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## Study of Chemotherapy in Combination With All-trans Retinoic Acid (ATRA) With or Without Gemtuzumab Ozogamicin in Patients With Acute Myeloid Leukemia (AML) and Mutant Nucleophosmin-1 (NPM1) Gene Mutation

**This study is currently recruiting participants.**

Verified July 2012 by University of Ulm

First Received on May 5, 2009. Last Updated on July 10, 2012 [History of Changes](#)

<b>Sponsor:</b>	University of Ulm
<b>Information provided by (Responsible Party):</b>	Dr. Richard Schlenk, University of Ulm
<b>ClinicalTrials.gov Identifier:</b>	NCT00893399

### ► Purpose

Primary Efficacy Objective:

- Evaluation of efficacy based on event-free survival (EFS) after induction and consolidation chemotherapy plus all-trans retinoic acid (ATRA) with or without gemtuzumab ozogamicin (GO) in adult patients with acute myeloid leukemia (AML) and mutant nucleophosmin-1 (NPM1)

Secondary Efficacy Objectives:

- Evaluation of efficacy based on complete remission (CR) rates, overall survival, cumulative incidences of relapse (CIR) and death (CID) in CR

Safety and Quality of Life (QoL) Objectives:

- Evaluation of safety based on toxicity induced by gemtuzumab ozogamicin (GO)
- Evaluation of safety based on duration of neutropenia and leukopenia after consolidation therapy, incidence of infection, duration of hospitalization
- Assessment of quality of life

<a href="#">Condition</a>	<a href="#">Intervention</a>	<a href="#">Phase</a>
Acute Myeloid Leukemia	Drug: Gemtuzumab Ozogamicin (Mylotarg) Drug: standard chemotherapy	Phase 3

Study Type: Interventional  
 Study Design: Allocation: Randomized  
 Endpoint Classification: Safety/Efficacy Study  
 Intervention Model: Parallel Assignment  
 Masking: Open Label  
 Primary Purpose: Treatment

Official Title: Phase III Study of Chemotherapy in Combination With ATRA With or Without Gemtuzumab Ozogamicin in Patients With Acute Myeloid Leukemia and NPM1 Gene Mutation

#### Resource links provided by NLM:

[Genetics Home Reference](#) related topics: [familial acute myeloid leukemia with mutated CEBPA](#)  
[Help Me Understand Genetics](#)

[MedlinePlus](#) related topics: [Acute Myeloid Leukemia](#) [Leukemia](#)

[Drug Information](#) available for: [Tretinoin](#) [Gemtuzumab ozogamicin](#)

[U.S. FDA Resources](#)

#### Further study details as provided by University of Ulm:

##### Primary Outcome Measures:

- Event-free Survival (EFS) [ Time Frame: two years ] [ Designated as safety issue: No ]

##### Secondary Outcome Measures:

- Rates of complete remission after induction therapy (CR) [ Time Frame: not later than 56 days ] [ Designated as safety issue: No ]
- Cumulative incidences of relapse (CIR) and death in CR (CID) [ Time Frame: two years ] [ Designated as safety issue: No ]
- Overall survival [ Time Frame: two years ] [ Designated as safety issue: No ]
- Days in hospital during each cycle and during the whole intervention [ Time Frame: 6 months ] [ Designated as safety issue: No ]
- Type, frequency, severity, timing and relatedness of AEs and laboratory abnormalities observed during different treatment cycles [ Time Frame: 6 months ] [ Designated as safety issue: Yes ]
- Incidence of infection after induction and consolidation therapy [ Time Frame: 6 months ] [ Designated as safety issue: Yes ]
- Duration of neutropenia and thrombocytopenia after induction and consolidation therapy [ Time Frame: 6 months ] [ Designated as safety issue: Yes ]
- Quality of life assessed by the EORTC Quality of Life Core Questionnaire (QLQ-C30), supplemented by information on self-assessed concomitant diseases, late treatment effects, and demographics according to Messerer et al [49] [ Time Frame: two years after completion of therapy ] [ Designated as safety issue: No ]

Estimated Enrollment: 276  
 Study Start Date: February 2010  
 Estimated Study Completion Date: February 2016  
 Estimated Primary Completion Date: February 2016 (Final data collection date for primary outcome measure)

<a href="#">Arms</a>	<a href="#">Assigned Interventions</a>
Experimental: 1 chemotherapy in combination with ATRA with gemtuzumab ozogamicin	Drug: Gemtuzumab Ozogamicin (Mylotarg) Induction Cycle 1, 2: GO 3mg/m <sup>2</sup> by intravenous infusion (IVI) on day 1 (total dose 3 mg/m <sup>2</sup> ). Start after etoposide IVI. No dose reduction is foreseen in elderly (> 60 yrs) patients.  Consolidation 1: GO 3mg/m <sup>2</sup> by intravenous infusion (IVI) on day 1 (total dose 3 mg/m <sup>2</sup> ). Start after first dose of high-dose cytarabine. No dose reduction is foreseen in elderly (> 60 yrs)

	<p>patients.</p> <p>Consolidation 2, 3: no GO</p> <p>Drug: standard chemotherapy</p> <p>Idarubicin, Etoposide, Cytarabine, ATRA, Pegfilgrastim</p>
<p>Active Comparator: 2</p> <p>chemotherapy in combination with ATRA without gemtuzumab ozogamicin</p>	<p>Drug: standard chemotherapy</p> <p>Idarubicin, Etoposide, Cytarabine, ATRA, Pegfilgrastim</p>

### Detailed Description:

#### 5.2.1. Choice of Standard Regimen

The protocol is based on the previous front line AMLSG protocols: AMLHD93 [50], AMLHD98A [51], AMLHD98B [22], AMLSG 06-04 [52], AMLSG 07-04 [30]. In all these trials induction therapy consisted on a combination of standard-dose cytarabine in combination with the anthracycline idarubicin and the epipodophyllotoxin etoposide. The regimen is abbreviated with ICE. Based on overall good results with ICE in terms of achievement of CR and, in particular, the fact, that NPM1mut was established as a favourable predictive factor for achievement of a complete remission after an induction therapy with ICE [13,16] the chemotherapeutic components in the induction therapy of the AMLSG 09-09 protocol have remained unchanged. As outlined in section 3.3, ATRA showed favourable results in NPM1mut AML in one retrospective analysis of a randomized study [13] and in one interim analysis of an active prospective randomized trial [30]. Since it is not possible to await the final results of the AMLSG 07-04 protocol before start of the current AMLSG 09-09 protocol ATRA is incorporated in both arms of the study based on the favourable clinical results in the absence of additional ATRA-related toxicity.

Postremission therapy is based on repetitive cycles of HDAC as a standard therapy in patients with normal karyotype AML [48,53]. Results of the German-Austrian AMLSG suggest that two cycles of HDAC - in combination with an anthracycline or mitoxantrone - may be equally effective [16]. In the current study, three courses of postremission with HDAC will be given according to the preceding AMLSG 07-04 protocol for comparability [30].

#### 5.2.2. Choice of Study Design

A standard two-arm randomized phase-III study design was chosen because all components and additionally the combinations of treatment regimens had been evaluated in dosage and efficacy in several phase II/III trials [13,16,22,30,34,52]. Based on these studies efficacy and toxicity of the standard arm of the study is well established. The addition of GO to induction and consolidation therapy in NPM1mut AML seems to be reasonable based on the consistent association of NPM1mut AML with a characteristic immunophenotype, i.e., low or absent CD34 expression and strong CD33 expression [7-11]. Due to the constitutional high CD33 expression and potential efficacy in that high expression was correlated to high response rates [33], GO represents a potentially highly effective agent in the treatment of patients with NPM1mut AML. The combination of GO in a dosage of 3mg/m<sup>2</sup> to intensive induction and consolidation treatment [32] as well as in combination with intensive salvage therapy including ATRA [34] has been demonstrated to be save and well tolerated.

## ► Eligibility

Ages Eligible for Study: 18 Years and older  
 Genders Eligible for Study: Both  
 Accepts Healthy Volunteers: No

### Criteria

#### Inclusion Criteria:

- Patients with confirmed diagnosis of acute myeloid leukemia according to the World Health Organization (WHO) classification.
- Presence of NPM1 mutation as assessed in one of the central AMLSG reference laboratories.

- Age  $\geq$  18 years. There is no upper age limit.
- No prior chemotherapy for leukemia except hydroxyurea to control hyperleukocytosis if needed for up to 5 days during the diagnostic screening phase.
- Non-pregnant and non-nursing. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within a sensitivity of at least 25 mIU/mL within 72 hours prior to registration.
- Female patients in the reproductive age and male patients must agree to avoid getting pregnant or to father a child while on therapy and within one year after the last dose of chemotherapy.
  - Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or begin two acceptable methods of birth control: one highly effective method (e.g., IUD, hormonal, tubal ligation, or partner's vasectomy), and one additional effective method (e.g., latex condom, diaphragm, or cervical cap).
  - "Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months.
  - Men must use a latex condom during any sexual contact with women of childbearing potential, even if they have undergone a successful vasectomy.
- Signed written informed consent.

#### Exclusion Criteria:

- AML with other recurrent genetic changes (according to WHO 2008):
  - AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFβ-MYH11
  - AML with t(15;17)(q22;q12); PML-RARA (or other translocations involving RARA)
  - AML with t(9;11)(p22;q23); MLLT3-MLL (or other translocations involving MLL)
  - AML with t(6;9)(p23;q34); DEK-NUP214
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1.
- Performance status WHO  $>$  2.
- Patients with ejection fraction  $<$  50% by MUGA or ECHO scan within 14 days of day 1.
- Organ insufficiency:
  - creatinine  $>$  1.5x upper normal serum level
  - bilirubin, AST or ALP  $>$  2.5x upper normal serum level, not attributable to AML
  - heart failure NYHA III/IV
  - severe obstructive or restrictive ventilation disorder.
- Uncontrolled infection.
- Severe neurological or psychiatric disorder interfering with ability of giving an informed consent.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year.
- Known positive for HIV.
- Bleeding disorder independent of leukemia.
- No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.

## **Contacts and Locations**

Please refer to this study by its ClinicalTrials.gov identifier: NCT00893399

### **Contacts**

Contact: Richard F Schlenk, MD 004973150045900 [richard.schlenk@uniklinik-um.de](mailto:richard.schlenk@uniklinik-um.de)

 [Show 48 Study Locations](#)

### Sponsors and Collaborators

University of Ulm

### Investigators

Principal Investigator: Richard F Schlenk, MD University of Ulm

### More Information

No publications provided

Responsible Party: Dr. Richard Schlenk, PD Dr., University of Ulm  
ClinicalTrials.gov Identifier: [NCT00893399](#) [History of Changes](#)  
Other Study ID Numbers: **AMLSG 09-09**  
Study First Received: May 5, 2009  
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Health Authority: Germany: Federal Institute for Drugs and Medical Devices

Keywords provided by University of Ulm:

adult patients  
NPM1 mutation

Additional relevant MeSH terms:

Leukemia	Tretinoin
Leukemia, Myeloid, Acute	Antineoplastic Agents
Leukemia, Myeloid	Therapeutic Uses
Neoplasms by Histologic Type	Pharmacologic Actions
Neoplasms	Keratolytic Agents
Gemtuzumab	Dermatologic Agents

ClinicalTrials.gov processed this record on July 29, 2012

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