Omacetaxine for Consolidation and Maintenance in Patients Age ≥ 55 with AML in First Remission: a Pilot Study

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SYNOPSIS

Title:

- Pilot Study of Omacetaxine for Consolidation and Maintenance for Patients Age ≥ 55 with AML in First Remission.

Objectives:
Primary Objectives:

- To assess the safety and tolerability of delivering omacetaxine for consolidation in adult patients age 55 and older with acute myelogenous leukemia (AML) in first complete remission following induction chemotherapy.

- To assess the safety and tolerability of delivering omacetaxine for maintenance in adult patients age 55 and older with acute myelogenous leukemia (AML) in first complete remission following 3 consolidation courses with omacetaxine.

Secondary Objectives:

- To assess the duration of remission.
- To evaluate disease-free survival (DFS).
- To evaluate overall survival (OS).
- To assess for minimal residual disease (MRD) by WT-1 PCR during consolidation and maintenance therapy with omacetaxine.

Treatment Plan:

The induction time will be the screening period for the study. Those who achieve remission and are willing and able to proceed with OMA consolidation/maintenance will continue onto the investigational part of the study.

Screening: Patients will receive one to two induction courses according to investigator discretion, with a 3+7 regimen (cytarabine/Ara-C and anthracycline) followed by up to one course of dose-adjusted high dose cytarabine. Each induction course consists of:

- Ara-C 100mg /m^2/dose by continuous infusion daily for 7 days.
- An anthracycline; either daunorubicin , idarubicin or mitoxantrone at standard doses daily for 3 days, starting on day 1.

The second induction will consist of dose-adjusted high dose Ara-C alone (1-1.5grm/m2 Q12 hrs on day 1, 3, and 5, per standard of care). The timing for initiation of the second induction depends upon results of marrow done 14-21 days after the first induction according to standard of care practice.

- Patients who do not achieve remission at the conclusion of 2 inductions will be considered screen failures and offered alternative therapies.

Consolidation:

- Omacetaxine 1.25 mg/m² sub-cutaneously twice daily for 5 consecutive days every 28 (± 8) days for a total of 3 cycles.

Maintenance:

- Subjects in continuous remission after 3 cycles of consolidation with omacetaxine will receive maintenance omacetaxine 1.25mg/m^2 twice daily for 3days, every 28 days, for up to 6 cycles.

Sample size and patient selection:

- ***Screening:*** 45 patients with newly diagnosed, untreated AML eligible for induction chemotherapy. Patients who received 1-2 cycles of hypomethylating therapy for cytoreduction are also eligible.

- ***Consolidation/maintenance:*** 15 patients in first complete remission after 2 inductions.

Assessment of response:

- Bone marrow biopsy and aspirate will be obtained at day 14-21 of the 1st cycle, and at day 28 or at count recovery, whichever occurs first.

- Prior to each consolidation cycle, responses will be evaluated with a complete blood count (CBC) and bone marrow aspiration/biopsy to document continued remission.

- Bone marrow aspirate to confirm continuous remission will be obtained every 3 months during maintenance, and as clinically indicated thereafter.

Statistical Methods:

- This study is an open label, pilot study. Continuous data will be described using descriptive statistics (n, mean, median, minimum, and maximum) while discrete data will be described using frequency counts and percentages.

Time line: 2-3 years, based on previous accrual in the target population.

1. BACKGROUND:

1.1 Acute Myelogenous Leukemia (AML) in older Adults

Outcomes of older patients with AML are poor due to chemotherapy-related toxicity and inherent resistant disease. Despite advances in supportive care, there has been no significant progress in the outcomes of these patients. In patients age ≥ 55, standard anti-leukemic induction chemotherapy (anthracycline + cytarabine 100-200 mg/m2/d for 7 -10 days) yields complete remission (CR) rates ranging from 38-48% with average early mortality of 30% (Table 1).

Table 1. Safety and efficacy of induction chemotherapy in patients with AML ≥ 55.

Study Group	Patients	CR (%)	Early death (%)
AMLCG[1]	511	39-42	27-34
BMRC[2]	636	46-48	30-52
CALGB[3]	556	41-47	31-54
SECSG[4]	111	53	20
EORTC-LCG-HOVON[5]	489	38-47	6-15

Induction with single agent chemotherapy results in comparable CR rates and overall lower early mortality rates (Table 2), but effects on relapse-free and overall survivals do not seem to have improved using these agents.

Table 2. Safety and efficacy of induction with single agent chemotherapy in AML. patients ≥ 55.

Treatment	Patients	CR (%)	Early death (%)
Clofarabine[6]	112	38	10
Decitabine[7]	55	24	4
Laromustine[8]	104	32	18
Low dose Ara-C [9]	102	18	26

Trials for older AML patients randomizing standard remission induction (i.e., anthracycline-containing) chemotherapy versus either palliative therapy[10] or less intensive chemotherapy (low dose Ara-C, LDAC) [11] have demonstrated a survival advantage for those patients who received the intensive induction regimen. In the study performed by Tilly et al in patients ≥ 65 years old, 87 patients were randomized to receive either LDAC 10 mg/m2 SC every 12 hours for 21 days or standard chemotherapy induction with rubidazone (a daunorubicin-derived agent) 100 mg/m2 IV for 4 days plus cytarabine 200 mg/m2 IV for 7 days. The combination chemotherapy arm was associated with a higher CR rate (52% versus 32%), and a trend toward improved survival (12.8 months versus 8.8 months); albeit at the cost of 31% early death rate vs. 10% for the lower dose arm.

Based on data from these 2 randomized trials, anti-AML induction chemotherapy appears to be the best approach to induce remission in carefully selected, older fit patients with newly diagnosed AML.

1.2 Role of High Dose Ara-C (HiDAC) in the AML induction regimen.

High dose cytarabine (HiDAC, doses > 1.5 g/m^2/d) administered during induction results in improved recurrence-free and overall survival in younger AML patients < 60,[12] but is associated with increased toxicities in older patients [13,14]. We have recently reported on the safety and efficacy of modified HiDAC induction for newly diagnosed patients ≥ 60 with AML (Arellano et al. ASCO 2010). HiDAC induction was well-tolerated, associated with high CR rates (69%), and comparable early mortality to standard dose cytarabine induction (19%). In our series, 37/59 (63%) patients were able to receive the 2 planned inductions. Of the 41/59 (69%) that achieved remission, 6, 11, and 10 patients received 1, 2, and 3 consolidations with HiDAC, respectively. **However, despite high initial CR rate (69%) and the delivery of standard consolidation in 80%, the median relapse-free survival was 11 months, and most patients died from relapsed leukemia.** Therefore, exploring alternative consolidation regimens is desirable. Since the current study opened, we have learned that prospectively, our patients did not tolerate the 2 consecutive cycles of modified HiDAC/daunorubicin due to cardiac toxicity, and have amended the protocol to limit induction to only 1 cycle of standard infusional cytarabine 100mg/m^2 over 24hrs. daily x 7 days and an anthracycline (daunorubicin, idarubicin, or mitoxantrone at standard doses). At count recovery or sooner if residual leukemia is present at the end of induction, 1 cycle of dose-adjusted high dose cytarabine can be administered (1-1.5gm/m2 IV Q12hrs. on days 1,3, and 5, per standard of care).

1.3 Consolidation Therapy for Older Patients with AML.

The optimal consolidation regimen for older adults with AML in remission is unknown. The Cancer and Leukemia Group B (CALGB) defined repeated cycles of high dose cytarabine (3g/m^2 IV every 12hrs on days 1, 3, and 5, repeated every 28 days) as the standard consolidation regimen for younger patients with AML in remission, based on a randomized trial comparing four courses of cytarabine at one of three doses: 100 mg/m^2 of body-surface area per day for five days by continuous infusion, 400 mg/m^2 per day for five days by continuous infusion, or 3 g/m^2 in a 3-hour infusion every 12 hours (twice daily) on days 1, 3, and 5 [15]. The benefit of the high dose cytarabine consolidation predominantly extended to younger patients with core binding factor AML, although those with normal cytogenetics derived a lesser benefit[16]. The trial, however did not show a benefit for patients age > 60, and only 29% of patients age > 60 received the intended cycles of high dose cytarabine. More recently, the German-Austrian AML Study Group carried out a clinical trial randomizing patients age 61 and older in fist remission from AML after 2 cycles of induction and one consolidation, to either a second intensive consolidation (idarubicin 12mg/m^2 IV days 1-3 and etoposide 100mg/m^2 IV on days 1-5) or a 1-year oral maintenance therapy (idarubicin 5mg po on days 1, 4, 7, 10, and 13; etoposide 100mg po on days 1 and 13; repeated on day 29 for 12 courses). Analysis according to second randomization on an intention-to-treat basis revealed a statistically significant lower cumulative incidence of relapse (P= 0.005) in patients assigned to the intensive second consolidation compared to those assigned to the oral therapy. This translated into a statistically significant better survival (P= 0.04) with estimated median

survival times from second randomization of 22.3 and 14.3 months in the intensive vs. oral arm, respectively. However, this trial concluded that while a second intensive consolidation was beneficial, it could only be extended to the fraction of patients who could be randomized after remission[17]. **Thus better, more tolerable consolidation regimens are needed for older patients with AML who achieve remission.**

1.4 Role of maintenance chemotherapy in AML

The role of maintenance therapy in AML is undefined. Several trials have shown no difference in survival between AML patients in first complete remission who receive protracted maintenance regimens vs. no maintenance or transplantation. Maintenance chemotherapy is therefore not part of standard AML therapy at the present time. A Cancer and Leukemia Group B (CALGB) study showed that patients who received maintenance therapy for 8 months versus 3 years had no significant differences in relapse rate or overall survival [3]. Another study showed that maintenance chemotherapy after intensive early consolidation treatment did not prolong survival [18]. Low–dose cytarabine maintenance therapy may prolong disease–free survival but does not improve survival in older patients with AML [5]. A Japanese study comparing three cycles of consolidation with maintenance to four cycles of consolidation without maintenance[19] found no statistical difference in the disease-free or overall survival rates between the two arms. A limitation may be that no studies have examined identical consolidation regimens followed by a randomization to maintenance or no maintenance chemotherapy. **In this study, we are investigating the safety and tolerability of an active and well-tolerated agent for maintenance therapy in older patients with AML.**

1.5 Omacetaxine for AML and MDS

Omacetaxine, an alkaloid agent derived from the bark of the Chinese evergreen tree, *Cephalotaxus harringtonia,* has activity in AML as single agent and in combination with other active agents. The mechanism of action of omacetaxine differs from conventional chemotherapy, primarily by inhibiting protein synthesis and does not appear to share cross-resistance with other anti-leukemic agents. In heavily pre-treated relapsed AML patients, using single agent omacetaxine showed 3-50% responses [20, 21] and 39 -83% used in combination for newly diagnosed AML[22-23] . The activity in older AML patients was 39-47% (advanced MDS and RAEB-t) [24]. Wu et al. reported on 32 patients (25 with advanced MDS and 7 with t-AML) who enrolled in a study to evaluate the efficacy and toxicity of the low-dose cytarabine and omacetaxine in combination with granulocyte colony-stimulating factor (G-CSF) (CHG protocol) in patients with advanced myelodysplastic syndromes (MDS) or MDS-transformed into acute myeloid leukemia (t-AML). All the patients received the CHG regimen comprising low-dose cytarabine (25 mg/day by intravenous continuous infusion on days 1-14), omacetaxine (1 mg/day, by intravenous continuous infusion on days 1-14), and G-CSF (300 mcg/day by subcutaneous injection on days 0-14. The overall response rate was 71.9% after the administration of one course of the CHG regimen. Of the 32 patients, 15 (46.9%) achieved complete remission (CR) and 8 (25%) achieved partial remission (PR). Among the 7 AML patients, 5 achieved CR and 2 achieved a PR. This regimen was followed by a post-remission therapy that included conventional chemotherapy, when CR was achieved. The median overall survival (OS) was 18.2 months. There were no statistically significant differences for CR, PR, and OS when the patients were grouped by age, % marrow blasts, and karyotypes. No

treatment-related deaths were observed. Myelosuppression was mild to moderate, and no severe non-hematological toxicity was observed[24].

Between 04/2007 and 04/2009, we enrolled 9 patients with advanced phase CML and the T315I mutation on the CGX635-CML-202 clinical trial and observed acceptable tolerability at a dose of 1.25 mg/m² sub-cutaneously twice daily for 14 consecutive days. The regimen was administered every 28 (±3) days on an outpatient basis. The treatment with omacetaxine was very well tolerated in patients up to age 79, and the drug was administered for a median duration of 4.5 months (range, 2-28). Data from ChemGenex shows that the median number of cycles administered on this study was 4, and the median days the drug was given per cycle was 11 days.

The anti-leukemic activity as well as the tolerability of omacetaxine at the 1.25mg/m^2 dose makes this drug an attractive alternative for consolidation and maintenance in older AML patients.

1.6 Rationale for the study

The outcome of older patients with AML is dismal with standard anti-leukemic chemotherapy, and only a minority of those patients can proceed with curative allogeneic stem cell transplantation. Despite good initial responses (CR 50-70%) with anti-leukemic induction chemotherapy, half of all patients will relapse within a year and 80% would have relapsed by 2 years. Therefore, alternative consolidations are needed. Given that omacetaxine is an active anti-leukemic agent that is well tolerated, we propose to conduct a prospective pilot study exploring safety and tolerability of omacetaxine to treat minimal residual disease in the form of consolidation and maintenance for patients age 55 and older with newly diagnosed AML in first complete remission. **This trial is a necessary step for an efficacy phase II trial.**

2. STUDY OBJECTIVES

Primary Objectives:

- To assess the safety and tolerability of delivering omacetaxine for consolidation in adult patients age 55 and older with acute myelogenous leukemia (AML) in first complete remission following induction chemotherapy.

- To assess the safety and tolerability of delivering omacetaxine for maintenance in adult patients age 55 and older with acute myelogenous leukemia (AML) in first complete remission following 3 consolidation courses with omacetaxine.

Secondary Objectives:

- To assess the duration of remission.
- To evaluate disease-free survival (DFS).
- To evaluate overall survival (OS).
- To assess for minimal residual disease (MRD) during consolidation and maintenance therapy with omacetaxine.

3. RESEARCH DESIGN AND METHODS:

3.1 Patient Selection:

3.1.1 Inclusion Criteria:

1. Diagnosis of AML including de novo, secondary, or with an antecedent hematologic disorder [AHD] according to the World Health Organization (WHO) criteria[25] (**Appendix A**).
2. Age ≥ 55 years.
3. Patient eligible for standard induction chemotherapy based on ECOG PS and vital organ function at the discretion of the treating physician.
4. Patients who received 1-2 cycles of hypomethylating therapy (decitabine azacitidine) are eligible.
5. Provide signed written informed consent.
6. Be able to comply with study procedures and follow-up examinations.
7. Be non-fertile or not pregnant or lactating & agree to use birth control during the study through the end of last treatment visit.
8. Adequate renal and hepatic function **at the time of second registration**:
    a. Total bilirubin ≤ 1.5 x institutional Upper Limit of Normal (ULN); and
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; and
    c. Serum creatinine ≤ 1.2 times the upper limit of normal.
9. ECOG performance ≤ 2 (**Appendix B**) **at the time of second registration**:
10. Patients with a history of carcinoma in remission, on no therapy or on hormonal therapy for the adjuvant treatment of breast carcinoma or prostate carcinoma are included in the study.

3.1.2 Exclusion Criteria:

1. Diagnosis of acute promyelocytic leukemia (APL, French-American-British [FAB] classification M3 or WHO classification of APL with t (15;17)(q22;q12), (*PML/RARa* and variants).
2. Prior treatment with omacetaxine
3. Relapsed or refractory AML.
4. Investigational agent received within 30 days prior to the first dose of study drug. If received any investigational agent prior to this time point, drug-related toxicities must have recovered to Grade 2 or less prior to first dose of study drug.
5. Psychiatric disorders that would interfere with consent, study participation, or follow-up.
6. Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
7. Any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver, or other organ system that may place the patient at undue risk to undergo the proposed therapy. This includes uncontrolled hypertension and uncontrolled diabetes, as cases of life threatening hyperglycemia have been reported (using continuous infusion at higher doses of omacetaxine).
8. Active carcinoma requiring systemic chemotherapy or radiation therapy.

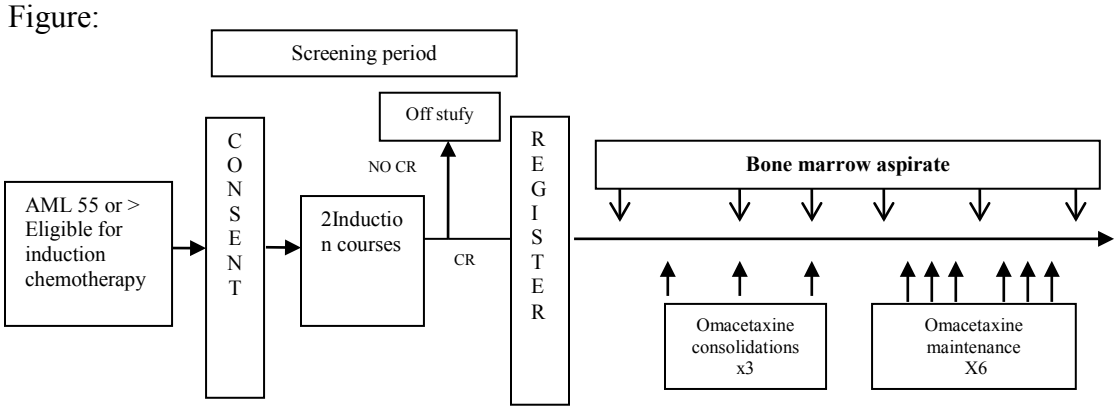
3.2. Patient Enrollment and Registration:

Patients will be pre-screened in the hospital (Emory University Hospital) or the out patient clinic at the Winship Cancer Institute of Emory University. All patients of age 55 and older with newly diagnosed AML deemed eligible for induction chemotherapy by the judgment of the treating hematologist will be offered to participate in the study. The primary leukemia physician (co-investigator) will discuss the study and counsel patient and family. The objectives of the study, procedures, alternative therapies and potential risks and benefits of participation will be explained. Eligible patients will sign a consent form approved by the Emory University Institutional Review Board (IRB). Protocol registration/screening procedures and eligibility checklist will be completed at the time of enrollment (**Appendix C**) will be completed. The protocol registration form, eligibility checklist and signed IRB-approved consent form will be collected and stored in a specifically designed clinical research area.

3.3 Specific Methods and Protocol Description:

3.3.1 Plan of Treatment:

Patients meeting inclusion criteria will start therapy as detailed below and as summarized in the Figure:



A. Induction:

Induction consists of 1 to 2 courses consisting of the following agents:
Cycle #1: Cytarabine at 100mgm^2/dose via continuous infusion daily for 7 days, starting on day 1.
Daunorubicin, idarubicin, or mitoxantrone at standard dosing daily for 3 days, starting on day 1.
Cycle #2: Cytarabine 1- 1.5gm/m^2/dose IV twice daily on days 1, 3 and 5.

- Study specific evaluations during induction (**See Appendix D**)

B. Consolidation:

- Omacetaxine 1.25 mg/m² sub-cutaneously twice daily for 5 consecutive days every 28 (± 8) days for 3 cycles, provided that prior to the next planned treatment cycle, the patient's absolute neutrophil count (ANC) recovers to $\geq$ 1 x 10^9/L and the platelet count recovers to $\geq$ 100 x 10^9/L. Patients with history of or suspected MDS prior to AML who fail to recover their ANC and platelets after induction chemotherapy, may start omacetaxine upon recovery to baseline pre-AML ANC and platelet count. Omacetaxine can be administered at Emory/Winship Cancer Institute or by self- injection at home.
- Evaluations during consolidation (see **Appendix E**)

C. Maintenance:

- Patients in continuous remission after 3 cycles of consolidation will receive maintenance omacetaxine 1.25mg/m^2 twice daily for 3 days, every 28 days for up to 6 cycles, provided that prior to the next planned treatment cycle, the patient's absolute neutrophil count (ANC) recovers to $\geq$ 1 x 10^9/L and the platelet count recovers to $\geq$ 100 x 10^9/L. . Patients with history of MDS prior to AML who fail to recover their ANC and platelets after induction chemotherapy, may start omacetaxine upon recovery to baseline pre-AML ANC and platelet count. Omacetaxine can be administered at Emory/Winship Cancer Institute or by self- injection at home.
- Evaluations during maintenance (see **Appendix F**)

D. Supportive Care (these guidelines are not protocol requirements as these as standard of care practices):

- Standard anti-microbial prophylaxis will be instituted for every patient enrolled in this study. Suggestions include: anti-viral (acyclovir or valacyclovir), anti-bacterial (fluoroquinolone, doxycycline, or standard alternative) and anti-fungal (azole or micafungin) prophylaxis will be initiated at the onset of neutropenia according to our institutional standard. Patients experiencing fever will be treated according to institutional practice, with blood cultures, imaging of suspected areas of infection, and empiric antibiotics targeted at the suspected cause of fever.
- Steroids may be used empirically to prevent a systemic inflammatory response syndrome (SIRS) during the first 5 days of both induction cycles, at the discretion of the treating physician.
- Hydroxyurea will be used to reduce the WBC to < 30,000, or a level considered safe by the treating physician, prior to initiating induction therapy. Patients may undergo leukapheresis if deemed necessary by the treating physician in patients believed to be experiencing leukostasis, based on clinical suspicion.
- Tumor lysis prophylaxis utilizing intra venous fluids and allopurinol (300mg/ day po) or rasburicase (variable dose) will be instituted per standard of care.
- Hematopoietic growth factors may be used at the discretion of the treating physician to accelerate count recovery after induction therapy in patients who have clearance of AML at day 14-21.

- Disseminated intra-vascular coagulation (DIC) will be treated based on our institutional practice, with transfusion of fresh frozen plasma, cryoprecipitate, and platelets, to prevent and/or treat bleeding complications.
- Patients with diabetes should have their blood glucose monitored and controlled due to the risk of life-threatening hyperglycemia with omacetaxine.

3.3.2 Patient Evaluations and Definition of Response:

- All patients will undergo standard of care pre-treatment testing that includes echocardiogram and baseline laboratory testing according to standard of care.
- A comorbidity score will be determined for all patients at diagnosis and at start of consolidation (using the co-morbidities listed in **Appendix G**).
- A Quality of Life Questionnaire (**appendix H**) will be obtained at baseline, start of consolidation and prior to each subsequent course of consolidation and maintenance. Data from these questionnaires will be reported descriptively.
- Disease status will be assessed by a bone marrow aspirate and biopsy upon count recovery following the induction, monthly during consolidation and quarterly (every 3 months) during maintenance therapy. Response to therapy will be classified according to criteria published by the International Working Group on Myeloid Malignancies [25] (**Appendix I**) and defined as follows:
    - **Complete Remission (CR):** Normocellular marrow with < 5% blasts, absence of auer rods and of any unique phenotype identical to what was found in the pretreatment specimen, with ANC $\geq$ 1 x 10^9/L and platelet count $\geq$ 100 x 10^9/L, and transfusion independence, as well as no residual evidence of extramedullary AML.
    - **Complete Response with incomplete blood count recovery (CRi):** Meets criteria for CR above, except for residual neutropenia (ANC < 1 x 10^9/L) or thrombocytopenia (platelets < 100x10^9/L)
    - **Complete Response with incomplete platelet recovery (CRp):** Meets criteria for CR above, but platelets are < 100x10^9/L.
    - **Cytogenetic Complete Remission (CRc):** Disappearance of cytogenetic abnormalities thought to be associated with the AML.
    - **Molecular Complete Remission (CRm):** Disappearance of molecular abnormalities thought to be related to the AML.
    - **Treatment failure:**
        - ***Resistant disease:*** Patient survives $\geq$ 7 days post-chemotherapy and has persistent AML in blood or bone marrow.
        - ***Aplasia:*** Patient survives $\geq$ 7 days post-chemotherapy, but dies while cytopenic, with an aplastic bone marrow.
    - **Morphologic relapse:** Reappearance of blasts post-chemotherapy in peripheral blood or bone marrow.
    - **Molecular/cytogenetic relapse:** Reappearance of molecular or cytogenetic abnormality.
    - **Clearance of Leukemia at the day 14 marrow:** < 5% blasts in a hypocellular marrow (<15% cellularity).

- **Overall survival (OS):** Time from entry onto trial until death from any cause.
- **Relapse free survival (RFS):** Time from Remission (CR, CRi, CRp) until disease relapse or death from any cause.
- **Event free survival (EFS):** Time from entry onto trial to treatment failure/relapsed disease, or death from any cause.
- **Remission duration:** Time from date of CR (or CRp, CRi) until disease relapse.

3.3.3 Safety Assessment and Study Tests:

Toxicities will be monitored by history, physical examination, and laboratory monitoring (CBC, serum chemistries to include renal and liver function tests) weekly during consolidation and monthly during maintenance according to standard of care (Appendices D-F). Toxicity will be assessed according to the NCI Common Toxicity Criteria Version 4.0 (available at the NCI web site http://ctep.cancer.gov/reporting/ctc.html). Adverse events will be monitored on an ongoing basis. No AEs will be collected during the screening period (the time from diagnosis to completion of the standard of care inductions).

3.3.4 Dose Modifications and Stopping Rules:

A. Omacetaxine

- ***Hematological toxicity:***
  - The following table summarizes dose adjustments for hematological toxicity during consolidation and maintenance with Omacetaxine and are based on time to count recovery to < grade 2 hematological toxicity. Hematologic toxicity only refers to WBC/neutrophils and platelets and not hemoglobin/hematocrit, given that anemia is expected and may not resolve after chemotherapy regardless of AML-status. Dose-reductions and delays do not apply to anemia.

Time to resolution to < grade 2 hematologic toxicity (days)	Action 1	Action 2: Hematologic toxicity after 1st dose reduction
≤ 36	No dose reduction	No dose reduction
> 36 and < 50	20% dose reduction, i.e. omacetaxine 1.25 mg/m² sub-cutaneously twice daily for 4 days during consolidation, or 1.25mg/m2 twice daily for 3 days during maintenance	Additional 25% dose reduction, i.e. omacetaxine 1.25 mg/m² sub-cutaneously twice daily for 3 days during consolidation, or 1.25mg/m2 twice daily for 2 days during maintenance
> 50	Perform bone marrow aspirate and biopsy. If relapse – patient will be taken off study. If hypoplastic marrow (cellularity < 10%), reassess after 2 weeks. If recovery achieved within 2 weeks post-marrow assessment, resume omacetaxine after 60% dose reduction; i.e. omacetaxine 1.25 mg/m² sub-cutaneously twice daily for 3 days during consolidation, or 1.25mg/m2 twice daily for 2 days during maintenance If no recovery 2 weeks post-marrow assessment, patient will be taken off study.	No further dose reduction. Patient will be taken off study

- ***Non-hematological toxicity:***

- Patient with grade III-IV non-hematological toxicity (deemed at least "possibly" related to omacetaxine) will have study drug held until toxicity has recovered to grade 1 or less. Treatment may resume after 20% dose reduction.

- Patient who develop grade II non-hematological toxicity that is related to omacetaxine will have study drug held at treating physician's discretion, until toxicity has recovered to grade 1 or less. Treatment will resume after 20% dose reduction.

- If grade III-IV non-hematological toxicity recurs after dose-reduction, the patient will discontinue protocol therapy.

- If grade III-IV non-hematological toxicity does not resolve to grade 1 or less by day 36 of therapy with omacetaxine, then patient will be taken off study.

B. Cytarabine

The following guidelines are not protocol requirements given that patients are receiving Institutional standard induction.
Doses of cytarabine can be ***reduced*** during the second induction in cases of decrease in the calculated creatinine clearance > 20% but less than 50%. HiDAC will be discontinued and patient taken off study if neurotoxicity occurs at any time during HiDAC therapy.

C. Daunorubicin, Idarubicin, or mitoxantrone

The following guidelines are not protocol requirements given that patients are receiving Institutional standard induction.

- Drug will be withheld and patients will be withdrawn from the study, if they experience a clinically significant decrease in left ventricular ejection fraction, leading to a diagnosis of symptomatic congestive heart failure.
    - Adjustments for hepatic and renal dysfunction will conform to recommendation from the package inserts and standard practice.

D. Stopping Rules

- Omacetaxine will be ***discontinued*** in cases of
    - Delay in recovery of ANC to $\geq$ 1,000/mcL and platelets to $\geq$ 100,000/mcL or to baseline ANC and platelets (for patients with history of underlying MDS) after 50 days.
    - Grade III-IV irreversible non-hematological toxicity attributable to omacetaxine
    - Recurrence of grades III-IV non-hematological toxicities after dose-reduction.
    - Recurrent leukemia.
    - Patient's or treating physician's request.

3.3.5. Correlative studies

Blood and marrow aspirates (and biopsies when indicated) will be obtained at diagnosis, prior to each cycle of consolidation and every 3 months during maintenance therapy.

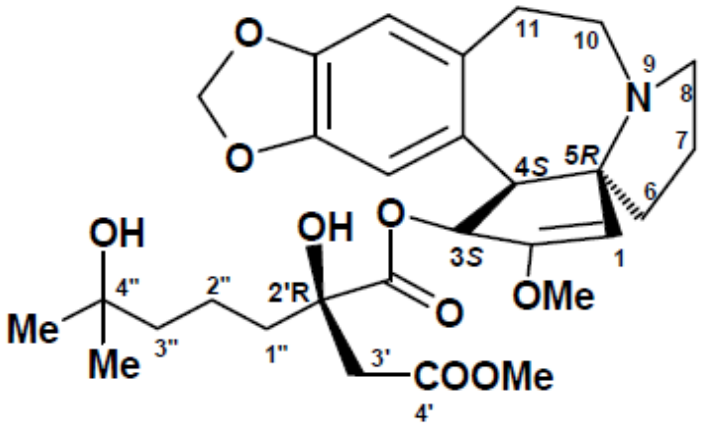
- Monitoring MRD using WT1 transcript during consolidation and maintenance therapy with omacetaxine.
- Tissue acquisition for future studies of AML among older adults.
- In cases where a marrow was obtained at Emory to establish the AML diagnosis, prior to enrolling on the study, study marrow can be waived if sufficient circulating blasts are present in the peripheral blood.
- In cases where the presence of disseminated intravascular coagulation (DIC) due to AML places the patient at risk of bleeding, marrow collection can be waived and instead peripheral blood collection will suffice for baseline collection.

3.4. Study Drugs:

3.4.1 Omacetaxine:

Generic Name: Omacetaxine, Homoharringtonine, NSC-141633
Chemical Name: Cephalotaxine,4-methyl-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate ester
Formula: C29 H39 N O9
Molecular Weight: 545.6 g/mo

Structure:



Drug description:

Omacetaxine is a cephalotaxine ester alkaloid derived from the plant Cephalotaxus fortunei. Cephalotaxines have the empirical composition C18H21NO4 and contain a methylenedioxypheno group, a secondary hydroxyl group, double bond and a vinyl methoxyl group. A variety of esters of cephalotaxine are known, and the two which have been investigated clinically are harringtonine, ester-2 and homoharringtonine, ester-3. Omacetaxine differs from harringtonine in having a methylene group inserted in the side chain. There are no known drug incompatibilities. A summary of chemistry, manufacturing, pharmacokinetics and toxicology is supplied in the Investigator's Drug Brochure.

Mechanism of action:
Omacetaxine inhibits protein synthesis and induces differentiation and apoptosis. Details are in the investigator's brochure. Kinetic studies of the effects of the agent on L-1210 cells showed a marked inhibition of thymidine incorporation, damage to tumor cells in G phase and S phase, block of the progression of cells in G2 phase into M phase and block of the traverse of the leukemic cells in G1 into S phase.

4. DATA COLLECTION:

Data will be entered onto specific case report forms, and will be managed by designated data managers and stored in the WCI database. Data will be then recorded on electronic spread sheets for statistical analyses.

5. ADVERSE EVENT REPORTING AND SAFETY MONITORING

Collection of adverse events information will be managed directly between the Study Coordinator and PI. A MedWatch Form Form will be completed for every SAE and those which meet FDA reporting requirements will be submitted to the FDA. A data and safety monitoring report will be filed with the IRB at least once per year in order to protect patients from any harm that might result from their participation in this study. See **Appendix L** for serious adverse events reporting and adverse events log.

Definition of Adverse Events (AE): An AE is defined as any untoward medical occurrence in a patient after administration of the study drug. An AE does not necessarily have a causal relationship with the use of the study drug. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not related to the study drug.

Definition of Serious Adverse Events (SAE): A serious adverse event (SAE) is any medical complication that results in one of the following outcomes: death, urgent medical intervention to prevent death or disability, inpatient hospitalization for more than 24 hours or prolongation of hospitalization because of complications that could be caused by the study drugs, new persistent or significant disability or incapacity, or exacerbation of a pre-existing significant disability or incapacity.

Progression or relapse of AML are not considered AEs or SAEs and will be tracked as outcomes in the Case Report forms.

Expedited Reports of SAE's and Unexpected SAE's: The PI will immediately notify Teva Pharmaceuticals of any SAE occuring after the second registration. SAEs (during OMA consolidation/maintenance). SAEs will be sent to the Teva Pharmacovigilance safety mailbox at us.clinops.sae@tevapharm.com or Fax #215-619-3825. The PI will review each report to determine whether the SAE is expected or unexpected, based on information available in the study drugs label, and the study consent document approved by the IRB. An SAE will be defined as "unexpected" only if it is not listed in any of these documents and it is not expected based on the patient's medical history. The PI/ study coordinator team will notify the IRB

immediately of any deaths possibly, probably or definitely associated with the study drug or procedures, and will notify the FDA of any unexpected fatal or life-threatening event within 7 days. All unanticipated problems involving risks to participants or others (UPs) will be reported to the IRB within 10 calendar days. Death from progression of AML is not an SAE.

The Study Coordinator is responsible for filing SAE reports, patient evaluation forms, and medical records in the study file for each patient, and forwarding all SAE reports to the PI. At 3-month intervals, the Study Coordinator will prepare summaries of all AE information, compiled from SAE reports, patient questionnaires, and review of available medical records for each patient. Summary reports tabulating the occurrence of all AEs will be forwarded to the PI.

The PI is responsible for reviewing all SAE reports to determine whether the SAE is expected or unexpected. The PI is responsible for following the reporting requirements of the IRB, and the FDA. The PI is responsible for filing a semi annual or annual report to the IRB according to the IRB requirements. The PI is responsible for responding to inquiries from the IRB.

5.1 Data Safety Monitoring Plan.

Patient safety, study efficacy and compliance will be reviewed at the (Leukemia Working Group) meetings. The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP)..

Data quality will be monitored on an ongoing basis by random checks of CRFs following the Leukemia Working Group meetings. Co-investigators and staff will be trained on the conduct of the protocol and any additional training based on protocol amendments at the Hematology/Leukemia multi-disciplinary meetings, which meets regularly. Recording, grading, and reporting of adverse events will be carried out contemporaneously with each patient's clinic visit and will abide by the guidelines provided by the Winship Cancer Institute Clinical Trials Office. Deviations will be added to the Deviation Log, which is updated and reviewed at the Leukemia Working Group meetings.

The Principal investigator is responsible for sending a yearly IND summary report, which includes an update and status of the study and a tabulation of the AEs/ SAEs, as well as status of the study subjects, to the FDA. The PI is also responsible for collecting, reviewing, analyzing and reporting to the FDA and other investigators any potential serious risks that qualify for reporting under the FDA's IND Safety Reporting regulations at 21 CFR §312.32, .64 and 21 CFR § 320.31. In addition, the Sponsor-Investigator must copy the Emory IRB on

any such reports and include an analysis of whether the Sponsor-Investigator believes the event constitutes an Unanticipated Problem Involving Risks to Subjects or Others.

6. STATISTICAL CONSIDERATIONS:

Safety: Target omacetaxine dose is the dose that can be delivered to 70% patients without dose limiting toxicity (DLT) as defined above (section 3.3.4). Safety analysis will be conducted through continuous monitoring of AE/SAE. If 2 of the first 3 patients experience DLT, we stop the trial. After that, we stop the trial if there is evidence that the target probability of DLT exceeds 30% and the probability of falsely stopping the trial is 10% or less. The following table gives the minimum number of DLTs in order to stop the trial and the probability of falsely terminating the trial if in fact the probability of DLT is 30% calculated using the binomial distribution. For example, if after enrolling 6 patients, 4 or more experienced DLT, then we stop the trial and conclude that the target probability of DLT is more than 30%. The probability of incorrectly stopping the trial is 0.07.

To be considered safe, the upper limit of the one-sided 95% CI of DLT among 15 patients must not be greater than 30%.

Number of Patients	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Number o DLTs to Stop Trial	**> 1**	**> 1**	**> 3**	**> 3**	**> 4**	**> 4**	**> 4**	**> 5**	**> 5**	**> 6**	**> 6**	**> 6**	**> 7**
Probability of falsely terminating the trial		**0.08**	**0.03**	**0.07**	**0.03**	**0.06**	**0.10**	**0.05**	**0.08**	**0.04**	**0.07**	**0.10**	**0.05**

Feasibility: Feasibility is defined as delivery of 9 cycles of therapy for at least 2/3 of the patients. The proportion of patients with full treatment delivery will be estimated with an exact 95% confidence interval.

Futility: Based on our previous data showing a median relapse-free survival of 13.8 months, we will consider our consolidation/maintenance regimen futile if $\geq$ 80% of those entering in CR relapse during consolidation/maintenance.

Kaplan-Meier curves will be used to estimate the distribution of time to relapse, relapse free survival, and overall survival.

Analysis of survival outcomes (OS, EFS, RFS) for patients who undergo transplantation in CR will include censoring and no censoring at the time of transplantation**.**

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APPENDIX A: THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF THE MYELOID NEOPLASMS

Acute myeloid leukemia with recurrent genetic abnormalities

- Acute myeloid leukemia with t(8;21)(q22;q22), (*AML1/ETO*)
- Acute myeloid leukemia with abnormal bone marrow eosinophils and
- inv(16)(p13q22) or t(16;16)(p13;q22), (*CBF_/MYH11*)
- Acute promyelocytic leukemia with t(15;17)(q22;q12), (*PML/RAR_*) and variants
- Acute myeloid leukemia with 11q23 (*MLL*) abnormalities

Acute myeloid leukemia with multilineage dysplasia

- Following MDS or MDS/MPD:
  - Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50% of cells in 2 or more myeloid lineages

Acute myeloid leukemia and myelodysplastic syndromes, therapy related

- Alkylating agent/radiation–related type
- Topoisomerase II inhibitor–related type (some may be lymphoid)
- Others

Acute myeloid leukemia, not otherwise categorized, classify as:

- Acute myeloid leukemia, minimally differentiated
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/acute monocytic leukemia
- Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma

Adapted from **Blood. 2002;100:2292-2302**

APPENDIX B: ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX C: ELIGIBILITY CHECK LIST AT THE TIME OF SECOND REGISTRATION

Demographics:

Patient Name: _____ UPN:_____ Age (years): _____

Patient Gender: o Male o Female Ethnicity _____

- Date Diagnosis of AML: ____ / ___ / _____
- DOB ____/ ___ / _____
- Age ≥ 55 years ☐ Yes ☐ No
- Informed consent ☐ Yes ☐ No
- Stated patient willingness to comply with study procedures ☐ Yes ☐ No
- Lack of active, uncontrolled fungal or viral infection ☐ Yes ☐ No
- ECOG performance status 0-2 _____ ☐ Yes ☐ No
- ECOG PS=_____
- Adequate hepatic and renal function? ☐ Yes ☐ No
- Total bilirubn < 1.5 x ULN ☐ Yes ☐ No
  - Total bilirbin =_____on ___/___/___
- AST < 2.5 x ULN ☐ Yes ☐ No
  - AST=_____ on ___/___/___
- ALT < 2.5 x ULN ☐ Yes ☐ No
  - ALT= _____ on ___/___/___
- Creatinine < 1.2 x ULN ☐ Yes ☐ No
  - Creatinine= _____ on ___/___/___
- Cytotoxic chemotherapy concluded > 4 weeks prior to enrollment? ☐ Yes ☐ No
  (1-2 cycles of hypomethylating agent allowed)

Secondary AML ☐ Yes ☐ No If yes, answer the following:

- Name of Antecendent hematological disorder _____
- Type of previous carcinoma if applicable_____
- Prior chemotherapy _____ concluding on _____/_____/_____
- Prior radiation therapy concluding on _____/_____/_____

Non-Fertile ☐ Yes ☐ No

If not non-fertile: 1. Method of contracept ion to be used _____

2. Date if negative pregnancy test: _____

Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study based on the inclusion/exclusion criteria described in the IRB submission, as approved by the IRB.

PI/designee signature*:	Date**:
Printed name of person assessing eligibility :	
Printed name of person completing this form:	

** This form should be signed by the PI or designee, as described on the delegation of authority log.
**Documentation of eligibility determination should be completed prior to registration.

APPENDIX D: EVALUATIONS DURING INDUCTION (DURING INDUCTION)

Test	Baseline
Research Samples: Peripheral blood (20mL), Bone Marrow Aspirate (10mL)*	X
Comordity Score	X
Quality of life Questionnaire	X

* Bone marrow aspirate and peripheral blood to be collected for correlative testing at baseline and at all subsequent SOC collections during induction.(only peripheral blood will be collected if a bone marrow biopsy presents a risk to the patient)

APPENDIX E: EVALUATIONS DURING CONSOLIDATION

Week	1	2	3	4	5	6	7	8	9	10	11	12
Day	1											
H&P	X	X	X	X	X	X	X	X	X	X	X	X
Medication review	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff.	X	X	X	X	X	X	X	X	X	X	X	X
CP Comp	X	X	X	X	X	X	X	X	X	X	X	X
Research samples: Peripheral blood (20mL) and Bone marrow aspirate (10mL)	X			X				X				X
Bone marrow aspirate[1]	X	X		X				X				X
Quality of life questionnaire	X			X				X				X
Comordity Score	X											

1. Bone marrow aspirate (biopsy if indicated based on suspicion of relapse) performed monthly during consolidation to document continuous remission. Molecular tests and cytogenetics obtained as clinically indicated. Research samples are obtained monthly during consolidation. (only peripheral blood will be collected if a bone marrow biopsy presents a risk to the patient)
2. *All time points have an up to 3-day window.

APPENDIX F: EVALUATIONS DURING MAINTENANCE

Week	1	4	8	12	16	20	24
Day	1						
H&P	X	X	X	X	X	X	X
Medication review	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X
CBC with diff.[1]	X	X	X	X	X	X	X
CP Comp	X	X	X	X	X	X	X
Research samples: Peripheral blood (20mL) and Bone marrow aspirate (10mL)	X			X			X
Bone marrow aspirate[2]	X			X			X
Quality of life questionnaire	X			X			X

1. CBC with differential will be collected weekly during maintenance and if counts remain stable (no neutropenia or significant thrombocytopenia), can decrease frequency to every other week.
2. Bone marrow aspirate (biopsy if indicated) performed every 3 months during maintenance. Molecular tests and cytogenetics obtained as clinically indicated. Research samples are obtained every 3 months during maintenance. (only peripheral blood will be collected if a bone marrow biopsy presents a risk to the patient)
3. *All time points have an up to 3-day window.

APPENDIX G: COMORBIDITY SCORING

(Blood. 2005;106: 2912-2919)

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity†	Patients with a body mass index > 35 kg/m^2	1
Infection†	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary‡	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3

To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.

APPENDIX H: QUALITY OF LIFE QUESTIONNAIRE

NAME: _____ DATE: ____ / ____ / ____

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

APPENDIX I: RESPONSE CRITERIA

- **Complete Remission (CR):** Normocellular marrow with < 5% blasts, absence of auer rods and of any unique phenotype identical to what was found in the pretreatment specimen, with ANC $\geq$ 1 x 10 ^{9}/L and platelet count $\geq$ 100 x 10^{9}/L, and transfusion independence, as well as no residual evidence of extramedullary AML.
- **Complete Response with incomplete blood count recovery (CRi):** Meets criteria for CR above, except for residual neutropenia (ANC < 1 x 10^{9}/L) or thrombocytopenia (platelets < 100x10^{9}/L)
- **Complete Response with incomplete platelet recovery (CRp):** Meets criteria for CR above, but platelets are < 100x10^{9}/L.
- **Cytogenetic Complete Remission (CRc):** Disappearance of cytogenetic abnormalities thought to be associated with the AML.
- **Molecular Complete Remission (CRm):** Disappearance of molecular abnormalities thought to be related to the AML.
- **Treatment failure:**
  - ***Resistant disease:*** Patient survives $\geq$ 7 days post-chemotherapy and has persistent AML in blood or bone marrow.
  - ***Aplasia:*** Patient survives $\geq$ 7 days post-chemotherapy, but dies while cytopenic, with an aplastic bone marrow.
- **Morphologic relapse:** Reappearance of blasts post-chemotherapy in peripheral blood or bone marrow.
- **Molecular/cytogenetic relapse:** Reappearance of molecular or cytogenetic abnormality.
- **Clearance of Leukemia at the day 14 marrow:** < 5% blasts in a hypocellular marrow (<15% cellularity).
- **Overall survival (OS):** Time from entry onto trial until death from any cause.
- **Relapse free survival (RFS):** Time from Remission (CR, CRi, CRp) until disease relapse or death from any cause.
- **Event free survival (EFS):** Time from entry onto trial to treatment failure/relapsed disease, or death from any cause.
- **Remission duration:** Time from date of CR (or CRp, CRi) until disease relapse.

APPENDIX J: OMACETAXINE INVESTIGATOR'S BROCHURE

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See attachment

APPENDIX K: OMACETAXINE PACKAGE INSERT AND INJEFCTION WORKSHEET

OMACETAXINE PACKAGE INSERT

See attachment


Synribo
(omacetaxine) PI_Re

INJECTION WORKSHEET

See attachment


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APPENDIX L: INSTRUCTIONS FOR OMACETAXINE INJECTION

See attachment

Synribo
(omacetaxine) instruc

APPENDIX M: SAE REPORTING AND AE LOG

STUDY TITLE: _____ **PI:** _____ **CONSENT DATE:** _____

TREATMENT START DATE: _____ **TREATMENT END DATE:** _____ **OFF STUDY DATE:** _____

Adverse Event	Start and stop dates	Serious	Grade**	Relationship to drug/device	Anticipated	Action taken with the drug/device	Other actions taken	Was the AE reported to the sponsor?	Was the AE reported to the IRB? ***	PI initials
	Start: _____ Stop: _____	□Yes □No	□Mild □Moderate □Severe □Life Threatening □Death	□Not related □Possibly □Probably □Related □Unknown	□Yes □No	□None □Reduced □Interrupted □Discontinued □Other		□Yes □No Date of report _____	□Yes □No Date of report _____	
	Start: _____ Stop: _____	□Yes □No	□Mild □Moderate □Severe □Life Threatening □Death	□Not related □Possibly □Probably □Related	□Yes □No	□None □Reduced □Interrupted □Discontinued		□Yes □No Date of report _____	□Yes □No Date of report _____	
	Start: _____ Stop: _____	□Yes □No	□Mild □Moderate □Severe □Life Threatening □Death	□Not related □Possibly □Probably □Related	□Yes □No	□None □Reduced □Interrupted □Discontinued		□Yes □No Date of report _____	□Yes □No Date of report _____	
	Start: _____ Stop: _____	□Yes □No	□Mild □Moderate □Severe □Life Threatening □ Death	□Not related □Possibly □Probably □Related	□Yes □No	□None □Reduced □Interrupted □Discontinued		□Yes □No Date of report _____	□Yes □No Date of report _____	

*** 0= not, 1= suspected**

Codes for action taken: **0= none, 1= OM dose reduced, 2= OM held, 3= OM restarted, 4= OM stopped due to this SAE, 5= patient admitted to the hospital, 6=taken off study**