for these three patients are used to update the posterior distributions for the probability of efficacy and toxicity and identify acceptable dose levels. The study terminates if no dose levels are acceptable. Otherwise, the acceptable doses are ranked using the Euclidean distance from (1.0, 0.0) and

the next cohort is treated at the dose with the minimum distance, under the restriction that we may only escalate or deescalate one dose level at a time (e.g., the second cohort can only escalate to dose level 2 or de-escalate to dose level -1). The second cohort is treated at the dose with the minimum distance and posterior distributions, and the list of acceptable doses and distances are then updated as before. This process continues until at least 20 subjects are enrolled in the study. The dose with the minimum distance at study completion is considered the optimal dose for further investigation. If none of the dose levels are acceptable at study completion, an optimal dose level will not be identified and the drug does not warrant further investigation.

Note that additional patient cohorts will not be enrolled until all patients at the current dose level have completed the planned induction treatment (defined as 14 doses of Omacetaxine) and are able to proceed with consolidation or salvage therapy (or if a patient in the cohort is removed from the study).

The OD will be defined as a dose level at which 30% or less of patients experience a hematologic toxicity and 60% or more patients achieve a CR.

5 Selection of patients

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the patient population is expected to be no different than that of other hematologic malignancy studies at the University of Illinois.

5.1. Inclusion Criteria

1. Newly diagnosed, untreated patients with AML according to the WHO classification for AML.[25] Prior short-term therapy (≤7 days) with hydroxyurea, steroids, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors, azacitidine, ATRA), or hematopoietic growth factors is allowed. A single or two-day dose of cytarabine (up to 3 g/m2) for emergency use is also allowed as prior therapy.

2. Patients age 18 to 70 years old who meet diagnostic criteria for AML.

3. ECOG performance status of 0-3 (appendix III).[26]

4. Adequate organ function, *if not suspected to be due to AML*, within 14 days of study registration, defined as:

System	Laboratory Values
Hepatic	
Total bilirubin AST and ALT	≤ 2.0 x ULN (unless due to hemolysis) ≤ 3 X ULN (unless believed to be due to tumor involvement)
Renal	
Serum Creatinine Creatinine Clearance	≤ 1.5 x ULN > 30 ml/min

6. Negative urine or serum pregnancy test in females. Patients of reproductive potential (males and females) must consent to and practice double-barrier methods of contraception during treatment and for 12 weeks following the last dose of Omacetaxine. Adequate contraception is defined as double-barrier protection (i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or

intrauterine device). Birth control pills, birth control patches and/or injections of hormones to prevent pregnancy are not considered an adequate method of preventing pregnancy, and double-barrier protection is required while on study and for 12 weeks after last dose. Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 12 weeks of completing treatment with Omacetaxine. This also applies to male patients whose partners become pregnant while the patient is on study or within the 12 week period after the last dose of study drug.

7. Patients must be willing and able to review, understand, and provide written consent before starting therapy.

5.2. Exclusion Criteria

1. Patients with AML age 70 or older.
2. Acute promyelocytic leukemia.
3. Investigational drug within 4 weeks of study entry.
4. Cardiac insufficiency grade III or IV New York Heart Association (NYHA)[27] (see Appendix IV).
5. Female subjects who are pregnant or breast feeding.
6. Patients who are HIV positive.
7. Active uncontrolled infection or severe systemic infection (enrollment is possible after control of infection).
8. Concurrent malignancy (other than AML) with an estimated life expectancy less than two years and requiring active therapy.
9. Psychological, familial, sociological, or geographical condition that would preclude study compliance and follow-up.
10. Uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or medically relevant active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
11. Pregnant or breastfeeding: Omacetaxine is a Pregnancy Category D medication and has caused embryo-fetal death in animals. Confirmation that the subject is not pregnant must be established by a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
12. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for enrollment in this study.

6 Registration

Registration will occur after the patient has signed the patient consent and eligibility is confirmed, but before any treatment has been administered. To be eligible for registration to this study, the patient must meet each of the criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is maintained by the Clinical Trial Office (CTO) and can be found for each individual subject within the subject shadow chart.

6.1. Registration with the Clinical Trials Office

Upon completion of the screening evaluation, eligibility checklist and obtaining consent, the study coordinator or designee will enroll the patient into the CTO data management system.

Omacetaxine dose levels will be assigned at registration.

6.2. Patients Who Do Not Begin Study Treatment

If a patient signs consent and is registered to the study, and is later found not able to begin the planned study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The patient will be considered a screen/baseline failure and be replaced. Further data will not be collected if the patient has not begun study treatment at the time of removal from trial. The reason for removal from study will be clearly indicated in CTO data management system.

If a patient begins treatment, and then treatment is discontinued for whatever reason, the patient must be followed per section 7.12.

7 Treatment Plan

7.1. Study Drug Administration

Cytarabine (100mg/m^2/day) in 1000ml NS as a continuous IV infusion over 24 hours x 7 days

Idarubicin (12 mg/m^2/day) IVPB in 100 mL NS over 15 minutes daily from Days 1 to 3

Omacetaxine (assigned dose) administered subcutaneously Q12 hours Days 1 to 7

Induction Chemotherapy Regimen							
Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cytarabine	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI	100 mg/m2 CI
Idarubicin	12 mg/m2 IV	12 mg/m2 IV	12 mg/m2 IV				
Omacetaxine	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h	Assigned dose subQ q12h

7.1.1. Omacetaxine Administration

Omacetaxine will be given subcutaneously every 12 h for Days 1-7. Cytarabine will be administered at a dose of 100 mg/m2 as a 24 h continuous infusion for Days 1-7. Idarubicin will be injected intravenously at a dose of 12 mg/m2 over 15 minutes Days 1, 2 and 3.

Pre-medication

Omacetaxine and Cytarabine, at low doses (i.e. 100mg/m2) are classified as having a low emetic risk per the National Comprehensive Cancer Network (NCCN) guidelines.[28] However Idarubicin is classified as having a moderate emetic risk. Therefore requiring acute anti-emetic premedication prior to administration of the drug. Antiemetic medications for breakthrough nausea will be prescribed at the primary investigator's discretion.

PREMEDICATION REGIMEN DESCRIPTION					
Agent	**Premedication Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ondansetron ODT	EPS, QT prolongation	8 mg	IV	Day 1, 2, 3	Administered 30 minutes prior to Idarubicin
Dexamethasone	Hyperglycemia,	10 mg	IV	Day 1, 2, 3	Administered 30 minutes prior to Idarubicin

Monitoring

All patients will be hospitalized during the induction chemotherapy regimen. All doses of Omacetaxine will be administered in an inpatient setting. Patients will be closely monitored for toxicities.

Supportive Measures

Monitoring for tumor lysis is recommended and aggressive hydration and allopurinol prophylaxis is strongly encouraged.

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

Venous Access: A central venous access device is strongly recommended for this study.

Blood Product Support: Appropriate use of all blood products is recommended. Use of CMV negative products is strongly encouraged for patients documented to be CMV negative and who may later undergo bone marrow transplantation. Blood products should be irradiated following the current FDA guidelines found at: http://www.fda.gov/cber/gdlns/gamma.html

Hematopoietic Growth Factors: Filgrastim (G-CSF) may be used at the treating physician's discretion, provided bone marrow evaluation demonstrates no evidence of AML, to enhance neutrophil recovery when clinically indicated. Routine use of filgrastim in clinically well patients awaiting count recovery is not recommended.

Prevention of Fungal Infections: Antifungal prophylaxis can reduce morbidity and fungal infection-related mortality in severely neutropenic chemotherapy recipients. Evidence for benefit is strongest for those conditions associated with > 15% rate of systemic fungal infection such as prolonged neutropenia, as observed in AML patients and stem cell transplant (SCT) recipients and is recommended for study patients. The choice of the prophylaxis should be made in consultation with institutional infection profiles and infectious disease guidelines.

Management of Fever and Neutropenia: Patients with an ANC < 500/μL (or < 1000/μL and falling) and an oral temperature > 38°C twice in 24 hours or > 38.3°C once, should have empiric systemic antibiotics initiated immediately after appropriate cultures are drawn. The specific choice of empiric antibiotics should be guided by the resistance patterns seen at the individual institution.

The antibiotic regimen chosen for febrile neutropenia should contain activity against gram-negative organisms and *Pseudomonas aeruginosa* in particular. Note: aminoglycosides increase the risk of nephrotoxicity.

The persistence of fever for > 3 days despite broad spectrum antibiotic therapy or the emergence of a new fever in a neutropenic patient warrants investigation for invasive fungal infection and initiation of empiric antifungal therapy. Antifungal options include amphotericin B (or lipid amphotericin products), voriconazole, echinocandins (micafungin, caspofungin, and anidulafungin), as well as combination therapy. The choice of specific agent(s) and length of therapy will be dictated by the suspected or confirmed fungal species, site of infection, and clinical status. Consultation with an Infectious Disease physician is recommended.

Hyperglycemia: Patients blood glucose will be checked three times a day with meals and at bedtime (TIDAC and QHS) if patient eating, and if patient is not eating or NPO will monitor blood glucose every 6 hours. Note: If no hyperglycemia observed after 4 doses of Omacetaxine, blood glucose will be only checked once daily thereafter. Insulin aspart high dose correction bolus sliding scale will be administered for elevated serum blood glucose as following:

If Premeal blood glucose (mg/dL):

- Notify physician if less than 70 mg/dL
  150 - 200 3 Units
  201 - 250 6 Units
  251 - 300 8 Units
  301 - 350 10 Units
  351 - 400 12 Units
  >400 14 Units and Notify physician
- if correction bolus given at bedtime, will check blood glucose 2-4 hours after insulin administration

Hypoglycemia: Patients will have blood glucose measurements as noted above. Patients with hypoglycemia will be treated with oral glucose or if necessary IV glucose to maintain blood glucose levels above 70 mg/dl. All patients will have a order for IV dextrose 50% for IV push, 25ml, if needed for blood glucose less than 70mg/dL

Precautions

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug. Male patients whose partners become pregnant while the patient is on study or within the 12 week period after last dose of study drug must inform the investigator immediately. Patients of reproductive potential (males and females) must practice double-barrier methods of contraception during treatment and for 12 weeks following the last dose of Omacetaxine. Adequate contraception is defined as double-barrier protection (i.e., condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device). Birth control pills, birth control patches and/or injections of hormones or (in males) surgical sterilization (i.e., status post-vasectomy) to prevent pregnancy are not considered an adequate method of preventing pregnancy, and double-barrier protection is required while on study and for 12 weeks after last dose, or the patient must completely abstain from heterosexual intercourse.

7.1.2. Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

7.1.2.1 Patient voluntarily withdraws from treatment (follow-up permitted);

7.1.2.2 Follow up bone marrow biopsy performed 7-10 days after completion of induction therapy demonstrates significant residual leukemic blasts, or significant cytoreduction with a high percentage of residual leukemic blasts and the patient requires a second induction therapy (see also Section 4.1.2).

7.1.2.3 Patient withdraws consent (termination of treatment and follow-up) or patient is unable to comply with protocol requirements;

7.1.2.4 Patient demonstrates disease progression

7.1.2.5 Patient experiences toxicity that makes continuation on the protocol unsafe;

7.1.2.6 Treating physician judges that continuation on the study would not be in the patient's best interest;

7.1.2.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

7.1.2.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment which would interfere with this study;

7.1.2.9 Lost to follow-up. *If a research subject cannot be located to document survival, the subject may be considered "lost to follow-up." All attempts to contact the subject must be documented.*

7.2. Drug Dose Level Assignment

7.2.1. Dose Finding Component

Dose level assignment will occur at the time of study registration

Dose Level	**Omacetaxine** mg/m^2
-1	0.5
1	0.625
2	1.25
3	2.0
4	3.0
5	4.2

7.2.2 Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v 4) [24]

The initial cohort will be 3 patients, and the following rule of hematologic toxicity will take effect.

7.2.3 Hematologic toxicity (HT) is defined as the following event occurring during induction:

- Incomplete hematologic recovery, ANC < 1.0 x 10^9/L (1000/μL) and platelet count < 100 x 10^9/L (100,000/μL) *with the* bone marrow documented to be free of leukemic infiltration.

7.2.4 Non-hematological toxicity is defined as any Grade 4 toxicity (excluding grade 4 infection), or an unresolved treatment-related ≥grade 3 non-hematologic toxicity that is present 6 weeks after the last dose of Omacetaxine (i.e., at day 50).

Dose escalation will occur based on the schema found in Section 12, and after consultation with the study statistician (Dr. Liu). HT's will be counted based on the number of patients with HT at a given dose level, not the absolute number of HTs. No single patient can trigger more than one HT event. Intra-patient dose escalation is not permitted.

7.3. Dose Modifications

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v 4). A copy of the CTCAE can be downloaded from the CTEP home page.[24]

The intent of the study design is for all patients to complete the induction therapy of Omacetaxine, Idarubicin and cytarabine, except for those patients who exhibit evidence of disease progression, experience an unacceptable toxicity or if the investigator determines that discontinuation of treatment is in the best interest of the patient.

Hematologic Toxicity: There will be no dose delays or dose reductions of study drugs for hematologic toxicity during Induction.

In the event of non-hematologic toxicity during Induction, the study drug may be stopped per the discretion of the Principal Investigator if the toxicity is determined to be clinically significant.

7.4. Permitted Concomitant Medications and Procedures

All other manifestations of the patient's malignancy and medical conditions should be treated at the discretion of the investigator in accordance with standards of medical care.

In appropriate settings, such as combinations with agents known to produce frequent thrombocytopenia, restricted uses of anticoagulants, antiplatelet agents and non-steroidal anti-inflammatory medication should be considered.

7.5. The Effects of Other Drugs on Omacetaxine

***Cytochrome P450 Enzymes (CYPs)*:** Omacetaxine mepesuccinate is not a substrate of CYP450 enzymes *in vitro.* Omacetaxine mepesuccinate and its derivative 4'desoxyhomoharringtonine (4'-DMHHT) do not inhibit major CYPs *in vitro* at concentrations expected clinically. The potential for Omacetaxine mepesuccinate or 4'-DMHHT to induce CYP450 enzymes has not been determined.

***Transporter Systems*:** Omacetaxine mepesuccinate is a P-glycoprotein (P-gp) substrate *in vitro*. Omacetaxine mepesuccinate and 4'-DMHHT do not inhibit P-gp mediated efflux of loperamide *in vitro* at concentrations expected clinically. [29]

7.6. Concomitant Medications and Non-Drug Therapies

All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of screening until the completion of the post-treatment follow-up visit.

7.7. Prohibited Concomitant Medications

Patients should not receive other anti-cancer therapy (cytotoxic, biologic, or radiation) while on treatment in this study.

7.8. Management of Clinical Events and Supportive Care Guidelines

Optimal patient care is to be provided to all patients. Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, or analgesics, when appropriate. Although acetaminophen at doses of ≤2 grams/day is permitted, it should be used with caution in patients with impaired liver function.

7.9. Nausea, Vomiting, Diarrhea

Prophylactic antiemetic therapy will be used in this study. 5-HT_3 receptor antagonist with corticosteroids will be administered. Because of the potential of benzodiazepines to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise. There is no prohibition against antiemetic use in the management of a patient who develops nausea or vomiting, or both.

Antidiarrheal medications will not be used prophylactically; however, patients determined to be free of infectious diarrhea can be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4 mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

7.10. Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
- Patient withdraws consent.
- There is evidence of progressive disease or unacceptable toxicity.
- The treating physician thinks a change of therapy would be in the best interest of the patient.

7.11. Follow-up

Study participants will follow in outpatient clinic at least every 2 months for a total of 6 months. A final study visit will occur 6 months (+/-1 week) after the last dose of Omacetaxine. This visit will end study participation unless there is ongoing toxicity that is at least possibly related to study treatment. In this case, the patient will be followed as medically appropriate until resolution or stabilization of the adverse event.

8 Study Parameters:

	Baseline, within 14 days of enrollment	Induction Phase[1]				Post-Induction Studies [~3-6 weeks][5]	Long Term Follow up Q2 months for 6 months
		Daily	Biweekly	Weekly	Day 14-17[6]		
Signed consent	x						
Medical history	x	x					
Review of prior therapy	x					x	x
Physical exam[11]	x	x					
Vital signs	x	x				x	x
Height[10], weight	x		x			x	x
Concomitant meds review	x	x				x	x
Performance status[2]	x			x		x	x
Symptom and toxicity	x	x				x	
CBC w/ diff	x	x				x	x
BMP	x		x			x	x
Albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein, uric acid, LDH, PT/INR, PTT, fibrinogen	x		x			x	x
Bone Marrow Aspirate and Biopsy and/or evaluation of extramedullary site	x				x	x[3]	
Cytogenetics (karyotype ± FISH)	x				x	x	
Bone Marrow or extramedullary site Immunophenotyping and cytochemistry	x				x	x	
Echocardiogram or MUGA scan	x					x	
HbA1C for diabetic patients	x					x	x
Urine pregnancy test for females of child-bearing potential	x						
EKG	x						
Lumbar puncture, if symptomatic or asymptomatic with special circumstances	x					x	

1: see section 7.1 for Induction Chemotherapy Regimen
2: For patients with unresolved treatment related toxicity, follow as medically appropriate until resolution or stabilization
3: BM to document status upon hematologic recovery (3-6 wks). BM may be repeated at later time points if recovery is delayed.
4: For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding, and an LP with intrathecal administration of chemotherapy should then be performed on these patients if no mass/lesion is detected on the imaging study. Consider screening LP at first remission for patients with M4 or M5 morphology or if WBC count >100,000/mcL at diagnosis.[23].
5: Post-Induction procedures will occur once upon bone marrow recovery with a window of 3-6 weeks. Note labs should be performed twice weekly from D14-17 BM to count recovery (or "off-study")
6: BM aspirate should be performed between 7 and 10 days after Induction chemotherapy is completed (i.e., Day 14-17).

7: If diabetic at baseline only.
8: Height at baseline only.
9: De-identified photographs of patients who develop skin changes that could potentially be related to Omacetaxine will be taken daily to document skin changes occurring on study.

9 Drug Formulation and Procurement

9.1. Omacetaxine[29]

9.1.1. Other names

Synribo, Omacetaxine mepesuccinate

9.1.2. Classification

Antineoplastic Agent, Cephalotaxine, Protein Synthesis Inhibitor

9.1.3. How supplied

Omacetaxine for Injection contains 3.5 mg Omacetaxine mepesuccinate; as a sterile, preservative-free, white to off-white lyophilized powder in a single-use vial.

9.1.4. Availability

Omacetaxine will be provided by Teva Pharmaceuticals.

9.1.5. Description

Omacetaxine contains the active ingredient Omacetaxine mepesuccinate, a cephalotaxine ester. It is a protein synthesis inhibitor. Omacetaxine mepesuccinate is prepared by a semi-synthetic process from cephalotaxine, an extract from the leaves of *Cephalotaxus sp*. The chemical name of Omacetaxine mepesuccinate is cephalotaxine, 4-methyl (2*R*)-hydroxyl-2-(4-hydroxyl-4-methylpentyl) butanedioate (ester).

The molecular formula is $C_{29}H_{39}NO_9$ with a molecular weight of 545.6 g/mol. Omacetaxine for injection is a sterile, preservative- free, white to off-white, lyophilized powder in a single-use vial. Each vial contains 3.5 mg Omacetaxine mepesuccinate and mannitol.

9.1.6. Storage, Handling, and Accountability

SYNRIBO is intended for subcutaneous administration after reconstitution with 1.0 mL of 0.9% Sodium Chloride Injection, USP. The pH of the reconstituted solution is between 5.5 and 7.0. Protect reconstituted solution from light. After administration, any unused solution should be discarded properly.

9.1.7. Administration

Omacetaxine mepesuccinate is an antineoplastic product. Follow special handling and disposal procedures.

Reconstitute Omacetaxine with one mL of 0.9% Sodium Chloride Injection, USP, prior to subcutaneous injection. After addition of the diluent, gently swirl until a clear solution is obtained. The lyophilized powder should be completely dissolved in less than one minute. The resulting solution will contain 3.5 mg/mL Omacetaxine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Use Omacetaxine within 12 hours of reconstitution when stored at room temperature and within 24 hours of reconstitution if stored at 2°C to 8 °C (36°F to 46°F).

9.1.8. Risks

The main toxic effect of Omacetaxine is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Blood counts will be monitored frequently. Patients will be monitored closely for signs of infection or neutropenic fever due to neutropenia or bleeding due to thrombocytopenia. Less serious toxicity includes hyperglycemia, nausea, vomiting, diarrhea abdominal pain, oral ulceration and atrial tachyarrhythmias such as atrial fibrillation.

See section 9.1.9 - **Warnings and Precautions**.

9.1.9. Warnings and Precautions

Myelosuppression: In uncontrolled trials with Omacetaxine, patients with chronic phase and accelerated phase CML experienced NCI CTC (version 3.0) Grade 3 or 4 thrombocytopenia (85%, 88%), neutropenia (81%, 71%), and anemia (62%, 80%), respectively. Fatalities related to myelosuppression occurred in 3% of patients in the safety population (N=163). Patients with neutropenia are at increased risk for infections, and should be monitored frequently and advised to contact a physician if they have symptoms of infection or fever.

Bleeding: Omacetaxine causes severe thrombocytopenia which increases the risk of hemorrhage. In clinical trials with CP and AP CML patients, a high incidence of Grade 3 and 4 thrombocytopenia (85% and 88%, respectively) was observed. Fatalities from cerebral hemorrhage occurred in 2% of patients treated with SYNRIBO in the safety population. Severe, non-fatal, gastrointestinal hemorrhages occurred in 2% of patients in the same population. Most bleeding events were associated with severe thrombocytopenia.

Hyperglycemia: Omacetaxine can induce glucose intolerance. Grade 3 or 4 hyperglycemia was reported in 11% of patients in the safety population. Hyperosmolar non-ketotic hyperglycemia occurred in 1 patient treated with Omacetaxine in the safety population. Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes. Avoid Omacetaxine in patients with poorly controlled diabetes mellitus until glycemic control has been established.

Embryo-Fetal Toxicity: Omacetaxine can cause fetal harm when administered to a pregnant woman. Omacetaxine mepesuccinate caused embryo-fetal death in animals. Females of reproductive potential should avoid becoming pregnant while being treated with Omacetaxine. There are no adequate, well-controlled studies of Omacetaxine in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

9.2. Cytarabine[30]

9.2.1. Other names

Cytosine arabinoside, Ara-C, Cytosar

9.2.2. Classification

Antineoplastic Agent, Antimetabolite; (Pyrimidine Analog)

9.2.3. How supplied

NDC 55390-131-10.....100 mg boxed vial; pack of 10
NDC 55390-132-10.....500 mg boxed vial; pack of 10
NDC 55390-133-01.....1 g boxed vial
NDC 55390-134-01.....2 g boxed vial

9.2.4. Availability

Commercially available from various manufacturers.

9.2.5. Description

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is

metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

9.2.6. Storage, Handling, and Accountability

Cytarabine should be stored in a controlled room temperature between 20° and 25°C (68° and 77°F). Hazardous agent: Use appropriate precautions for handling and disposal. Procedures for proper handling and disposal of anti-cancer drugs should be considered. Cytarabine Injection is supplied in a sterile, preserved solution.

9.2.7. Administration

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion, injection/subcutaneously or intrathecally. Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells seem to respond to somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

Relatively constant plasma levels can be achieved by continuous intravenous infusion.

In many chemotherapeutic programs, cytarabine is used in combination with other cytotoxic drugs. The addition of these cytotoxic drugs has necessitated changes and dose alterations. The dosage schedules for combination therapy outlined below have been reported in the literature.

9.2.8. Risks

Immediate side effects include allergic reactions associated with low blood pressure, shortness of breath, hypotension, back pain and hives. These will be treated with medications, fluids and oxygen. Anaphylaxis resulting in acute cardiopulmonary arrest has been reported, but is rare.

The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Blood counts will be monitored frequently. Patients will be monitored closely for signs of infection or neutropenic fever due to neutropenia or bleeding due to thrombocytopenia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction. See section 9.2.9 **Warnings and Precautions**.

9.2.9. Warnings and Precautions

Cytarabine for the use in induction therapy should be administered in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of cytarabine is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction. When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours post

injection. This problem tends to be less severe when the drug is infused.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Extensive chromosomal damage, including chromatid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Cytarabine is embryotoxic and teratogenic and produced peri- and postnatal toxicity in various species. Sperm head abnormalities were observed following cytarabine treatment in mice.

Cardiovascular: An increase in cardiomyopathy with subsequent death has been reported following experimental high dose cytarabine and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule dependent.

Gastrointestinal: Peritonitis and Typhlitis with concurrent neutropenia and thrombocytopenia, have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to nonoperative medical management.
Severe and at times fatal, GI toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high dose (2-3 g/m^2) schedules of cytarabine). These reactions include severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis, bowel necrosis; and necrotizing colitis.

Tumor Lysis Syndrome: Like other cytotoxic drugs, cytarabine may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacologic measurements as might be necessary to control this problem.

Hematologic Effects: Cytarabine is a potent bone marrow suppressant; the severity depends on the dose of the drug and schedule of administration. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and during induction therapy, should have leukocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications (possibly fatal) of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia).

Hepatic/Biliary/Pancreatic and/or Renal Function: The human liver apparently detoxifies a substantial fraction of an administered cytarabine dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with cytarabine. Use the drug with caution and at reduced dose in patients whose liver function is poor. Periodic checks of bone marrow, liver and kidney function should be performed in patients receiving cytarabine. Acute pancreatitis has been reported to occur in patients being treated with cytarabine in combination with other drugs.

Hypersensitivity Reactions: Anaphylactic reactions have occurred with cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine.

Immunosuppressant Effects/Increased Susceptibility to Infections: Administration of live or live- attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cytarabine may result in serious or fatal infections. Vaccination with a live vaccine should be

avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Neurologic: Severe and at times fatal, CNS toxicity (different from that seen with conventional therapy regimens of cytarabine) has been reported following high dose (2-3 g/m^2) schedules of cytarabine. These reactions include cerebral and cerebellar dysfunction including personality changes, somnolence, convulsion and coma, usually reversible. Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Respiratory: Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema have occurred following high dose schedules with cytarabine therapy. A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose cytarabine therapy used for the treatment of relapsed leukemia.

Skin: Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard cytarabine treatment programs.

9.3. Idarubicin[31]

9.3.1. Other names

Idamycin PFS, Idamycin®

9.3.2. Classification

Antineoplastic Agent, Anthracycline, Antibiotic

9.3.3. How supplied

IDARUBICIN (Idarubicin hydrochloride for injection, USP) NDC 0013-2526-86 20 mg single dose vial. Available in single vials.

9.3.4. Availability

Commercially available from various manufacturers. See package insert for further information.

9.3.5. Description

IDARUBICIN® (Idarubicin hydrochloride for injection, USP) is a sterile, semi-synthetic antineoplastic anthracycline for intravenous use. Chemically, Idarubicin hydrochloride is 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxyhydrochloride, (7S-cis).

9.3.6. Storage, Handling, and Accountability

Store at controlled room temperature, 15° to 30°C (59° to 86°F), and protect from light. IDARUBICIN, a sterile lyophilized powder for reconstitution and intravenous administration, is available in a 20 mg single use only vial. Each 20 mg vial contains 20 mg Idarubicin Hydrochloride, USP and 200 mg of Lactose NF (hydrous) as an orange-red, lyophilized powder.

9.3.7. Administration

For I.V. administration only. Do not administer I.M. or SubQ; administer as slow push over 3-5 minutes, preferably into the side of a freely-running saline or dextrose infusion **or** as intermittent infusion over 10-15 minutes into a free-flowing I.V. solution of NS or D_5W.

9.3.8. Risks

Idarubicin is a potent bone marrow suppressant. Idarubicin should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy or radiotherapy unless the benefit warrants the risk.

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent for induction, consolidation or maintenance. Careful hematologic monitoring is required. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Facilities with laboratory and supportive resources adequate to monitor drug tolerability and protect and maintain a patient compromised by drug toxicity should be available. It must be possible to treat rapidly and completely a severe hemorrhagic condition and/or a severe infection.

Pre-existing heart disease and previous therapy with anthracyclines at high cumulative doses or other potentially cardiotoxic agents are co-factors for increased risk of Idarubicin-induced cardiac toxicity and the benefit to risk ratio of Idarubicin therapy in such patients should be weighed before starting treatment with Idarubicin.

Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur following therapy with Idarubicin. Appropriate therapeutic measures for the management of congestive heart failure and/or arrhythmias are indicated.

Cardiac function should be carefully monitored during treatment in order to minimize the risk of cardiac toxicity of the type described for other anthracycline compounds. The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area or in patients with anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis. While there are no reliable means for predicting congestive heart failure, cardiomyopathy induced by anthracyclines is usually associated with a decrease of the left ventricular ejection fraction (LVEF) from pretreatment baseline values.

Since hepatic and/or renal function impairment can affect the disposition of Idarubicin, liver and kidney function should be evaluated with conventional clinical laboratory tests (using serum bilirubin and serum creatinine as indicators) prior to and during treatment. In a number of Phase III clinical trials, treatment was not given if bilirubin and/or creatinine serum levels exceeded 2 mg%. However, in one Phase III trial, patients with bilirubin levels between 2.6 and 5 mg% received the anthracycline with a 50% reduction in dose. Dose reduction of Idarubicin should be considered if the bilirubin and/or creatinine levels are above the normal range.

See section 9.3.9 **Warnings and Precautions**.

9.3.9. Warnings and Precautions

Idarubicin for the use in induction therapy in AML should be administered in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of Idarubicin is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Idarubicin can induce myocardial toxicity and pre-existing cardiac function should be evaluated. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction.

Myelosuppression: Severe myelosuppression is the major toxicity associated with Idarubicin therapy, but this effect of the drug is required in order to eradicate the leukemic clone. During the period of myelosuppression, patients are at risk of developing infection and bleeding which may be life-threatening or fatal.

Gastrointestinal: Nausea and/or vomiting, mucositis, abdominal pain and diarrhea were reported frequently, but were severe (equivalent to WHO Grade 4) in less than 5% of patients. Severe enterocolitis with perforation is rare. The risk of perforation may be increased by instrumental

intervention. Perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

Dermatologic: Alopecia was reported frequently and dermatologic reactions including generalized rash, urticaria and a bullous erythrodermatous rash of the palms and soles have occurred. The dermatologic reactions were usually attributed to concomitant antibiotic therapy. Local reactions including hives at the injection site have been reported. Recall of skin reaction due to prior radiotherapy has occurred with Idarubicin administration.

Hepatic and Renal: Changes in hepatic and renal function tests have been observed. These changes were usually transient and occurred in the setting of sepsis and while patients were receiving potentially hepatotoxic and nephrotoxic antibiotics and antifungal agents. Severe changes in renal function (equivalent to WHO Grade 4) occurred in no more than 1% of patients, while severe changes in hepatic function (equivalent to WHO Grade 4) occurred in less than 5% of patients.

Cardiac: Congestive heart failure (frequently attributed to fluid overload), serious arrhythmias including atrial fibrillation, chest pain, myocardial infarction and asymptomatic declines in LVEF have been reported in patients undergoing induction therapy for AML. Myocardial insufficiency and arrhythmias were usually reversible and occurred in the setting of sepsis, anemia and aggressive intravenous fluid administration. The events were reported more frequently in patients over age 60 years and in those with pre-existing cardiac disease.

10 Adverse Event Documentation and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. [22]
Note: throughout this section the generic term "drug" refers to Omacetaxine.

10.1. Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator its occurrence places the patient or subject at immediate risk of death.

Serious Adverse Event or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- 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 serious 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.

If either the investigator or TEVA believes the event is life-threatening or serious, the event must be evaluated by the investigator for expedited reporting (21CRF 312.32(a)).

The primary Investigator of the study will report all serious adverse events to the University Of Illinois IRB (the IRB of record), TEVA pharmaceuticals and, if serious and either likely, possibly, probably, or definitely related to study drug, to the FDA. The Investigator will communicate the occurrence of serious adverse events to both the IRB and Teva within 24 hours of becoming aware of the event. The information will be reported to TEVA via us.clinops.sae@tevapharm.com or via fax at 215-619-3825. *Reporting of Adverse Events to Teva does not preclude the responsibility of the Investigator to report adverse events to the FDA.* The reporting period begins when the subjects starts study drug, and ends after the discontinuation of dosing or completion of the subject's participation in the study if the last scheduled visit occurs at a later time. The investigator must notify Teva of any serious adverse events of which he becomes aware that may occur after this time which he believes to be definitely, likely or possibly related to the study product.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process or underlying medical conditions are considered *unexpected;* however, they will not be reportable per section 11.3.

Unanticipated (unexpected) problems/events as defined by the University Of Illinois IRB (the IRB of record) are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator's Brochure or *not* part of an underlying disease.
Note: The major discord between the FDA and IRB definitions is whether or not the underlying disease is included when considering expectedness.

UPIRSO: Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that researchers promptly report "any unanticipated problems involving risk to subjects or others" (UPIRSOs). The University of Illinois IRB defines a UPIRSO as any problem or event which in the opinion of the local researcher was *unanticipated, reflects new or increased risk to the subjects and at least possibly related* to the research procedures.
In addition, the IRB has defined the following problems/events as reportable using the Prompt Report form found on the IRB website:

- Any accidental or unintentional change to the IRB-approved protocol that increases risk or has the potential to recur
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research
- Any breach in confidentiality that may involve risk to the subject or others
- Any complaint of a subject that cannot be resolved by the research staff
- Any other possibly related event which in the opinion of the investigator constitutes an unanticipated risk

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in section 11.3. For the IRB this is 5 working days.

10.2. Adverse Event Documentation

Adverse events occurring from the first dose of Omacetaxine up to and including 30 days after administration of the last dose must be documented. Adverse events attributed to a study-related procedure which occur prior to the initiation of study treatment must be documented as well.

For the purposes of this study, all adverse events will be documented with the grade, expectedness and relationship to study therapy determined by the principal investigator.

All patients will be monitored with appropriate event documentation in the CTO data management system through the final study visit per Section 7, as it is expected that most treatment related adverse events will occur during this period.

Adverse Event toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definitely: A causal relationship that can only be the result of the investigational medicinal product and there is no other plausible cause of the AE.

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered investigational. Reporting of adverse events follows the guidelines for investigational agents.

10.3. Required Reporting: IRB, FDA, TEVA, and Cancer Center's Regulatory Coordinator

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy AE to:
University of Illinois IRB	**UPIRSO**: Events which are Unanticipated Problems, Involving Risk to Subjects or Others (e.g. serious and unexpected adverse events)	5 Working Days	UIC IRB Prompt Report Form	University of Illinois IRB	UICC's CTO Regulatory Coordinator
	Other Problems or Events meeting the definition of UPIRSO in section 11.1	5-15 Working Days per IRB requirements	UIC IRB Prompt Report Form		
FDA	Unexpected and fatal or life threatening suspected adverse reaction	As soon as possible but no later than 7 Calendar-Day	Medwatch Form FDA 3500A for Mandatory Reporting* *Copy sponsor on this correspondence.	Fax SAE to IND/IDE Regulatory Health Project Manager, Techiya (Thea) Toaff, R.N., B.S.N., Division of Oncology Products 1 at 1-301-796-9845. E-mail: techiya.toaff@fda.hhs.gov – follow-up with written report submitted as an amendment to: MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787	
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	As soon as possible but no later than 15 Calendar-Day			
	All other events per CRF 312.33	At time of IND annual report	Summary format	Submit as part of the IND annual report	
Note: Events due to the disease under treatment or an underlying medical condition will not require expedited reporting to the FDA for the purposes of this study					
TEVA Pharmaceuticals.	All serious adverse events regardless of expectedness or relationship with any study drug per section 11.4	Within 24 hours of knowledge	OnCore (Paper report can be generated from system)	TEVA Pharmaceuticals SAE and Pregnancy Reporting Contact Information: TEVA Pharmaceuticals Pharmacovigilance Email to: us.clinops.sae@tevapharm.com Or Fax to: (215) 619-3825	
	Pregnancy in a female patient or the partner of a male patient per section 11.5		Pregnancy Reporting Form OnCore (Paper report generated from system)		
UICC's CTO Regulatory Coordinator	All serious events regardless of expectedness or attribution through 180 days (+1 week) after the last dose of study drug(s)	Within 24 hours of knowledge	OnCore (Paper report generated from system)	UICC's CTO Regulatory Coordinator	Not applicable

11 Study Data Collection and Monitoring

11.1. Data Management

This study will report clinical data using the CTO data management system utilizing study specific case report forms. Key study personnel are trained on the use of case report forms and will comply with protocol specific instructions for data collection.

Patient demographics, patient specific study treatment calendars, adverse events and other information required for IRB annual reporting will be maintained with the CTO data management system.

11.2. Case Report Forms

Participant data will be collected using protocol specific case report forms (CRFs). The CRFs will be approved by the study's Principal Investigator and the study biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into the CTO data management system at time of study entry, completing CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3. Data Safety and Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Illinois Cancer Center's Data & Safety Monitoring Plan (DSMP).
For the purposes of data and safety monitoring, this study is classified as moderate. Therefore the following requirements will be fulfilled:

- The PI will complete and submit a semi-annual Trial Progress Report to the Cancer Center Data and Safety Monitoring Committee (DSMC) with the understanding the Cancer Center Protocol Review Committee (CCPRC) may require more frequent reporting.
- The PI will comply with at least yearly monitoring of the project by the Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 10.3 to the Cancer Center's SAE Coordinator and the University of Illinois IRB.

In addition, at the time of the continuing review with the University of Illinois IRB, a copy of the report with any attachments will be submitted to the Protocol Review Committee (PRC).

11.4. Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the study's Sponsor-Investigator and/or any designees, the local IRB, government regulatory bodies, and University of Illinois compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.5. Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB.
In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

12 Statistical Considerations

12.1. Analysis plan for primary objective

The OD will be determined using the EffTox Design.[32] EffTox is a Bayesian adaptive design that seeks to determine the optimal dose for further study in Phase II by considering a trade-off between efficacy and toxicity. EffTox uses the Bayesian paradigm and, therefore, all inference will be based on the posterior distributions of the parameters of interest. Efficacy is summarized by the probability of CR and toxicity is summarized by the probability of HT. Efficacy will be modeled using a Bayesian logistic regression model with linear and quadratic terms for dose, while toxicity will use a Bayesian logistic regression model with only a linear term for dose. The two logistic regression models will be linked using a copula model that accounts for correlation between efficacy and toxicity.[32] Using the posterior distributions for the logistic regression parameters we are able to derive the posterior distribution for the probability of efficacy and toxicity at each dose. A dose is considered acceptable if there is a 0.2 posterior probability that the probability of efficacy is greater than 0.6 and 0.2 posterior probability that the probability of toxicity is less than 0.3.

Acceptable doses are ranked using the Euclidean distance between the estimated probabilities of efficacy and toxicity and the point (1.0, 0.0), which represents the ideal combination of perfect efficacy with no toxicity. The dose with the minimum distance is considered the optimal dose.

The EffTox design begins by treating a cohort of three patients at dose level 1. The efficacy and toxicity outcomes for these three patients are used to update the posterior distributions for the probability of efficacy and toxicity and identify the acceptable dose levels. The study terminates if no dose levels are acceptable. Otherwise, the acceptable doses are ranked using the Euclidean distance from (1.0, 0.0) and the next cohort is treated at the dose with the minimum distance under the restriction that we may only escalate or deescalate one dose level at a time (i.e. the second cohort can only escalate to dose level 2 or de-escalate to dose level -1). The second cohort is treated at the dose with the minimum distance and the posterior distributions, and the list of acceptable doses and distances are then updated as before. This process continues until at least 20 subjects are enrolled in the study. The dose with the minimum distance at study completion is considered the optimal dose for further investigation. If none of the dose levels are acceptable at study completion, an optimal dose level will not be identified and the drug does not warrant further investigation.

Summary of the Basic EffTox algorithm

Step 1	Treat the first cohort of three patients at dose level 1
Step 2	Observe the efficacy and toxicity outcomes and estimate the probability of toxicity and efficacy for each dose
Step 3	Identify the acceptable doses and calculate the desirability measure for all acceptable doses
Step 4	If no doses are found to be acceptable, the trial is terminated and no doses are selected for further evaluation
Step 5	Otherwise, treat the next cohort at the most desirable dose under the restriction that no untried dose may be skipped when escalating. Cohorts will include 3 patients. Return to step 2 until the maximum sample size is reached.
Step 6	When the trial reaches the maximum sample size and there is at least one acceptable dose, the dose with the maximum desirability will be considered the OD.

12.2. Analysis plan for secondary objectives

(i) Activity. Clinical response will be measured using European LeukemiaNet criteria (see appendix I and II) and proportion of responders will be presented along with 95% confidence intervals. Proportion of patients with clinical response will be presented by each dose level along with 95% confidence intervals. We will use Chi-square/Fisher/s exact test to evaluate whether the proportions of clinical response vary among dose level. We will also consider using the logistic regression model to test for specific forms (e.g., a linear trend) of dose-response relationship. Such analysis can potentially provide more power to detect dose-response relationships and provide more information about the nature of dose-response relationships, as compared with the chi-square/Fisher's Exact test. We will use SAS 9.3 (Cary, NC) to perform these analyses. Overall survival, relapse-free survival and event-free survival will be computed using Kaplan-Meier estimates. The means of the survival times and their 95% confidence intervals will also be computed using SAS 9.3 (Cary, NC).

(ii) Adverse effects will be graded using the NCI's Common Terminology Criteria for Adverse Events CTCAE v4. Hematologic toxicity is defined in section 7.2.3. Proportion of patients with each grade of adverse events will be presented by each dose level along with 95% confidence intervals. We will use Chi-square/Fisher/s exact test to evaluate whether the distribution over the grades of adverse events vary among dose level. We will also consider using the logistic and/or ordinal regression model to test for specific forms (e.g., a linear trend) of dose-AE relationship. Such analysis can potentially provide more power to detect dose-AE relation and provide more information about the nature of dose-AE relation, as compared with the chi-square/Fisher's Exact test. We will use SAS 9.3 (Cary, NC) to perform these analyses.

13 Stopping rules

Criteria for Stopping

Study will be stopped if >35% of patients develop Grade 3 or greater treatment-related clinical non-hematological toxicity (excluding ≥ grade 3 infection, nausea, vomiting, diarrhea or alopecia without maximal medical intervention and/or prophylaxis) during the induction therapy or up to 4 weeks after Omacetaxine therapy. Toxicity will be measured according to the CTCAE v4.1[23]

14 Conduct of the Study

14.1. Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

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Appendix I – Definitions of Response to Treatment in AML*

Category	Definition
Complete remission (CR)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L (1000/µL); platelet count > 100 x 10^9/L (100,000/µL); independent of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia < 1.0 x 10^9/L (1000/µL) or thrombocytopenia < 100 x 10^9/L (100 000/µL)
Morphologic leukemia-free state	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)	No standard definition; depends on molecular target
Treatment Failure	
Resistant Disease	Failure to achieve CR or CRi or failure to achieve CR, CRi, or PR; only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

*Adapted from European LeukemiaNet [31]

Appendix II - Definitions of Survival in AML*

Overall Survival	Defined for all patients of a trial; measured from the date of entry into a study to the date of death from any cause; patients not known to have died at last follow-up are censored on the date they were last known to be alive
Relapse-free Survival	Defined only for patients achieving CR or CRi; measured from the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined
Event-free Survival	Defined for all patients of a trial; measured from the date of entry into a study to the date of induction treatment failure, or relapse from CR or CRi, or death from any cause; patients not known to have any of these events are censored on the date they were last examined

*Adapted from European LeukemiaNet [33]

Appendix III – ECOG Performance Status

ECOG Score	Performance Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden
5	Dead

Adapted from ECOG Definitions [26]

Appendix IV – New York Heart Association Classification

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Adapted from the American Heart Association Guidelines [27]