A double-blind, placebo-controlled, randomized, multicenter phase II trial to assess the efficacy of temsirolimus added to standard primary therapy in elderly patients with newly diagnosed AML

Study protocol

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CONFIDENTIAL

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Coordinating Investigator:	Christian H. Brandts, MD
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PROTOCOL SIGNATURE PAGE

This protocol has been approved by the Sponsor represented by the Coordinating Investigator. The following signature documents this approval.

13-4-2012

Christian H. Brandts, MD — Date

Coordinating investigator (Leiter der klinischen Prüfung) representing the sponsor

PRINCIPAL INVESTIGATOR STATEMENT

Principal Investigator:

_____ _____

Signature of Investigator — Date

_____

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, the applicable parts of the ICH Good Clinical Practices guidelines, the European Regulations or local regulations governing the conduct of clinical studies as outlined in the study contract.

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2 ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AMLCG	AML Cooperative Group
AP	Alkaline phosphatase
APL	Acute promyelocyticleukaemia
AR	Adverse reaction
AraC	Cytosine arabinoside
AST	Aspartate transaminase
ATU	Temporary authorization for use
ATIII	Antithrombin III
CALGB	Cancer and Leukemia Group B
CBC	Complete blood count
CNS	Central nervous system
CpG-islands	Cytosine-phospho-guanine islands
CR	Complete remission
CRc	Complete cytogenetic remission
CRm	Complete moleculargenetic remission
CRF	Case report form
CT	Chemotherapy
CTCAE	Common terminology criteria for adverse events
CTCN	Clinical Trials Center Network Frankfurt
CYP	Cytochrom P
DL	Dose level
DNA	Desoxyribonucleic acid
Dnmt	DNA methyltransferase
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
FAB	French-American-British cooperative group
Flt	Fms like tyrosine kinase
FISH	Fluorescence in situ hybridization
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
HiDAC	High dose-cytarabine
HIV	Human immunodeficiency virus
IB	Investigator`s brochure

ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
ITD	Internal tandem duplication
KGU	Klinikum der Goethe-Universität
LDH	Lactatedehydrogenase
MDS	Myelodysplastic syndrome
MI	Myocardial infarction
MRD	Minimal residual disease
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NPM	Nucleophosmin
NYHA	New York Heart Association
OS	Overall survival
PAT	Patienten
PB	Peripheral blood
PTT	Partial thromboplastin time
PVC	Polyvinyl chloride
RFS	Relapse free survival
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous injection
SUSAR	Suspected unexpected serious adverse reaction
t_{max}	Time to maximal plasma concentration
UAR	Unexpected adverse reaction
UCT	University Cancer Center Frankfurt
ULN	Upper limit of normal
WHO	World Health Organization

3 BACKGROUND INFORMATION / INTRODUCTION

In acute myeloid leukemia (AML) treatment failure and relapse are frequently observed despite intensive chemotherapy and allogeneic bone marrow transplantation, leading to a cure in less than 30% of adults with AML [1]. Prognostic factors include age over 60 years, cytogenetics and molecular aberrations such as mutations in Flt3 (Flt3-ITD) and NPM. In patients over 60 years induction chemotherapy with cytarabine and an anthracycline (such as daunorubicin or mitoxantrone) leads to complete remission in only approximately 50% [2]. Consolidation therapy following the induction of an initial complete response is essential to prevent relapse. Three options are generally available: allogeneic or autologous bone marrow transplantation or chemotherapy. Transplantation is more often used in young patients with adverse karyotypes and chemotherapy in good prognosis or elderly patients [2]. Non-transplant consolidation chemotherapy regimens commonly contain cytarabine. While consolidation therapy following the induction is essential to maintain complete remission, relapse frequently occurs leading to a long-term disease-free survival in 10% to 20% [2].

AML is a clonal, malignant disorder that results from genetic and epigenetic changes in pluripotent stem or slightly more differentiated progenitor cells. The aberrant cells gain a growth and/or survival advantage in relationship to the normal pool of stem cells. The most common genetic aberrations seen in acute myeloid leukemia (AML) are oncogenic K-RAS and N-RAS-mutations as well as activating mutations of the receptor tyrosine kinase Flt3 (Flt3-ITD). Both oncogenic RAS and Flt3-ITD, as well as other receptor tyrosine kinases activated in AML (such as cKIT and PDGFRβ), activate the phosphatidylinositol 3-Kinase (PI3K) / AKT pathway in myeloid cells, which regulates proliferation and apoptosis in myeloid leukemia cells [3]. As a result, AKT was found to be activated in 86% of AML patients [3], which leads to the activation of mTOR in AML [4].

Monotherapy with inhibitors of mTOR have demonstrated clinical efficacy in a variety of hematological malignancies. Clinical trials of temsirolimus, everolimus, rapamycin and AP23573 are ongoing in several hematological diseases, including acute and chronic myeloid leukemia, lymphoma and multiple myeloma. In a study of patients with refractory/relapsed AML, a more than 50% blast reduction in the peripheral blood or bone marrow was observed in 4 out of 9 patients treated for 28 days with rapamycin alone [7]. Two of the 4 responders were still alive at 8 and 10 months [7]. A phase II trial of rapamycin in elderly patients with high-risk myelodyplastic syndrome (MDS) demonstrated an overall hematological response in

16% (3/19) of treated patients with one major and two minor responses [8]. AP23573 is currently tested in a phase II study in patients with relapsed and refractory hematological malignancies. Preliminary results demonstrated some responses in patients with AML [9]. These clinical data have consistently demonstrated a clinical effect of monotherapy with mTOR inhibitors in recurrent and refractory disease. Several trials have investigated the treatment of temsirolimus in the treatment of mantle-cell lymphoma [5, 6].

Temsirolimus is now an approved agent for the first-line treatment of advanced renal cell carcinoma (at a dose of 25mg iv on a weekly schedule) and recurrent or refractory mantle cell lymphoma (at an initial dose of 175mg iv weekly for 3 weeks, followed by weekly 75mg iv). Based on the 25mg iv dose, the most severe reported toxicities include sensitivity /allergy reactions, hyperglycemia / glucose intolerance, infections, interstitial lung disease (pneumonitis) hyperlipidemia, intracerebral bleeding, renal failure, intestinal perforation and impaired wound healing. The most frequently observed toxicities include anemia, nausea, skin rash, anorexia, edema and asthenia.

Several lines of evidence suggest an additive (or even synergistic) effect of mTOR inhibitors with cytotoxic drugs [10], suggesting that temsirolimus may be particularly effective when combined with standard chemotherapy to treat AML. Recently, a phase II trial combining temsirolimus (25 mg iv day 1 and day 8 per course) with clofarabine in elderly with relapsed or refractory AML has indicated encouraging anti-leukemic activity in this difficult-to-treat patient population [10a]. In summary, 54 patients were evaluated for response and toxicity, the median age was 70 years. Overall, 11 patients (21%) achieved a complete remission (CR, CRi), despite advanced AML. Importantly, inhibition of phospho-S6RP, a downstream effector of mTOR, was documented in 12/21 (57%) patients analysed, and correlated with an improved rate of clinical response: 7/12 (58%) responded vs 0/9 patients with no detectable target inhibition. The authors concluded that the regimen combining temsirolimus (at a dose of 25 mg iv day 1 and day 8 per course) with clofarabine can be safely administered to elderly patients with advanced AML, with encouraging anti-leukemic activity [10a].

AML relapse originates from remaining leukemia-initiating cells, which are not eradicated by conventional chemotherapy. These malignant cells have retained the capacity of self-renewal, a biological characteristic first described for hematopoietic stem cells (HSC). It has been shown that deletion of PTEN in murine hematopoietic stem cells leads to the development of leukemia while depleting the HSC pool [11]. Importantly, this was mediated by mTOR as

rapamycin-treatment depleted leukemia-initiating cells and restored normal HSC function [11]. This data is supported by findings in human AML, which found rapamycin most effective in the clonogenic compartment of the leukemic clones (i.e. the leukemia-initiating cells) [7]. Together, these findings have fuelled great interest in the development of mTOR inhibitors, as they may specifically target leukemia-initiating cells and thus prevent relapse.

The Study Alliance Leukemia (SAL, http://www.sal-aml.org) has successfully performed several multicenter trials with a similar study design. A recently completed trial evaluated the role of sorafenib in combination with standard chemotherapy in the treatment of elderly patients with newly diagnosed AML, allowing to predict the multicenter recruitment rate [11a]. Furthermore, the EFS of the control group was used for power calculations of the TOR-AML protocol. In the ongoing AZA-AML trial, a run-in phase to determine the optimal dose of azacitidine combined with standard chemotherapy was successfully performed, serving as a blue-print for the TOR-AML trial. The leaders of the SAL study group have reviewed the presented protocol.

4 STUDY OBJECTIVES

4.1 Rationale for this study

Standard chemotherapy is capable of eliminating most AML blasts, while leukemia-initiating cells are not sufficiently eradicated. As a consequence, refractory disease and relapse frequently occur in AML, especially in elderly patients. We propose that the addition of temsirolimus may improve standard AML chemotherapy. Furthermore, temsirolimus may specifically target the leukemia-initiating cells in AML, thereby reducing the risk of leukemia relapse.

4.2 Benefit / risk ratio

Patients eligible for this trial have a risk of treatment failure with standard chemotherapy of 70-80% at two years. Treatment failure is not compatible with long-term survival in these elderly patients. Included in these numbers are disease-related events (refractory disease, relapse) and treatment-related mortality that has to be expected to reach up to 10% in this patient group. The risk of this trial is that addition of temsirolimus to the standard treatment increases treatment-related mortality due to higher toxicity. Therefore the optimal temsirolimus dose level will be tested in the run-in part of this study, which will precede the randomized main part.

The possible benefit of the trial is to decrease the rate of treatment failure in the trial population. For a single patient, this could result in increased life-span, ideally without evidence of leukemia. Given the extensively high rate of treatment failure and the high toxicity of the currently available standard therapy, the medical need for novel, rational therapeutic approaches for this patient population is overwhelming. As pointed out above, the molecular rationale for the therapeutic administration of temsirolimus in AML is well founded. Thus, the Benefit/Risk ratio for a patient to participate in this trial seems very favorable.

4.3 Study objectives

4.3.1 Run-in part

- to determine the optimal temsirolimus dose for the main part of the study

4.3.2 Main Part

4.3.2.1 Primary objectives

- to compare the median Event Free Survival (EFS)* and the EFS probability of all AML patients between the temsirolimus and the control group

4.3.2.2 Secondary objectives

- to compare the median Event Free Survival (EFS) of AML patients with different cytogenetic and molecular risk groups[1]
- to compare the rate of early response (< 5 % bone marrow blasts on d15) after the first induction cycle between the temsirolimus and the control group
- to compare the rate of early response after the first induction cycle of AML patients with different cytogenetic and molecular risk groups[1]
- to compare the Complete Remission (CR) rate of the temsirolimus with the control group
- to compare the CR rate of AML patients with different cytogenetic and molecular risk groups[1]
- to compare Relapse Free Survival (RFS) of AML patients between the temsirolimus and the control group
- to compare Relapse Free Survival (RFS) of AML patients with different cytogenetic and molecular risk groups[1]
- to compare the Overall Survival (OS) of all AML patients between the temsirolimus and the control group
- to compare the Overall Survival (OS) of AML patients with different cytogenetic and molecular risk groups[1]
- to compare the rate of molecular remissions of the temsirolimus with the control group
- to compare the toxicity of the temsirolimus and the control treatment
- to compare the rate of molecular relapse after molecular remission of all AML patients between the temsirolimus and the control group after induction therapy and in the course of the first remission
- to evaluate potential biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers as well as indicators of autophagy in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma

*** EFS defined as:** Time interval from day 1 of study treatment until treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR, CRi or morphologic leukemia-free state will be recorded.

[1] **Cytogenetic and molecular risk groups** (13)

Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	-5 or del(5q); -7; abnormal (17p); complex karyotype‡

*Includes all AMLs with normal karyotype except for those included in the favorable subgroup;
‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3)

4.4 Study design

In order to address the toxicity profile of temsirolimus added to induction chemotherapy, a **run-in part** with 12 (to 18) patients will be conducted. Patients in this part of the study will be randomized between dose level 1 (12.5mg, n=6) and dose level 2 (25mg, n=6). The optimal dose-level will be determined after 1-2 induction cycles.

After the run-in part, the study will be on hold until the decision by the Data Safety Monitoring Board on dose finding is completed, which may include an additional 6 patients at previously tested or additional dose levels or schedules.

After having determined the optimal dose level in the run in part, the **main part** of the study will start. In the main part, patients will be randomized between temsirolimus and placebo for induction and

consolidation chemotherapy. For maintenance therapy the study will be unblinded. Maintenance treatment is only given in patients randomized in the temsirolimus arm of the study.

All patients receive:

- standard induction and consolidation chemotherapy
- temsirolimus or placebo during chemotherapy on day -1 and 8
- 8-week maintenance therapy with weekly temsirolimus or observation

For further details see chapter 6.

5 SELECTION, RANDOMIZATION AND WITHDRAWAL OF PATIENTS

5.1 Number of patients

For the run-in part, accrual of 12 (up to 18) patients is planned (see chapter 6.3.1). According to the power calculations given in section 9.1, n = 200 patients will be included in the main (controlled) part of the study with an equal allocation rate to both treatment arms.

5.2 Admission criteria

5.2.1 Inclusion criteria

- Patients with newly diagnosed AML (except APL) according to the FAB classification, including AML evolving from MDS or other hematological diseases and AML after previous cytotoxic therapy or radiation (secondary AML).
- Bone marrow aspirate or biopsy must contain ≥ 20% blasts of all nucleated cells or differential blood count must contain ≥ 20% blasts. In AML FAB M6 ≥ 30% of non-erythroid cells in the bone marrow must be leukemic blasts. In AML defined by cytogenetic aberrations the proportion of blasts may be < 20%.
- Age ≥ 61 years
- Informed consent, personally signed and dated to participate in the study
- Willingness of male patients whose sexual partners are women of child-bearing potential (WOCBP), to use an effective form of contraception (pearl index < 1%) during the study and at least 6 months thereafter. Effective forms of contraception are complete sexual abstinence, combined oral contraceptive, hormone IUCD, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant or depot contraceptive injection in combination with a second method of contraception like a condom or a cervical cap / diaphragm with spermicide or surgical sterilisation (vasectomy) in male patients. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or surgical sterilization or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months).

5.2.2 Exclusion criteria

- Patients who are not eligible for standard chemotherapy as described in chapter 6.2 and 5.3
- Previous treatment for AML, except leukapheresis for patients with hyperleukocytosis (leukocytes > 100,000/µl and / or leukostatic syndrome) or hydroxyurea

- Known central nervous system manifestation of AML
- Cardiac Disease: Heart failure NYHA III° or IV°; active coronary artery disease (MI more than 6 months prior to study entry is permitted); serious cardiac ventricular arrhythmias, defined as: ventricular extrasystoly grade LOWN IV, sustained or non-sustained ventricular tachycardias, and history of ventricular fibrillation / ventricular flutter, unless patient is protected by an internal cardioverter / defibrillator or ventricular arrhythmia was attributable to a myocardial ischemia > 6 months before study entry.
- Chronically impaired renal function (creatinine clearance < 30 ml / min)
- Chronic pulmonary disease with relevant hypoxia
- Inadequate liver function (ALT and AST ≥ 2.5 x ULN) if not caused by leukemic infiltration
- Total bilirubin ≥ 1.2 mg/dL if not caused by leukemic infiltration
- Uncontrolled active infection
- Concurrent malignancies other than AML with an estimated life expectancy of less than two years and requiring therapy
- Known HIV and/or hepatitis C infection
- Evidence or history of CNS disease, including primary or metastatic brain tumors, seizure disorders
- History of organ allograft
- Concomitant treatment with kinase inhibitors, angiogenesis inhibitors, calcineurin inhibitors and Mylotarg
- Serious, non-healing wound, ulcer or bone fracture
- Allergy to study medication or excipients in study medication
- Investigational drug therapy outside of this trial during or within 4 weeks of study entry
- Any severe concomitant condition which makes it undesirable for the patient to participate in the study or which could jeopardise compliance with the protocol

5.3 Registration and randomization

5.3.1 Registration

Registration and randomization will be performed by the coordinating study center:

Study Center of the Department of Medicine II, Hematology / Oncology

Goethe University, Frankfurt

Registration from Monday to Friday (working days) from 9:00 a.m. till 4:00 p.m. by facsimile:

Fax: (069) 6301-7463

For further questions contact Tel: (069) 6301-6366.

Details for registration are:

- registration number (see below), sex and date of birth
- Diagnosis (according to the FAB-classification)
- Inclusion and exclusion criteria
- Study center, name of the physician, phone and fax number of the center
- Patient number

5.3.2 Patient numbering

Upon signing the informed consent, each patient in the study will be uniquely identified by a patient number, which is a combination of his/her center code and 3-digit patient number. At each site, the first patient is assigned patient number 001, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 002, the third patient is assigned patient number 003). Once assigned to a patient, the patient number will not be reused. The patient identification list will be kept at the Investigator Site File.

5.3.3 Randomization Procedure

The randomization lists will be deposited at the coordinating study center in Frankfurt/Main**.** After patient registration, the randomization result will be reported to the trial site via fax response on the registration form (Registrierungsbogen). The registration number (and - during the run-in part - the randomization result) will be noted in the patient file and the registration form becomes part of the trial documentation forms (CRF).

As the placebo drug is provided by the study centers' pharmacies, the centers' pharmacies have to be unblinded to prepare either the active study drug or the placebo drug for the randomized patients at their site. Therefore, a randomization list for the patients of the particular site will be provided by the sponsor and will be kept at the respective center pharmacy. In order to maintain the double-blind character of the study, the investigators of this study must not have access to the randomization list.

5.3.4 Unblinding

After a patient has completed the second consolidation treatment cycle, the treating center will be unblinded. The center will request unblinding by sending the respective order form to the central study center via fax. The central study center will consequently inform the study center about the nature of the study treatment via fax.

The event of obtaining the information on the nature of the study treatment has to be documented both in the patient file and in the CRF.

In emergency situations requiring unblinding, the central study center can be contacted and the treatment code may be broken. In case of emergency situations requiring immediate unblinding and happening outside the central study center's working hours, the center pharmacy at the particular study site can be contacted and the treatment code may be broken. In case of unscheduled unblinding the Safety Desk should be informed immediately via fax.

5.4 Withdrawal of patients

A patient is free to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator may also withdraw the patient at any time in the interest of the patient`s safety. The primary reason for withdrawal must be recorded in the patient's medical record and on the withdrawal form in the Case Report Form (CRF).

Patients eligible for ETAL2 study enrollment may be withdrawn from the TOR-AML trial at any time at the Investigator's discretion. The reason for withdrawal (enrollment into ETAL2 trial) must be recorded on the withdrawal form in the Case Report Form (CRF).

However, these patients should preferably be identified prior to enrollment into the TOR-AML trial and enrolled into ETAL2. Specifically, enrollment into the ETAL2 trial should be considered for patients that fulfill all of the following criteria:

(1) "fit for allogeneic transplantation", as determined by the investigator
(2) known high-risk cytogenetics or a probability of CR below 40% (as determined by the AML-score at www.aml-score.org)
(3) age between 61 and 72 years

6 STUDY, STANDARD AND CONCOMITANT TREATMENTS

6.1 Investigational product

Temsirolimus is a specific inhibitor of mTOR and interferes with the synthesis of proteins regulating proliferation, growth, autophagy and survival of tumor cells. Treatment with temsirolimus leads to cell cycle arrest in the G1 phase in the treated tumor cells and also inhibits tumor angiogenesis by reducing synthesis of VEGF. In Germany, the drug currently has got a marketing authorisation for the treatment of renal cell carcinoma (RCC) and mantle cell lymphoma (MCL).

For full details of the pre-clinical and clinical information please refer to the 'Fachinformation Deutschland'.

6.1.1 Relevant physical, chemical and pharmaceutical properties

The product is provided as a concentrate; the drug product for supply of clinical trials is a vial with 30 mg temsirolimus concentrate in 1.2 ml. Because addition to aqueous solutions leads to precipitation of the product, the concentrate should be diluted in the supplied diluent only.

6.1.2 Instructions for storage and handling

The vial containing the temsirolimus concentrate should be stored under refrigeration at 2-8°C and be protected from light. The concentrate may only be used until the expiration date provided on the vial.

For intravenous infusion, the concentrate has to be attenuated in 1.8 ml supplied diluent leading to a concentration of 10 mg study medication or placebo per ml. The concentrate-diluent mixture is stable for 24h at controlled room temperature. The intended dose will rapidly be added to 250 ml 0.9% sodium chloride. Administration of study medication must be completed within 6h after final dilution in the 250 ml 0.9% sodium chloride.

During preparation and administration, study drug should be light-protected. As the solution is not compatible with PVC-containing infusion material (temsirolimus concentrate contains polysorbate 80) the sodium chloride injection container should be of non-DEHP-containing materials (glass, polyolefin, polyethylene or polypropylene). Visual inspection for particulate matter and discoloration has to be performed prior to administration.

The solution has to be administered by 30-60 minute infusion.

For further information please refer to the 'Fachinformation Deutschland'.

6.1.3 Interactions with concomitant medications

Pharmacokinetic studies about the interaction between temsirolimus and other drugs inducting or inhibiting CYP-enzymes have been performed.

As temsirolimus can be metabolized by the CYP3A4 isoenzyme, strong CYP3A4 inducers may reduce exposure to the major metabolite of temsirolimus and should be avoided. If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a temsirolimus dose increase should be considered, such as from 25 mg/week up to 50 mg/week, as long as the inducer is administered. Strong CYP3A4 inducers include but are not limited to dexamethasone, phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, rifampacin, and St. John´s Wort (for a complete list see website below).

Strong CYP3A4 inhibitors may increase blood concentrations of the major metabolite of temsirolimus and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a temsirolimus dose reduction should be considered, such as from 25 mg/week down to 12.5 mg/week. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the temsirolimus dose is adjusted back to the dose used prior to initiation of the strong CYP3A4 inhibitor. Strong CYP3A4 inhibitors include but are not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole. Grapefruit juice may also increase plasma concentrations of sirolimus (a major metabolite of temsirolimus) and should be avoided.

A list of strong CYP3A4 inducers and inhibitors is available at: http://medicine.iupui.edu/flockhart

6.1.4 Drug accountability

The study's active drug (temsirolimus) will be distributed to the center pharmacies by the central pharmacy of this study.

The center pharmacy is responsible for ordering more supply at least three working days ahead of time.

For the active drug each center pharmacy has to keep a drug accountability log provided by the sponsor. The placebo drug (250 ml 0.9% NaCl) is provided by the center pharmacies. In order to maintain the double-blind character of the study, the center pharmacies will always label both the prepared active drug and the placebo in the same fashion before delivering them to the medical ward (label includes Patient name, Patient ID, study code TOR-AML, and dose level in mg).

The person applying the study medication has to document the drug application and - in case of a failure to administer the medication - a short statement, why medication was not applied, in a patient record.

6.2 Standard cytotoxic therapy

Chemotherapy is administered according to general standards defined by national and international expert groups. All drugs are approved. Therefore the standard cytotoxic treatment is NOT an investigational product in this study. All statements regarding dosage and timing of the standard chemotherapy are recommendations based on long-standing experience with this therapy. In the best interest of the patient individual deviations from the schedule are possible and sometimes required particularly in the target population of this trial, which are older patients.

Supportive care of the patients will be conducted according to general standards of care for acute leukemia patients and is not part of this trial.

6.2.1 Cytarabine (AraC)

For all drug information on cytarabine (AraC) please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

6.2.2 Daunorubicin

For all drug information on daunorubicin please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

6.2.3 Mitoxantrone

For all drug information on mitoxantrone please refer to the "Fachinformationsverzeichnis Deutschland" in its latest version.

6.2.4 Overlapping toxicities of temsirolimus and standard cytotoxic therapy

Potential overlapping toxicities of temsirolimus and standard cytotoxic therapy include:

- Increased severity and duration of hematological toxicity, including anemia, thrombocytopenia and leukopenia
- Increased risk or severity of nephrotoxicity

- Further non-hematological overlapping toxicities cannot be ruled out

6.2.5 Dose reduction in standard cytotoxic therapy

In principle, dose reduction of standard cytotoxic therapy is not permitted in this study – with the exception of individual cases in the best interest of the patient. In case that overlapping toxicities of standard cytotoxic treatment and temsirolimus should require a dose reduction, the dose of temsirolimus must be reduced (for dose modification and delay see 6.3.3).

If individual cases of severe toxicities should require an additional dose reduction of standard cytotoxic therapy, the coordinating investigator should first be consulted, if possible, before dose reduction. Dose reduction and reason for dose reduction should be documented. Depending on the toxicities and dose modification, the patient might be withdrawn from the study.

6.3 Treatment

6.3.1 Run-in part: Dose finding for temsirolimus

In order to address the toxicity profile of temsirolimus added to induction chemotherapy, a **run-in part** with 12 (to 18) patients will be conducted. Patients in this part of the study will be randomized between dose level 1 (12.5mg, n=6) and dose level 2 (25mg, n=6). The optimal dose-level will be determined after 1-2 induction cycles.

After the run-in part, the study will be on hold until the decision by the Data Safety Monitoring Board on dose finding is completed, which may include an additional 6 patients at previously tested or additional dose levels or schedules.

All toxicity during induction therapy will be graded according to the Common Toxicity Criteria for Adverse Events v. 4.0 (CTCAE).

DLT in the run-in part of the trial is defined as:

- CTCAE Grade 4 neutropenia (ANC <0.5 x 109/L) lasting ≥ day 42 after last chemotherapy
- CTCAE Grade 4 thrombocytopenia (platelets < 25 x 109/L) lasting ≥ day 42 after last chemotherapy
- CTCAE Grade 3 non-hematologic temsirolimus-related adverse events (excluding hypertension and nausea / vomiting which is not medically managed)

Patients must be evaluable for DLT assessment. Patients with early death during induction due to events unrelated to temsirolimus treatment e.g. infection will not be considered as DLT. Patients with neutropenia or thrombocytopenia due to refractory or recurrent AML will not be considered for DLT. If such cases occur additional evaluable patients will be included.

If < 2 out of 6 patients experience DLT at dose level 2 during induction chemotherapy, dose level 2 will be chosen for temsirolimus during the main part. If > 2 of 6 patients experience DLT at dose level 2 and < 2 out of 6 patients experience DLT at dose level 1, then dose levels 1 will be chosen for temsirolimus during the main part. If 2 out of 6 patients experience DLT at dose level 2 and ≤ 2 patients experience DLT at dose level 1, the Data Safety Monitoring Board (DSMB) may opt to include additional 6 patients in dose level 2 of the run-in phase.

Depending on the results, the DSMB may consider an additional dose level to be tested in 6 additional patients or terminate the trial.

6.3.1.1 Scheme of the run-in part

Induction		**Consolidation**	
1. cycle	**(2. cycle)** **at blast persistence**	**1. cycle**	**2. cycle**
7+3	**(HAM elderly)**	**HD-AraC**	**HD-AraC**
Temsirolimus d -1, 8		**Temsirolimus d -1, 8**	

6.3.1.2 Treatment schedule for induction chemotherapy

AraC	100 mg/m²/day	continuous infusion over 24 hours	day 1-7
Daunorubicin	60 mg/m²/day	infusion over 1-2 hours	day 3, 4 and 5
Temsirolimus	12.5 mg or 25 mg abs.	infusion over 30-60 minutes	day -1 and 8

6.3.1.3 Decision making on second induction

Bone marrow will be analyzed on day 15:

In case of **morphologic leukemia-free state** (< 5% blasts in an aspirate, no blasts in peripheral blood and no extramedullary disease), no second induction chemotherapy is given.
In case of **partial remission** (decrease of bone marrow blast percentage to 5% - 25% and decrease of pretreatment bone marrow blast percentage by at least 50%) or **treatment failure** (no morphologic leukemia-free state, no partial remission), a (second) induction cycle with HAM (elderly) + temsirolimus should be administered on day 22 of first induction chemotherapy if possible.

6.3.1.4 Treatment schedule for induction II chemotherapy

HAM (elderly) induction II for patients with PR or treatment failure:

HD-AraC	1g/m^2 (2 x daily)	infusion over 3 hours	day 1, 3, 5
Mitoxantrone	10mg/m^2	infusion over 30-60 minutes	day 3-5
Temsirolimus	12.5 or 25mg abs.	infusion over 30-60 minutes	day -1 and +8

6.3.1.5 Consolidation therapy I and II

All patients in CR/CRi should receive **two cycles of consolidation chemotherapy**, if conditions described below are fulfilled.

Precondition for consolidation therapy:

CR/CRi with neutrophils > 1000/µl and platelets > 75,000/µl up to 42 days after last chemotherapy

- Start of consolidation therapy **not earlier than one week and not later than 2 weeks** after confirmation of CR
- If patients' condition does not allow for immediate consolidation chemotherapy it may be postponed for **up to 4 weeks after confirmation of CR/CRi**
- If patients' condition does not allow for consolidation chemotherapy within 4 weeks from confirmation of CR: observation (depending on treatment arm)

No CRi with neutrophils > 1000/µl and platelets > 75,000/µl up 35- 42 days after last chemotherapy

- Bone marrow evaluation should be considered from day 35 in order to exclude relapse

CRi with neutrophils > 1,000/µl and platelets > 75,000/µl between day 43 and day 59

- Reduced dose of temsirolimus or placebo in the forthcoming cycles (for dose reduction see 6.3.3).

No CRi with neutrophils > 1,000/µl and platelets > 75,000/µl by day 54 - 60

- Bone marrow evaluation should be considered to from day 54 in order to exclude relapse
- Observation. The decision is made by the investigator.

6.3.1.6 Treatment schedule for consolidation chemotherapy I and II

AraC	1g/m² 2 x/day	infusion over 3 hours	day 1, 3 and 5
Temsirolimus	12.5 mg or 25 mg abs.	Infusion over 30-60 minutes	day -1 and 8

6.3.1.7 Maintenance therapy

Patients in the run-in part will not receive temsirolimus maintenance treatment.

6.3.2 Main (controlled) part

After having determined the optimal dose level in the run-in part, the main part of the study will start. In the main part, patients will be randomized between temsirolimus and placebo for induction and consolidation. For maintenance therapy the study will be unblinded. Maintenance therapy is only given in patients randomized in the temsirolimus arm of the study.

Note: For the purpose of clarity, the daily dose of temsirolimus during both induction and consolidation therapy in the main (randomized) part of this protocol is described as 25 mg. However, if the data safety monitoring board (DSMB) decides otherwise, the correct dose of temsirolimus in each part of the protocol will be amended to the protocol for the main part prior to start of the main part.

6.3.2.1 Scheme of the Main (controlled) part

Induction		Consolidation	
1. cycle	**(2. cycle)** **at blast persistence**	**1. cycle**	**2. cycle**
7+3	**(HAM elderly)**	**HD-AraC**	**HD-AraC**
Temsirolimus/Placebo d -1, 8		**Temsirolimus/Placebo d -1, 8**	

6.3.2.2 Treatment schedule for induction chemotherapy

AraC	100 mg/m^2/day	continuous infusion over 24 hours	day 1-7
Daunorubicin	60 mg/m^2/day	infusion over 1-2 hours	day 3, 4 and 5
Temsirolimus/ Placebo	25 mg abs.	infusion over 30-60 minutes	day -1 and 8

6.3.2.3 Decision making on second induction

Bone marrow will be analyzed on day 15:

In case of **morphologic leukemia-free state** (< 5% blasts in an aspirate, no blasts in peripheral blood and no extramedullary disease), no second induction chemotherapy is given.

In case of **partial remission** (decrease of bone marrow blast percentage to 5% - 25% and decrease of pretreatment bone marrow blast percentage by at least 50%) or **treatment failure** (no morphologic leukemia-free state, no partial remission), a (second) induction cycle with HAM (elderly) + temsirolimus/placebo will be administered on day 22 of first induction chemotherapy if possible.

6.3.2.4 Treatment schedule for induction II chemotherapy

HAM (elderly) induction II for patients with PR or treatment failure:

HD-AraC	1g/m^2 (2 x daily)	infusion over 3 hours	day 1, 3, 5
Mitoxantrone	10mg/m^2	infusion over 30-60 minutes	day 3-5
Temsirolimus /Placebo	25mg abs.	infusion over 30-60 minutes	day -1 and +8

If the duration of the aplasia exceeds 42 days the dose of temsirolimus/placebo should be reduced according to the dose reduction scheme (5.3.5) in these patients for the following temsirolimus/placebo applications.

6.3.2.5 Consolidation therapy I and II

All patients in CR/CRi should receive **two cycles of consolidation chemotherapy**, if conditions described below are fulfilled.

Precondition for consolidation therapy:

CR/CRi with neutrophils > 1000/µl and platelets > 75,000/µl up to 42 days after last chemotherapy

- Start of consolidation therapy **not earlier than one week and not later than 2 weeks** after confirmation of CR
- If patients' condition does not allow for immediate consolidation chemotherapy it may be postponed for **up to 4 weeks after confirmation of CR/CRi**
- If patients' condition does not allow for consolidation chemotherapy within 4 weeks from confirmation of CR: Maintenance therapy should be started (arm A) or observation (arm B)

No CRi with neutrophils > 1000/µl and platelets > 75,000/µl at 35 - 42 days after last chemotherapy

- Bone marrow evaluation should be performed between day 35 and 42 to exclude relapse

CRi with neutrophils > 1,000/µl and platelets > 75,000/µl between day 43 and day 59

- Reduction dose of temsirolimus / placebo should be considered in the forthcoming cycles (for dose reduction see section 5.3.4).

No CRi with neutrophils > 1,000/µl and platelets > 75,000/µl by day 54 – 60

- Bone marrow evaluation should be considered after day 54 in order to exclude relapse
- Patients may proceed directly to maintenance therapy (arm A) or observation (arm B). The decision is made by the investigator.

6.3.2.6 Treatment schedule for consolidation chemotherapy I and II

AraC	1g/m² 2 x/day	infusion over 3 hours	day 1, 3 and 5
Temsirolimus/ Placebo	25 mg abs.	Infusion over 30-60 minutes	day -1 and 8

6.3.2.7 Maintenance therapy

Maintenance therapy should be started after confirmed CR/CRi with hematological recovery (neutrophils > 1,000/µl, platelets > 75,000/µl) from the second consolidation cycle, not earlier than day 28 of second consolidation cycle.

Following unblinding (see section 5.3.4), patients will be administered:

Arm A (temsirolimus)	25mg abs i.v.	weekly, for 8 weeks
Arm B (placebo)	observation	weekly, for 8 weeks

6.3.2.7.1 Arm A (study arm)

The following recommendation applies only to patients randomized to the temsirolimus arm (arm A).

CR/CRi with neutrophils > 1,000/µl and platelets > 75,000/µl before day 35 after consolidation chemotherapy (and patients considered unsuitable for consolidation chemotherapy in CR/CRi with neutrophils > 1,000/µl and platelets > 75,000/µl)

- Maintenance therapy with temsirolimus 25 mg abs. i.v. weekly for eight weeks

- Start of maintenance therapy within 1 week after confirmation of CR/CRi but not earlier than day 28 of last chemotherapy

No CRi with neutrophils > 1,000/µl and platelets > 75,000/µl at 35 - 42 days after last chemotherapy

- Bone marrow evaluation should be performed between day 35 and 42 to exclude relapse

CRi with neutrophils > 1,000/µl and platelets > 75,000/µl between day 43 and day 59

- Dose of temsirolimus should be maintained in the forthcoming cycles (for dose reduction see section 5.3.4).

No CRi with neutrophils > 1,000/µl and platelets > 75,000/µl by day 54 – 60

- Bone marrow evaluation should be considered after day 54 in order to exclude relapse
- Patients should not receive maintenance therapy.

For dose reductions of temsirolimus, see 6.3.3. **The dosage of temsirolimus may be re-escalated after two cycles of maintenance therapy under certain conditions (see 6.3.3.1).**

6.3.2.7.2 Arm B (control arm)

Patients will not receive specific maintenance therapy, but will be followed similar to patients treated in arm A.

6.3.3 Dose modification and delays of temsirolimus / placebo

The modifications of temsirolimus or placebo should follow the following pre-defined dose levels:

initial dose:	25 mg abs.
Dose level -1:	20 mg abs.
Dose level -2:	15 mg abs.
Dose level -3:	Discontinue from study

6.3.3.1 General dose modifications

If a dose reduction at dose level -3 is required, the patient should be permanently discontinued from the study treatment.

As a general rule, grade 3 toxicity should be followed by permanent dose reduction of temsirolimus during that therapy phase (chemotherapy phase or maintenance phase). If a grade 3 toxicity during the chemotherapy phase resolves after dose reduction of temsirolimus, **the dosage of temsirolimus may be re-escalated after two cycles of maintenance therapy if ≤ grade 2 toxicity occurs after the first two cycles of maintenance therapy.** If during the following two maintenance cycles still no grade 3 or 4 toxicity occurs, another dose escalation up to 25mg can be considered.

Resolution of an adverse event is defined as disappearance or reduction of the adverse event to < grade 3 toxicity. For patients with grade 2 or greater toxicities present at baseline resolution to at least baseline levels will apply.

6.3.3.2 Dose modifications for hematological toxicity

Hematological toxicities during the period of chemotherapy and the expected subsequent myelosuppression should only be considered relevant if a grade 4 neutropenia or thrombopenia persists ≥ 42 days after start (day 1) of the last chemotherapy cycle. In this case the dose of temsirolimus should be reduced by one dose level for all subsequent chemotherapy cycles and the first two maintenance cycles.

However, different criteria will apply after hematopoietic recovery from the last chemotherapy course during the subsequent maintenance therapy.

Table 1-1 illustrates dose modifications and delays for hematological toxicities during the maintenance therapy:

Table 1-1: Hematological Criteria for Dose Delay and Dose Modification of temsirolimus during maintenance therapy

Grade	Dose Delay	Dose Modification
Grade 0-2	Treat on time	No Change [b]
Grade 3	Treat on time	DECREASE one dose level [c,d]
Grade 4	DELAY [a] until ≤ Grade 2	DECREASE one dose level [d]

Table 1-1: Hematological Criteria for Dose Delay and Dose Modification of temsirolimus during maintenance therapy
a. If no recovery after 30 days delay, treatment will be discontinued b. If ≤ grade 2 toxicity occurs after the first two cycles of maintenance therapy, the dose will be increased by one dose level to a maximum dose of 25 mg. If during the following two maintenance cycles still no grade 3 or 4 toxicity occurs, another dose escalation up to 25mg can be considered. c. If the myelosuppression persists for >21 days, the dose will be reduced by one dose level d. If dose reduction below dose level -2 is required, treatment will be discontinued

6.3.3.3 Dose modifications for non-hematological toxicity

Table 1-2 summarizes the recommendations for dose delays and modifications for all non-hematological adverse events.

Table 1-2: Non-hematological Criteria for Dose Delay and Dose Modification of temsirolimus/placebo		
Grade	Dose Delay	Dose Modification
Grade 0-2	Treat on time	No Change [b]
Grade 3 and 4	DELAY [a] until ≤ Grade 2	DECREASE one dose level [c]
If the same grade 3/4 non-hematological toxicity reoccurs after first reduction	Discuss treatment discontinuation with coordinating investigator	
a. If no recovery after 30 days delay, treatment will be discontinued b. If ≤ grade 2 toxicity occurs after the first two cycles of maintenance therapy, the dose will be increased by one dose level to a maximum dose of 25 mg. If during the following two maintenance cycles still no grade 3 or 4 toxicity occurs, another dose escalation up to 25mg can be considered. c. If a dose reduction below dose level -2 is required, treatment will be discontinued		

These recommendations apply, if the adverse event is considered to be related to temsirolimus, but not to the chemotherapy.

6.4 Concomitant medications / therapy

Hydroxyurea may be used according to the centers` standard practice to decrease initial leukocytosis before starting with temsirolimus/placebo on day -1 of the first induction therapy cycle.

Leukocytapheresis is not contraindicated in this study and may be an option to decrease elevated leukocyte counts (i.e., leukocytes > 100,000/µl and/or leukostatic syndrome).

All appropriate and supportive care for disease-related symptoms will be provided to all patients. Sufficient anti-emetic prophylaxis is required prior to the administration of standard chemotherapy and temsirolimus according to the study centers' standard procedures. Symptomatic treatments should be used as needed and may be given as prophylactics in subsequent cycles. This should include sufficient hydration, alkaline treatment (i.e. Uralyt® or other) and prophylactic treatment with allopurinol in order to prevent occurrence of tumor lysis syndrome.

As **allergic/hypersensitivity reactions may occur** in patients receiving temsirolimus, an H_1 antihistamine should be administered to patients before the start of the intravenous temsirolimus infusion.

Anti-microbial prophylaxis including antifungal prophylaxis in the presence of myelosuppression should be given according to the study centers' standard procedures. In addition, according to common practice, a pneumocystis jirovecii prophylaxis should be conducted with pentamidine inhalations 300 mg every 4 weeks from the first week of induction therapy until the end of consolidation therapy. Weekly monitoring of CMVpp65 antigen or CMV DNA qualification in case of severe leucopenia is recommended until the end of the maintenance therapy and pre-emptive therapy will be started in case of positive results.

It is optional to give G-CSF or Pegfilgrastim to patients during the treatment course according to the study center practices regarding the use of growth factors. If G-CSF or Pegfilgrastim is used, it should be given after confirmation of adequate blast clearance after the first course of induction therapy, on day 10 of the second course of chemotherapy (two days after the end of the last cytarabine infusion) and on day 7 of consolidation therapy (two days after the end of the last cytarabine infusion).

Furthermore, it is to the discretion of the participating centers, which type of G-CSF preparation they choose to treat their patients. Available preparations include filgrastrim (Neupogen®), lenograstrim (Granocyte®) and the pegylated form pegfilgrastrim (Neulasta®).

Possible drug interactions as described in Section 6.1.3 should be considered.

7 STUDY PROCEDURES

7.1 Study evaluations

Diagnostic procedures follow the general standard of good clinical practice for the diagnosis and treatment monitoring of AML patients.

7.1.1 Evaluations before study inclusion (screening) and treatment

- Complete blood count (CBC) with differential and platelets
- Serum chemistries: electrolytes, calculated creatinine, urea, uric acid, bilirubin, AP, AST and / or ALT, LDH, lipase, cholesterol, triglycerides, glucose, phosphate
- Coagulation: PTT, quick, fibrinogen, ATIII
- Urine analysis
- Blood type
- Full history and clinical examination
- Vital signs
- Body height and body weight
- Performance status (ECOG)
- ECG
- Echocardiography or MUGA scan[4]
- Ultrasound of the abdomen
- Lung function test
- Bone marrow biopsy
- Bone marrow aspirate or peripheral blood:
    - Cytomorphological examination incl. cytochemistry
    - Immunophenotyping
    - Cytogenetics
    - Molecular genetic analyses for the presence of Flt3-ITD, genomic ratio of the presence of Flt3-ITD vs. Flt3-WT, for NPM1 mutations and for the presence of BCR-ABL, PML-RARα, AML1-ETO and CBFß-MYH11 translocation products
    - Asservation of bone marrow and peripheral blood cells (Ficoll-treated) in a central tissue repository[5]

[4] The same method for determination of the left ventricular function should be used for each patient throughout the study participation

[5] The material from the central tissue repository will be used for exploratory research purposes. These analyses are optional and will not be part of the medical report of this trial

7.1.2 Evaluations on day 1 of 1st induction chemotherapy cycle (i.e. after temsirolimus/placebo and before the first administration of cytarabine)

(for full details about evaluations please refer to 7.2)

- Complete blood count (CBC) with differential and platelets
- Asservation of 10ml heparinized peripheral blood (Ficoll-treated cells) in a central tissue repository[5]

7.1.3 Evaluations during further treatment

(for full details about evaluations please refer to 7.2)

- Complete blood count (CBC) with differential and platelets
- Bone marrow aspirate (cytomorphology, immunophenotyping, cytogenetics, molecular genetics)
- Asservation of bone marrow and peripheral blood cells (Ficoll-treated) in a central tissue repository (only bone marrow or peripheral blood remaining after standard diagnostics)[5].
- Control of CBC (with differential and platelets), coagulation and serum chemistries (including creatinine)
- Performance status (ECOG)
- Physical examination
- Body weight
- Diagnostic procedures i.e. in case of severe infections will follow standard procedures
- Evaluations performed before the first course of induction therapy will be repeated prior to each following course if necessary in the investigator's opinion
- ECG and echocardiography / MUGA scan[4] as often as necessary in the investigator's opinion
- Lung function test as often as necessary in the investigator's opinion

7.1.4 Evaluations at the end of maintenance therapy

(for full details about evaluations please refer to 7.2)

- Performance status
- Physical examination
- Vital signs
- CBC (with differential and platelets), coagulation and serum chemistries Urine pH

[4] The same method for determination of the left ventricular function should be used for each patient throughout the study participation

[5] The material from the central tissue repository will be used for exploratory research purposes. These analyses are optional and will not be part of the medical report of this trial.

- Bone marrow aspirate
- Asservation of vital bone marrow cells (Ficoll-treated bone marrow), bone marrow RNA, DNA and protein lysates, serum and plasma in a central tissue repository (remaining material after completion of standard diagnostic procedures)[5]
- Lung function test

7.1.5 Evaluations in suspected case of relapse

- CBC (with differential and platelets)
- Bone marrow aspirate
- Asservation of vital bone marrow cells (Ficoll-treated bone marrow), bone marrow RNA, DNA and protein lysates, serum and plasma in a central tissue repository (remaining material after completion of standard diagnostic procedures)[5]

7.1.6 Evaluations during follow up (standard routine parameters)

In case of relapse, study exclusion or refusal of informed consent, patients should be followed until one year after the start of the induction therapy. These follow-up evaluations include:

- Bone marrow aspirate in case of suspected relapse
- CBC with differential monthly
- Performance status (ECOG) monthly
- All other follow-up investigations according to general standards and according to the investigator's decision

[5] The material from the central tissue repository will be used for exploratory research purposes. These analyses are optional and will not be part of the medical report of this trial.

7.2 Schedule of evaluations

	Within 10 days prior to 1st course of 1st induction therapy	Day 1 of 1st induction therapy before the first administration of cytarabine	During and between induction therapy until hematological recovery	d 15 ± 2	Before 2nd course of induction therapy (if applicable)	d 35-42 after last course of induction	Before 1st course of consolidation therapy	Before 2nd course of consolidation therapy	Start of maintenance therapy	During maintenance therapy or observation	End of maintenance therapy	Follow –up: until one year after 1st induction therapy	Suspected relapse (during study treatment or follow-up)
Informed consent	X												
Medical history	X												
Performance status and physical examination[a]	X				X	(X)	X	X	X	weekly	X	X	
Vital Signs (blood pressure and pulse)[a]	X				X	(X)	X	X	X	weekly	X		
Body weight and height[a]	X				X		X	X					
CBC (with differential and platelets)[a]	X	X[c]	Once weekly		X	X	X	X	X	weekly	X	X	X[e]
Chemistry, including liver function, cholesterol, triglycerides, glucose, creatinine, phosphate, coagulation[a]	X		Once weekly		X	(X)	X	X	X	weekly	X		
Urinalysis[a]	X												
ECG and echocardiography / MUGA scan[b,g]	X												
Ultrasound of the abdomen[a]	X												
Lung function test[a]	X						X				X		
Assessment of AE and relevant CoMed			After each cycle during induction/consolidation and monthly during maintenance										
Bone marrow (BM) aspirate	X			X			X	X	X[d]	X[d]	X	X	X[e]
BM biopsy	X												
BM / PB for cell repository	X	X[f]											

[a] In addition, these evaluations should be repeated as often as necessary in the opinion of the treating physician

[b] The same method for determination of the left ventricular function should be used for each patient throughout the study participation

[c] Material for differential CBC may be stored and analyzed on the next working day

[d] At suspected relapse

[e] For patients with suspected or confirmed relapse. For patients with neutrophils < 1,000/µl or platelets < 75,000/µl ≥ 30 days after start (day 1) of the last induction therapy or of a consolidation therapy cycle, these evaluations will be performed between day 30 and 35

[f] 10ml of heparinized peripheral blood only (after temsirolimus/placebo; before start of induction chemotherapy)

[g] These evaluations should be repeated as often as necessary in the opinion of the treating physician, especially in patients with a history of heart disease or when a heart disease or cardiotoxicity is clinically suspected

7.3 Bone marrow and blood diagnostics including central repository

The diagnosis of AML will be performed at the discretion of the participating centers, while material for the central repository has to be sent to one of the central laboratories of the SAL in Frankfurt, Dresden or Münster. Material for diagnostics may be sent to one of the three central laboratories of the SAL in Dresden, Frankfurt or Münster (address see 1). Reference diagnosis is a usual procedure in the management of AML.

Respective order forms can be downloaded from the German Leukemia Trial Registry at

http://www.kompetenznetz-leukaemie.de/content/aerzte/studien/studienregister/.

7.3.1 Cytomorphological examination and cytochemistry

Initial leukemia diagnostics and differentiation are based on the morphology of peripheral blood and bone marrow smears as well as on cytochemical examinations. If the bone marrow aspirate is not available, diagnosis will be based on the bone marrow biopsy or on peripheral blood. This should include a Pappenheim staining, a peroxidase reaction and an esterase reaction. Diagnosis and classification of the AML will be performed according to FAB criteria as well as according to the WHO classification. These analyses will be performed in the local participating centers.

The laboratories in Dresden, Frankfurt and Münster participate in round robin tests within the scope of the "network of excellence for acute and chronic leukemias" and offer reference laboratory diagnostics for discussion of questionable cases. To be able to quickly assess the diagnostic material, bone marrow and peripheral blood smears are requested for all patients at diagnosis (for shipping modalities, see 7.3). For discussion of cytomorphology, the laboratories in Dresden, Frankfurt or Münster can be contacted.

7.3.2 Immunophenotyping

An immunophenotyping of the leukemia cells should be performed for all patients. These analyses can be performed at the local study centers or at a laboratory of the investigators' choice. The immunophenotyping should be performed according to the proposals by the "network of excellence acute and chronic leukemias".

7.3.3 Cytogenetics

For each patient a cytogenetic examination should be performed at diagnosis. Chromosomal G-banding will be performed. Fluorescent-in-situ-hybridizations will be performed if

necessary. The cytogenetic examination will be performed by the local study centers or at a laboratory of the investigators' choice.

7.3.4 Molecular genetic analyses

All molecular genetic analyses may be performed at the participating centers or at a laboratory of the investigators' choice.

Molecular genetic analysis should include:

- determination of the presence or absence of BCR-ABL, PML-RARα, AML-ETO, and CBFβ-MYH11 fusion transcripts as determined by qualitative or quantitative RT-PCR
- Nucleophosmin 1 mutational status
- Determination of the presence or absence of Flt3-ITD and a quantification of the Flt3-ITD to Flt3-WT genomic ratio in case of the detection of Flt3-ITD

7.3.5 Central cell repositories and shipment modalities

For all patients diagnostic material should be send to one of the three central laboratories of the SAL for future scientific analysis:

10 ml bone marrow (Heparin)

20 ml peripheral blood (Heparin)

7.3.6 Requested material during treatment

Please refer to 7.2: Schedule of evaluations.

On day 1 after start of temsirolimus or placebo peripheral blood should be collected before the start of induction therapy for molecular biological analysis and sent to one of the three central laboratories of the SAL.

2 x 5 ml peripheral blood (Heparin)

Order forms can be downloaded from the German Leukemia Trial Registry at http://www.kompetenznetz-leukaemie.de/content/aerzte/studien/studienregister/.

All other follow-up tests in bone marrow or peripheral blood will be performed locally or at laboratories of the investigators' choice.

Order forms can be downloaded from the German Leukemia Trial Registry at http://www.kompetenznetz-leukaemie.de/content/aerzte/studien/studienregister/

Shipment is recommended from Monday through Thursday, if possible in the morning by express delivery or courier.

7.4 Duration of the study

Accrual time: 24 months	Follow-up period[a]: 12 months

[a] In case of a relapse / treatment failure, a study exclusion or a refusal of informed consent, the patients overall survival will be followed up until one year after the start of the first induction cycle.

Assuming an accrual time of 24 months and a duration of follow-up (of the last included patient) of approximately 12 months, the total duration of the study will be approximately 48 months.

7.5 End of study

The study will end one month after the end of the therapy, observation or follow-up period of the last patient.

7.6 Criteria for removal from study / premature end of study

7.6.1 Individual reasons (Criteria for removal of patients)

Patients will be removed from the trial for the following reasons:

- Drug-related toxicity
- Patient decision
- Incompliance
- Physician's decision

7.6.2 General reasons

The Coordinating Investigator, the BfArM and the EC have the right to terminate this clinical study at any time for reasonable medical or administrative reasons. Any possible premature

discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.). In terminating the Coordinating Investigator will assure that adequate consideration is given to the protection of the patients´ interest.

8 ADVERSE EXPERIENCES

8.1 Introduction

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable signs, symptoms, or medical conditions occurring after signing the informed consent even if the event is not considered to be related to the study drug. Please refer to Section 6 for the protocol-specific definitions of study drug and study treatment. Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. SAEs occurring after signing the Informed Consent are recorded on the Serious Adverse Event CRF. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Where possible, a diagnosis rather than a list of symptoms should be given.

8.2 Severity of adverse events

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information CRF page. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

During the Run-in-Phase of the study, adverse events of all grades have to be documented in the Adverse Events CRF.

During the main part of the study, AEs grade 1 and grade 2 will be documented only in the patients file and AEs grade 3 and grade 4 will be documented in the Adverse Events CRF. (Since the majority of toxicities is expected from the underlying chemotherapy and is well known and documented in historic cohorts the documentation of adverse events will be restricted to grade 3-4.)

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation or progression of the disease.

8.3 Adverse events associated with Laboratory Abnormalities

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF.

8.4 Evaluation of adverse events

As far as possible, all adverse events which fulfill the above mentioned criteria for documentation in the CRF should be evaluated to determine:

1. The severity grade (mild, moderate, severe, life-threatening, fatal)
2. Its relationship to the study drug temsirolimus (related/unrelated)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious (see below)

8.5 Serious adverse events

A serious adverse event (SAE) is defined as an AE which:

- results in death
- is life-threatening (defined as an event in which the patient or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes), including uncomplicated cytopenias
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Any other medical event considered serious by the treating physician

Any event including death that is clearly related to progression of leukemia is not regarded as SAE.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.7.

Careful medical judgment should be exercised to determine, if there is a causal relationship between an SAE and the investigational product. The following guidance is provided:

Certain:

- A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration which cannot be explained by concurrent disease or other drugs or chemicals.
- The response to withdrawal of the drug (dechallenge) should be clinically plausible.
- The event must be pharmacologically or phenomenologically definitive, using a satisfactory rechallenge procedure, if necessary.

Probable:

- A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Clinically reasonable response on withdrawal (dechallenge).
- Rechallenge information is not required to fulfill this definition.

Possible:

- A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease, or other drugs or chemicals.
- Information on drug withdrawal may be lacking or unclear.

Unlikely:

- A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration in which a causal relationship appears to be improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Unrelated:

- A clinical event, including laboratory test abnormality, caused by other drugs, chemicals, underlying diseases.

In the complex medical situation of patients receiving an intense therapy with concomitant medications and the study drug, it will be difficult or impossible in many cases to assess "possible" relation to the study drug. Therefore, in case that the investigator assigns a "possible" correlation to the study drug the final decision on relation to the study drug and the prior description in the "Fachinformation" will be made during regular conferences of the DSMB.

8.6 Investigators responsibilities

Adverse events should be documented appropriately in the patient file. Such events may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at

each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome. Information about common side effects already known about the investigational drug can be found in the 'Fachinformation' or will be communicated between updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.7 Serious adverse events reporting

If an adverse event is serious (see definition in section 8.5), additional reporting to the sponsor is required:
The investigator must inform the sponsor of any SAE within 24 hours of being aware of the event. Information not available at the time of initial reporting should be provided in a follow-up.

Any SAEs experienced within 30 days after end of study treatment should only be reported to the sponsor if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. All Serious Adverse Event Reports sent to the sponsor must include the patient number, age, sex, weight, height, severity of reaction (Grade 1-5 according to CTCAE criteria), relationship to study drug (related, probably related, possibly related, probably unrelated, unrelated, not assessed), date and time of administration of study medications and all concomitant medications, and medical treatment provided. The investigator must assess and record the relationship of each SAE to the study drug temsirolimus (certain, probable, possible, unlikely, unrelated), complete the SAE Report Form in English, and send the completed, signed form immediately by fax to the Safety Desk.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries) should be collected subsequently, if not available at the time of the initial report. Follow-up information is immediately sent to the

sponsor, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report.

Re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

All Serious AEs whether related or unrelated to investigational product must be reported by confirmed facsimile transmission the complete SAE page to the address below. The fax confirmation should be placed together with the SAE form in the Investigator Site File.

Protocol-specific clarifications to this definition and exceptions for SAE reporting:

Myelosuppression, thrombocytopenia, anaemia and associated complications are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemia cells). Therefore, myelosuppression-associated complications such as fever, infections, bleeding will be reported on the Adverse Events CRF as an adverse event even if it is associated with hospitalization or prolonged hospitalization.

In this context only prolonged myelosuppression, i.e. pancytopenia with marrow hypocellularity on day 42 or later from start of last cytotoxic therapy without evidence of leukemia, will require immediate reporting on an SAE form. This protocol-specific rule applies only for induction and consolidation courses, not during maintenance therapy.

In case a patient leaves this protocol to receive another more intensive cytostatic therapy (that is for persistent or recurrent disease), the following modification applies: AEs and SAEs occurring within 30 days after last protocol treatment and after first administration (day 1) of the other, more intensive therapy have only to be recorded on the present protocol when the investigator suspects the event to be related to this protocol treatment.

The investigator is responsible for assessment of seriousness, severity (CTCAE v 4.0) and causality of the SAE. The SAE form should be completed with as much information as possible. The investigator should not wait for full details before making the initial report.

If the event is fatal or life threatening, the investigator must fax any relevant follow-up information of the reported SAE to the Safety Desk within additional 8 days. In case of death, a copy of the autopsy protocol should be provided, if any. For SAEs, which are not fatal or life threatening, the investigator must fax follow-up information as soon as possible.

In case of death, the investigator has to supply sponsor, competent authority and Ethics Committee with all details requested.

Safety-Desk-Contact
Study Center of the Department of Medicine II Hematology / Oncology J.W. Goethe University Hospital Theodor-Stern-Kai 7 60590 Frankfurt **Fax: (069) 6301-7463** For further information you may contact: Tel: (069) 6301-6366

It is the duty of the Safety Desk to inform the marketing authorization holder involved according to stipulation.

The initial SAE and follow-up SAE reports will be evaluated by the sponsor and if the SAE is not previously documented in the "Fachinformation" and is thought to be related to the study drug temsirolimus, the SAE Contact Center may urgently require further information from the investigator for Health Authority reporting. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported by the sponsor to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC.

The Safety Desk will provide information for the Safety Data Monitoring Board as requested.

8.8 Reporting of SUSARs

In case of the occurrence of a SUSAR it is the responsibility of the sponsor of the study to report these to the BfArM, the leading Ethics Committee, the Marketing Authorisation Holder as well as to the investigators of the trial – in line with the relevant national and European regulations. SUSARs will not be reported on national or international level to investigators of

other ongoing studies with the study drug and will not be reported to the IRBs of the participating centers.

The sponsor will inform relevant Regulatory Authorities and the Ethics Committee:

- of all relevant information about serious unexpected adverse events as defined above that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.
- of all other serious unexpected events suspected as defined above as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

8.9 Annual Safety Reports

Once a year throughout the clinical trial or on demand, the sponsor shall provide the BfArM and the leading Ethics Committee with an annual safety report.

8.10 Birth control during study participation

Male patients whose sexual partners are women of child-bearing potential (WOCBP), must use an effective form of contraception (pearl index < 1%) during the study and at least 6 months thereafter. Effective forms of contraception are complete sexual abstinence, combined oral contraceptive, hormone IUCD, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant or depot contraceptive injection in combination with a second method of contraception like a condom or a cervical cap / diaphragm with spermicide or surgical sterilization (vasectomy) in male patients. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or surgical sterilization or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months).

Prior to study enrolment, male patients who have WOCBP as partners must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The patient must sign an informed consent form documenting this discussion.

Each pregnancy in a patient's partner must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.11 Documentation of Concomitant Medication

During the induction and consolidation therapy a wide spectrum of concomitant medication is expected which is not relevant for the evaluation of the study drug. The documentation of concomitant medication will be restricted to:

- chemotherapy including steroids and intrathecal therapy
- irradiation
- antimicrobial prophylaxis (antibacterial, antifungal, antiviral)
- Growth factors
- Comedications known for CYP3A4 metabolism

Other concomitant medications such as standard supportive care including transfusions, antiemetic drugs etc. will not be documented routinely. In case of adverse events grade 3-4 the investigator will document possible correlation to concomitant medications.

Please refer to chapter 6.4 for concomitant and restricted therapies.

8.12 Warnings and Precautions

8.12.1 Investigational product (temsirolimus)

8.12.1.1 Summary of known adverse drug reactions

Hypersensitivity and known adverse drug reactions to the investigational product temsirolimus may include:

The most frequent adverse reactions (>30%) attributed to temsirolimus are rash, asthenia, mucositis, nausea, edema and anorexia. Due to frequency of gastrointestinal disorders antiemetic prophylaxis and therapy is required according to the study center's standard procedures.

Hematological toxicities are the second most common adverse reactions. Hematological grade IV toxicity is expected after induction and consolidation therapy. For the case that the time to hematological regeneration from the last chemotherapy course exceeds 42 days dose modifications of temsirolimus are required (see6.3.3).

Other frequent adverse reactions (>10%-30%) in patients receiving temsirolimus are bacterial and viral infections, dyspnoea, mucositis, diarrhea and pain.

As additional common adverse events are allergic/hypersensitivity reactions, an H_1 antihistamine should be administered in patients before starting the intravenous temsirolimus infusion.

Rare serious adverse reactions associated with temsirolimus include interstitial lung disease, bowel perforation and acute renal failure.

The most common laboratory abnormalities that occur with a frequency greater than 30% are hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated serum alkaline phosphatase and elevated serum creatinine.

This may result in the need for an initiation or increase in the dose of hypergylcemic or lipid lowering therapy. Serum chemistry should be tested before and during treatment with temsirolimus regularly.

While there is no evidence that temsirolimus affects the ability to drive or operate machinery, patients experiencing vertigo or other symptoms that could interfere with their ability to drive a car or operate machinery should refrain from driving and operating machinery while under treatment with temsirolimus.

8.12.1.2 List of adverse drug reactions

As reported in the summary of product characteristics for 25mg temsirolimus i.v. (mostly from clinical information on renal cell carcinoma patients):

System organ category	Preferred term	Frequency
very common >10% -100%; common >1% -10%; uncommon >0.1%-1%; rare < 0,1%		
Infections and infestations	bacterial and viral infection (incl. infection, cellulutis, bronchitis, sinusitis, herpes zoster, herpes simplex)	very common
	upper respiratory tract infection	very common
	urinary tract infection (incl. dysuria, urinary frequency, urinary tract infection, urinary urgency)	very common
	pharyngitis	very common
	pneumonia (incl. interstitial pneumonia)	very common
	rhinitis	common
	folliculitis	common
	sepsis (incl. sepsis, septic shock)	common
Blood and lymphatic system disorders	thrombocytopenia	very common
	anemia	very common
	neutropenia	very common
	leukopenia	very common
	lymphocytopenia	very common
Immune system disorders	allergic/hypersensitivity reactions	common
Metabolism and nutrition disorders	hypokalaemia	very common
	anorexia	very common
	hyperglycemia/diabetes mellitus	very common
	hypercholesterolaemia	very common
	hyperlipaemia	common
	dehydration	common
	hypocalcaemia	common
	hypophosphataemia	common
Psychiatric disorders	insomnia	very common
	anxiety	very common
	depression	common
Nervous system disorders	dysgeusia	very common
	ageusia	common
	dizziness	common
	paraesthesia	common

Eye disorders	conjunctivitis	common
	eye haemorrhage	common
Vascular disorders	thrombosis (incl. deep venous thrombosis, thrombosis)	common
	hypertension	common
Respiratory, thoracic and mediastinal disorders	dyspnea	very common
	epistaxis	very common
	cough	very common
	pneumonitis	common
Gastrointestinal disorders	diarrhea	very common
	nausea	very common
	vomiting	very common
	stomatitis (incl. aphtous stomatitis, mouth ulceration, stomatitis, glossitis, oral pain))	very common
	abdominal pain	very common
	gingivitis	common
	dysphagia	common
	bowel perforation	common
	gastrointestinal haemorrhage (incl. gastrointestinal haemorrhage, rectal haemorrhage)	common
	gingivitis	common
	gastritis	common
Skin and subcutaneous tissue disorders	rash	very common
	pruritus	very common
	nail disorders	very common
	dry skin	very common
	acne	common
	moniliasis	common
	fungal dermatitis	common
	ecchymosis	common
Musculoskeletal and connective tissue disorders	arthralgia	very common
	back pain	very common
	myalgia (incl. muscle cramps, leg cramps, myalgia)	very common
General disorders and administrative site conditions	oedema (incl. oedema, facial oedema, peripheral oedema, scrotal oedema, genital oedema, generalised oedema)	very common
	pain	very common

	asthenia	very common
	pyrexia	very common
	mucositis	very common
	chills	very common
	chest pain	common
Investigations	AST increased	common
	ALT increased	common
	blood creatinine increased	common

Further details of the side effect profile of temsirolimus can be found in the current version of the ”Fachinformation”. The ‘Fachinformation’ will be filed in the Investigator Site File and will be the relevant reference document for the side effect profile. In case of updates, no amendment of the study protocol will be written unless changes in therapy or other recommendations result from the new ‘Fachinformation’. The updated ‘Fachinformation’ will be filed in the Investigator Site File.

8.12.2 Standard cytotoxic therapy (cytarabine, daunorubicin and mitoxantrone)

For information of all known adverse drug reactions please refer to the “Fachinformationsverzeichnis Deutschland” in its latest version.

9 STUDY OUTCOME AND STATISTICAL ANALYSIS

9.1 Power and Sample Size Calculation

A single stage design with fixed sample size was chosen. The accrual time will be 24 months with a follow-up time of 12 months (see 7.4).

Let m_0 and m_1 be the median event free survival times for the control and the temsirolimus arm respectively. The Logrank test will be used to test the null hypothesis

$H_0 : m_1/m_0 = 1$

against the two-sided alternative

$H_1: m_1/m_0 \neq 1.$

The allocation ratio was determined to be $n_1/n_0 = 1.0$.

A total of 146 evaluable patients are expected to be sufficient to detect a prolongation of the median EFS from 7 to 11.75 months with a power of 80% and a significance level of α=0.05. This change is considered to be clinically relevant. Under the assumption of loss to follow-up, or of alternate post-remission treatment (i.e. bone marrow transplantation), or protocol violation in up to 54 patients, total accrual to the phase II part of this trial is planned for 200 patients (100 per arm).

9.2 Statistical Analysis Plan

The statistical analysis will be performed according to the intention to treat principle (ITT analysis). This means that every patient included into the study and randomized to one treatment arm will be evaluated in that arm, even if he does not receive study-medication, or if any other violations of the study protocol occur.

- The primary endpoint (median EFS) will be compared between both treatment arms using two-sided stratified Logrank test. This part of the analysis is considered as confirmatory.
- Analyses of secondary endpoints will include, among others, relapse free survival, early response rate, morphologic and molecular CR-rate, overall survival, minimal residual disease, evaluation of potential biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers as well as indicators of autophagy in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma
- Patients undergoing allogenic bone marrow transplantation are censored for EFS and OS at the time of bone marrow transplantation.

- In addition to the ITT-analysis a per protocol analysis (PP-analysis) will be performed. This analysis will include only those patients who could be treated with full adherence to the protocol. Besides this, the PP-analysis will parallel the ITT-analysis.

9.3 Number of patients

Under the above assumptions (see9.1), total accrual to the controlled phase of this trial is planned for 200 patients. The sample size calculation accounts for loss to follow-up in 1/4 of recruited patients (i.e. 54 patients) within 24 months.

9.4 Efficacy

Evaluation of bone marrow aspirate, peripheral blood counts and differentials are used to assess the efficacy of the study medication.

Response criteria

Response criteria are defined according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [12].

Morphologic leukemia-free state:

- Bone marrow (aspirate with marrow spicules): < 5% blasts, absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Peripheral blood with no blast cells and either less than 1,000/µl granulocytes and/or less than 100,000/µl platelets

Morphologic Complete Response (CR):

- Platelet count >100,000/µl
- Granulocyte count of >1,000/µl
- Bone marrow (aspirate with marrow spicules): < 5% blasts, absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value

Cytogenetic Complete Response (CRc):

- Platelet count >100,000/µl
- Granulocyte count of >1,000/µl

- Bone marrow (aspirate with marrow spicules): < 5% blasts, absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value
- Reversion to normal karyotype (based on conventional banded studies and FISH)

Molecular Complete Response (CRm):

- Platelet count >100,000/µl
- Granulocyte count of >1,000/µl
- Bone marrow (aspirate with marrow spicules): < 5% blasts, Absence of Auer rods
- No evidence of persisting leukemia by flow cytometry (Sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent hemoglobin value
- Normal cytogenetics (based on conventional banded studies and FISH)
- Molecularly negative (no detection of pre-treatment genetic markers with a methodology providing a sensitivity of at least $1:10^3$)

Partial Remission (PR):

- Platelet count >100,000/µl
- Granulocyte count of >1,000/µl
- Bone marrow (aspirate with marrow spicules): Decrease of bone marrow blast percentage to 5% - 25% and decrease of pretreatment bone marrow blast percentage by at least 50%

Death in Aplasia:

- Death occuring ≥ 7 days following completion of initial chemotherapy (CT); death while cytopenic, with aplastic bone marrow and without evidence of persisting leukemia

Death from indeterminate cause:

- Death occurring before completion of therapy, or < 7 days post CT; Patients who die ≥ 7 days post CT with no PB blasts, but bone marrow examination not performed or not evaluable; Patients who do not complete the first course of therapy

Morphologic relapse:

- Reappearance of blasts post CT in PB or ≥ 5% blasts in the bone marrow or development of extramedullary disease

In addition to these response criteria, incomplete CR (CRi) is defined as:
CR with incomplete recovery (CRi) with neutrophils < 1,000/µl and platelets < 100,000/µl

Treatment failure is defined as:
no morphologic leukemia-free state, no partial remission

In addition, **early treatment response at day 15** after start of first induction chemotherapy is defined as:
Good response: < 5% blasts
Poor response: ≥ 5% blasts

9.5 Definition of Study Endpoints

Event free survival (EFS):
Time interval from day 1 of study treatment until treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR, CRi or morphologic leukemia-free state will be recorded.
For a patient with none of these events before the end of study follow-up, observation of EFS will be censored at the date of his or her last follow-up examination.

Relapse free survival (RFS):

Time interval from the day of documentation of CR until relapse or death from any cause.

Overall survival (OS):
Time interval from day 1 of study treatment to the day of death. For a patient who is not known to have died by the end of follow-up, observation of OS will be censored on the date the patient was last known to be alive.

Complete remission rate (CR rate):

The proportion of patients in complete remission (CR, as defined above) after induction chemotherapy.

Early response rate:

The proportion of patients with a morphologic leukemia-free state (as defined above, < 5% blasts) in the first treatment assessment on day 15 after start of first induction chemotherapy.

10 PROTOCOL AMENDMENTS/DEVIATIONS

10.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Coordinating Investigator, the Protocol Committee and discussed with the Marketing Authorization Holder. Written verification of IRB/EC as well as BfArM approval will be obtained before any substantial amendment is implemented.

10.2 Protocol deviations

When an emergency occurs that requires a deviation from the treatment with the study drug for a patient, a deviation will be made in the best interest of the patient and only for that patient. A decision will be made as soon as possible to determine whether or not the patient (for whom the deviation from protocol was effected) is to continue in the study. The patient's medical records will completely describe the deviation from the protocol and state the reasons for such deviation.

10.3 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this should be discussed with the coordinating investigator. If it is considered for a protocol amendment it cannot be implemented before it is agreed upon by the sponsor and approved by the IRB/IEC/REB and BfArM (in case of substantial amendments).

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) of this trial will consist of three members of the scientific community not involved in this trial. The committee will communicate regularly (by phone conference) with the Coordinating Investigator of the trial. The decision on the final dose for the main phase of the trial will be made in collaboration with the DSMB.

During the main part of the study, the DSMB will confer on a regular basis. The schedule and tasks of the DSMB will be written in a detailed DSMB charter. Notably, an interim analysis will be performed after 50 evaluable patients per treatment arm (temsirolimus vs. placebo) to determine the safety and the effectiveness (as measured by the % of patients with complete remission) of temsirolimus. In case the rate of complete remissions in patients of arm A (temsirolimus) is <50% of the remission rate in patients of arm B (placebo), the DSMB may opt to advise a discontinuation of the trial.

In case the DSMB has well founded reasons to suspect that risks of one treatment arm exceed the potential benefit, the DSMB has the right to request any information to be able to detect differences between the treatment arms. The DSMB will give recommendations about the continuation of the trial and/or about necessary trial amendments.

In the complex medical situation of patients receiving an intense therapy with concomitant medications and the study drug, it will be difficult or impossible in many cases to assess a "possible" relation to the study drug. Therefore, in case that the investigator assigns a "possible" correlation to the study drug the final decision on relation to the study drug and the prior description in the "Fachinformation" will be made during regular conferences of the DSMB.

11.2 Reference Laboratories

Reference cytomorphology and molecular diagnostics

As stated above, one of the three diagnostic reference centers of the SAL can be contacted for central review.

11.3 Selection of centers

The participating centers are experienced centers for treatment of acute myeloid leukemia, myelodysplastic syndromes and stem cell transplantation. This is documented by long standing collaboration within multicenter study groups. The centers have been selected based on their experience in treatment of AML and conduct of clinical trials, their large patient number and scientific merits in the field of leukemia research. The pre-requisites for study participation will be documented on a site feasibility form. A pre-study visit will not take place.

11.4 Sponsor responsibilities

Sponsor responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the Directive 2001/20/EC of the European Union, the German Drug Law and the GCP-V. The sponsor will take measures to ensure that the study is conducted according to these laws and regulations as closely as possible and according to the Declaration of Helsinki.
The sponsor delegates all tasks associated with the study to the Coordinating Investigator (LKP, Leiter der klinischen Prüfung). This agreement is signed by both parties in a delegation contract.

11.5 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the Directive 2001/20/EC of the European Union, the German Drug Law and the GCP-V. The investigator will ensure that the study is conducted according to these laws and regulations as closely as possible and according to the Declaration of Helsinki. All tasks of the investigators are summarized in a contract and signed by LKP and investigators.

11.6 CRF documentation

For each patient enrolled, a CRF must be completed and signed by the investigator or sub-investigator within a reasonable time period after data collection. The investigator will sign and date the indicated places on the CRF. These signatures will indicate that the investigator inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.

As described in the ICH GCP Guidelines (E6), 'essential documents', including CRFs, source documents, consent forms, laboratory test results, and medication inventory records, will be archived by the investigator according to the current rules and regulations.

11.7 Database management and quality control

Data items from the Case Report Forms are entered into the study database by qualified staff at the study center following their own internal standard operating procedures. Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by data management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the Case Report Forms at the investigator site, and a copy is sent to CRO data management personnel so the resolutions can be entered centrally into the database. When the database has been declared to be complete and accurate, the database will be locked.

11.8 Study Files and Retention of Records

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data) be retained by the investigator for as long as needed to comply with national and international regulations. The investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.9 Delegation of tasks

The principal investigator may delegate tasks to sub-investigators at the site or to qualified staff members. He is responsible to select staff members and to keep overview on quality of their work. The distribution of tasks must be documented in a delegation log.

11.10 Monitoring, audits and inspections

The study will be monitored by a qualified and appropriately trained person appointed by the sponsor.

The investigator, or a designated member of the investigator's staff, must be available for telephone monitoring or at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each monitoring visit so that the accuracy and completeness may be checked.

The investigator will permit study-related monitoring visits and audits by the IRB/EC and regulatory inspection(s) (e.g., BfArM, FDA, EMEA, or RP (Regierungspräsidium), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

12 REGULATORY CONSIDERATIONS

12.1 Institutional Review Board / Independent Ethics Committee approval

It is the responsibility of the investigator to provide all requested information about qualification of the respective trial site and trial staff to the sponsor. The sponsor will submit the application to the IRB/IEC.

The trial may only be conducted as approved by the Ethics Committee and the competent authority. Substantial amendments may only be implemented after approval. Additional trial sites may only recruit patients after the sponsor obtained approval for the site.

In compliance with European regulations/ICH-GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the study central office and the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is responsible for giving any requested support for any monitoring, inspection or audit visit. The investigator has to be available during these visits.

12.2 Competent local authorities

The sponsor will notify the competent local authority about the conduct of this trial before starting recruitment. The sponsor shall inform the competent local authority within 90 days of termination of the clinical trial. Where the clinical trial has been suspended or interrupted by the sponsor, notification shall take place within 15 days, giving the reasons for suspension or interruption.

12.3 Informed Consent

The investigator must obtain informed consent of a patient or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines. Tests and analyses which are part of standard procedures in the management of ALL may of course take place before informed consent and will be used for study inclusion and documentation.

Documentation that informed consent occurred prior to the patient's entry into the study and the informed consent process should be recorded in the patient's source documents. The original consent form, signed and dated by the patient and by the person consenting the patient prior to the patient's entry into the study, must be maintained in the investigator's study files.
A copy of the Patient Information and signed Consent Form must be given to the patient or the patient's legal guardian.

12.4 Confidentiality

The sponsor affirms the patient's right to protection against invasion of privacy. The investigator permits representatives of the BfArM or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.
The investigator must ensure that the patient's encryption is maintained. On the CRFs or other documents submitted to the study central office, patients should be identified by a patient study number only. Documents that are not for submission to the study central office (e.g., signed informed consent forms) should be kept in confidence by the investigator.

12.5 Patient insurance

According to §40 Article 1 No. 8 and Article 3 AMG (German Drug Law) the Sponsor of the study must obtain insurance coverage for eventually occurring damage caused by the treatment or any actions taken according to the treatment plan.
Insurance of the study has been obtained at:
Name of insurance company:
Address:
Contact Phone:
Policy Number:
Date of issuance:
Date of expiration: N/A

12.6 Financing

The study will be supported by Pfizer Pharma GmbH by delivery of the active study drug free of charge and financial support for study organization.

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14 APPENDICES

Synopsis of the study

Title of the study	A double-blind, placebo-controlled, randomized, multicenter phase II trial to assess the efficacy of Temsirolimus added to standard first-line therapy in elderly patients with newly diagnosed AML
Short title of the study	TOR-AML
German title of the study	Eine doppelblinde, plazebo-kontrollierte, randomisierte, multizentrische Phase II Studie zur Erfassung der Wirksamkeit von Temsirolimus zusätzlich zur Standard-Erstlinienchemotherapie bei Patienten > 60 Jahre mit neudiagnostizierter AML
Objective(s)	The hypothesis of this study is that the addition of temsirolimus may improve standard AML chemotherapy and that temsirolimus may specifically target the leukemia-initiating cells in AML, thereby reducing the risk of leukemia relapse. Run-in part Objective • to determine the optimal temsirolimus dose for the main part of the study Main part: Primary objective • to compare the median Event Free Survival (EFS)* and the EFS probability of all AML patients between the temsirolimus and the control group Secondary objectives • to compare the median Event Free Survival (EFS) of AML patients with different cytogenetic and molecular risk groups[1] • to compare the rate of early response (< 5 % bone marrow blasts on d15) after the first induction cycle between the temsirolimus and the control group • to compare the rate of early response after the first induction cycle of AML patients with different cytogenetic and molecular risk groups[1] • to compare the Complete Remission (CR) rate of the temsirolimus with the control group • to compare the CR rate of AML patients with different cytogenetic and molecular risk groups[1] • to compare Relapse Free Survival (RFS) of AML patients between the temsirolimus and the control group • to compare Relapse Free Survival (RFS) of AML patients with different cytogenetic and molecular risk groups[1] • to compare the Overall Survival (OS) of all AML patients between the temsirolimus and the control group • to compare the Overall Survival (OS) of AML patients with different cytogenetic and molecular risk groups[1] • to compare the rate of molecular remissions of the temsirolimus with the control group • to compare the toxicity of the temsirolimus and the control treatment • to compare the rate of molecular relapse after molecular remission of all AML patients between the temsirolimus and the control group after induction therapy and in the course of the first remission

	• to evaluate potential biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers as well as indicators of autophagy in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma *** EFS defined as:** Time interval from day 1 of study treatment until treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR, CRi or morphologic leukemia-free state will be recorded. **[1] Cytogenetic and molecular risk groups** Favorable t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype) Intermediate-I* Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype) Intermediate-II t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse Adverse inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged -5 or del(5q); -7; abnormal(17p); complex karyotype‡ *Includes all AMLs with normal karyotype except for those included in the favorable subgroup; ‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3)
Endpoint(s)	<u>Run-In-Part</u> Endpoint • optimal temsirolimus dose for the main part of the study <u>Main Part</u> Primary endpoint • median Event Free Survival (EFS) and EFS probability Secondary endpoints • rate of early response (< 5 % bone marrow blasts on d15) after the first induction cycle of all AML patients • complete remission (CR) rate after induction therapy • median relapse-free survival (RFS) and RFS probability after reaching CR • median Overall Survival (OS) and OS probability • rate of molecular remissions and molecular relapses • toxicity according to CTC • biomarkers indicating the course of disease, including genetic, epigenetic, transcriptional and protein markers as well as indicators of autophagy in leukemic blasts, bone marrow, peripheral blood cells, serum and plasma
Study Design	In order to address the toxicity profile of temsirolimus added to induction chemotherapy, a **run-in part** with 12 (to 18) patients will be conducted. Patients in this part of the study will be randomized between dose level 1 (12.5mg, n=6) and dose level 2 (25mg, n=6). The optimal dose-level will be determined after 1-2 induction cycles.

	After the run-in part, the study will be on hold until the decision by the Data Safety Monitoring Board on dose finding is completed, which may include an additional 6 patients at previously tested or additional dose levels or schedules. After having determined the optimal dose level in the run in part, the **main part** of the study will start. In the main part, patients will be randomized between temsirolimus and placebo for induction and consolidation chemotherapy. For maintenance therapy the study will be unblinded. Maintenance therapy is only given in patients randomized in the temsirolismus arm of the study. All patients receive: • standard induction and consolidation chemotherapy • temsirolimus or placebo during chemotherapy on day -1 and 8 • 8-week maintenance therapy with weekly temsirolimus or observation
	Run-in-part Chemotherapy is conducted according to general standards and is not part of the study treatment **Induction 7+3+ Temsirolimus:** Cytarabine 100mg/m^2/24hrs i.v. day 1-7 Daunorubicin 60mg/m^2 i.v. day 3-5 Temsirolimus 12.5 or 25mg abs i.v. day -1 and +8
	Bone marrow will be analyzed on day 15: In case of **morphologic leukemia-free state** (< 5% blasts in an aspirate, no blasts in peripheral blood and no extramedullary disease), no second induction chemotherapy is given. In case of **partial remission** (decrease of bone marrow blast percentage to 5% - 25% and decrease of pretreatment bone marrow blast percentage by at least 50%) or **treatment failure** (no morphologic leukemia-free state, no partial remission), a (second) induction cycle with HAM (elderly) + temsirolimus will be administered on day 22 of first induction chemotherapy, starting with temsirolimus on day 21 (day -1 of second induction cycle). **HAM (elderly) induction II for patients with PR or treatment failure:** Cytarabin (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Mitoxantrone 10mg/m^2 i.v. day 3-5 Temsirolimus 12.5 or 25mg abs i.v. day -1 and +8
	Precondition for consolidation therapy: - Morphologic complete remission (CR): bone marrow blasts < 5%; absence of extramedullary disease; absolute neutrophil count > 1000/µL; platelet count ≥ 100 000/µL; independence of red blood cell transfusions; or - CR with incomplete recovery (CRi) with neutrophils > 1,000/µl and platelets > 75,000/µl after induction therapy. All patients in CR / CRi will receive two cycles of consolidation chemotherapy not earlier than one week after confirming CR /CRi with neutrophils > 1,000/µl and platelets > 75,000/µl. If, in the opinion of the treating physician, the patient´s condition does not allow for consolidation chemotherapy, consolidation chemotherapy can be postponed for up to 4 weeks after a CR / CRi with neutrophils > 1,000/µl and platelets > 75,000/µl is reached. If the patient is still not considered suitable for consolidation chemotherapy after 4 weeks, the patient will proceed directly to observation. Patients who do not achieve CR / CRi with neutrophils > 1,000/µl and platelets > 75,000/µl until day 42 after last chemotherapy will be withdrawn from the study.

	Consolidation I (high-dose cytarabine)+Temsirolimus: Cytarabine (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Temsirolimus 12.5/25mg i.v. day -1 and +8
	Consolidation II (high-dose cytarabine)+Temsirolimus: Preconditions for start: see above. Cytarabine (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Temsirolimus 12.5/25mg i.v. day -1 and +8
	Maintenance Patients in the run-in part will not receive temsirolimus maintenance treatment.
	Main part Chemotherapy is conducted according to general standards and is not part of the study treatment. The anticipated temsirolimus dose for the main part of the trial is 25 mg. In case that safety data during the run-in phase are in favor of a lower dose (e.g. 12.5 mg) an amendment of the protocol will be submitted before start of the main part. **Induction 7+3+Temsirolimus or Placebo:** Cytarabine 100mg/m^2/24hrs i.v. day 1-7 Daunorubicin 60mg/m^2/3hrs i.v. day 3-5 Temsirolimus 25mg i.v. or placebo day -1 and +8
	Bone marrow will be analyzed on day 15: In case of **morphologic leukemia-free state** (< 5% blasts in an aspirate, no blasts in peripheral blood and no extramedullary disease), no second induction chemotherapy is given. In case of **partial remission** (decrease of bone marrow blast percentage to 5% - 25% and decrease of pretreatment bone marrow blast percentage by at least 50%) or **treatment failure** (no morphologic leukemia-free state, no partial remission), a (second) induction cycle with HAM (elderly) + temsirolimus / placebo will be administered on day 22 of first induction chemotherapy, starting with temsirolimus/placebo on day 21 (day -1 of second induction cycle). **HAM (elderly) induction II for patients with PR or treatment failure:** Cytarabin (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Mitoxantrone 10mg/m^2 i.v. day 3-5 Temsirolimus 25mg abs i.v. or placebo day -1 and +8

	Precondition for consolidation therapy: CR or CRi with neutrophils > 1,000/µl and platelets > 75,000/µl. All patients in CR/CRi will receive two cycles of consolidation chemotherapy not earlier than one week after confirming CR /CRi with neutrophils > 1,000/µl and platelets > 75,000/µl. If, in the opinion of the treating physician, the patient´s condition does not allow for consolidation chemotherapy, consolidation chemotherapy can be postponed for up to 4 weeks after a CR/CRi with neutrophils > 1,000/µl and platelets > 75,000/µl is reached. If the patient is still not considered suitable for consolidation chemotherapy after 4 weeks, the patient will proceed directly to maintenance therapy or observation. Patients who do not achieve CRi with neutrophils > 1,000/µl and platelets > 75,000/µl on day 42 after last chemotherapy will undergo bone marrow aspiration between day 35 and 42 to exclude relapse. Patients that achieve CRi with neutrophils > 1,000/µl and platelets > 75,000/µl between day 43 and day 59 will receive a reduced dose of temsirolimus or placebo in the forthcoming cycles (for dose reduction see below). Patients that do not achieve CRi with neutrophils > 1,000/µl and platelets > 75,000/µl by day 60 will undergo bone marrow aspiration between day 54 and 60 to exclude relapse and may proceed directly to maintenance therapy or observation at the discretion of the leading investigator.
	Consolidation I (high-dose cytarabine): Cytarabine (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Temsirolimus 25mg i.v. or placebo i.v. day -1 and +8
	Consolidation II (high-dose cytarabine): Preconditions for start: see above. Cytarabine (HD-AraC) 1g/m^2/3hrs i.v. (2 x daily) day 1, 3, 5 Temsirolimus 25mg i.v. or placebo i.v. day -1 and +8
	Maintenance (following unblinding): starting after confirmed CR/CRi with hematological recovery (neutrophils > 1,000/µl, platelets > 75,000/µl) from the second consolidation cycle, not earlier than day 28 of second consolidation cycle. Arm A (temsirolimus) 25mg i.v. weekly, for 8 weeks Arm B (placebo) observation weekly, for 8 weeks
	If **significant myelosuppression** during maintenance therapy occurs (neutrophils < 1,000/µl, platelets < 75,000/µl) maintenance therapy with temsirolimus will be paused until hematological recovery. In case of persistence of the myelosuppression for >21 days or of a severe myelosuppression (CTC grade 4) the dose of temsirolimus will be permanently reduced according to the dose reduction scheme.
	Dose reduction and dose delay: In case of hematological and non-hematological toxicities, dose reductions of temsirolimus (or placebo) may be necessary. **Hematological toxicities** During the period of chemotherapy, hematological toxicities will only require dose modifications if a grade 4 neutropenia or thrombopenia persists ≥ 42 days after start of last chemotherapy cycle. After a relapse is excluded by bone marrow aspiration between day 35 and 42, therapy with temsirolimus/placebo will be delayed until hematological recovery (CR or CRi with neutrophils > 1,000/µl and platelets > 75,000/µl) and the dose will be reduced by one dose level for all subsequent chemotherapy cycles and the first two maintenance cycles according to the dose reduction scheme below.

However, different criteria will apply after hematopoietic recovery from the last chemotherapy course during the subsequent maintenance therapy.

Hematological Criteria for Dose Delay and Dose Modifications of Temsirolimus during **maintenance therapy**		
Grade	**Dose delay**	**Dose modification**
Grade 0 - 2	Treat on time	No change
Grade 3	Treat on time	DECREASE one dose level
Grade 4	DELAY[a] until ≤ Grade 2	DECREASE one dose level
[a]If no recovery after 30 days delay, maintenance treatment will be discontinued.		

Non-hematological toxicities

Dose modifications of non-hematological toxicities during chemotherapy and maintenance therapy are summarized here:

Non-hematological Criteria for Dose Delay and Dose Modifications of Temsirolimus or placebo		
Grade	**Dose delay**	**Dose modification**
Grade 0 - 2	Treat on time	No change
Grade 3 and 4	DELAY until ≤ Grade 2	DECREASE one dose level
If the same grade 3/4 non-hematological toxicity reoccurs after first dose reduction	Discuss treatment discontinuation with leading investigator	

These recommendations apply, if the adverse event is considered to be probably related to temsirolimus treatment but not to the chemotherapy. The dose of temsirolimus will be reduced according to the following scheme:

initial dose (starting dose)	**25 mg abs.**
Dose level -1:	20 mg abs.
Dose level -2:	15 mg abs.
Dose level -3:	Discontinue from study
Reduced dose levels will be maintained throughout the chemotherapy phase and the first two maintenance phase cycles. If patients with reduced temsirolimus dose do not experience any grade 3 or grade 4 toxicity during the first two maintenance phase cycles, the temsirolimus dose will be escalated at one dose level. If during the following two maintenance cycles still no grade 3 or 4 toxicity occurs, another dose escalation up to 25mg can be considered.	

Key inclusion and exclusion criteria

Key inclusion criteria

- Patients with newly diagnosed AML (except APL) according to the FAB classification, including AML evolving from MDS or other hematological diseases and AML after previous cytotoxic therapy or radiation (secondary AML).
- Bone marrow aspirate or biopsy must contain ≥ 20% blasts of all nucleated cells or differential blood count must contain ≥ 20% blasts. In AML FAB M6 ≥ 30% of non-erythroid cells in the bone marrow must be leukemic blasts. In AML defined by cytogenetic aberrations the proportion of blasts may be < 20%.
- Age ≥ 61 years
- Informed consent, personally signed and dated to participate in the study
- Willingness of male patients whose sexual partners are women of child-bearing potential (WOCBP), to use an effective form of contraception (pearl index < 1%) during the study and at least 6 months thereafter.

	Effective forms of contraception are complete sexual abstinence, combined oral contraceptive, hormone IUCD, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant or depot contraceptive injection in combination with a second method of contraception like a condom or a cervical cap / diaphragm with spermicide or surgical sterilisation (vasectomy) in male patients. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or surgical sterilization or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). <u>Key exclusion criteria</u> • Patients who are not eligible for standard chemotherapy as described in chapter 6.2 • Previous treatment for AML, except leukapheresis for patients with hyperleukocytosis (leukocytes > 100,000/uL and / or leukostatic syndrome) or hydroxyurea • Known central nervous system manifestation of AML • Cardiac Disease: Heart failure NYHA III° or IV°; active coronary artery disease (MI more than 6 months prior to study entry is permitted); serious cardiac ventricular arrhythmias, defined as: ventricular extrasystoly grade LOWN IV, sustained or non-sustained ventricular tachycardias, and history of ventricular fibrillation / ventricular flutter, unless patient is protected by an internal cardioverter / defibrillator or ventricular arrhythmia was attributable to a myocardial ischemia > 6 months before study entry. • Chronically impaired renal function (creatinin clearance < 30 ml / min) • Chronic pulmonary disease with relevant hypoxia • Inadequate liver function (ALT and AST ≥ 2.5 x ULN) if not caused by leukemic infiltration • Total bilirubin ≥ 1.2 mg/dL if not caused by leukemic infiltration • Uncontrolled active infection • Concurrent malignancies other than AML with an estimated life expectancy of less than two years and requiring therapy • Known HIV and/or hepatitis C infection • Evidence or history of CNS disease, including primary or metastatic brain tumors, seizure disorders • History of organ allograft • Concomitant treatment with kinase inhibitors, angiogenesis inhibitors, calcineurin inhibitors and Mylotarg • Serious, non-healing wound, ulcer or bone fracture • Allergy to study medication or excipients in study medication • Investigational drug therapy outside of this trial during or within 4 weeks of study entry • Any severe concomitant condition which makes it undesirable for the patient to participate in the study or which could jeopardise compliance with the protocol
Study type	double-blind, placebo-controlled, randomized, multicenter phase II study with preceding dose-finding run-in-part
Statistical analysis	<u>Run-in part</u> DLT in the run-in part of the trial is defined as • CTCAE Grade 4 neutropenia (ANC <0.5 x 109/L) lasting ≥ day 42 after last chemotherapy • CTCAE Grade 4 thrombocytopenia (platelets < 25 x 109/L) lasting ≥

	day 42 after last chemotherapy • CTCAE Grade 3 non-hematologic temsirolimus-related adverse events (excluding hypertension and nausea / vomiting which is not medically managed) Patients must be evaluable for DLT assessment. Patients with early death during induction due to events unrelated to temsirolimus treatment e.g. infection will not be considered as DLT. Patients with neutropenia or thrombocytopenia due to refractory or recurrent AML will not be considered for DLT. If such cases occur additional evaluable patients will be included. If < 2 out of 6 patients experience DLT at dose level 2 during induction chemotherapy, dose level 2 will be chosen for temsirolimus during the main part. If > 2 of 6 patients experience DLT at dose level 2 and < 2 out of 6 patients experience DLT at dose level 1, then dose levels 1 will be chosen for temsirolimus during the main part. If 2 out of 6 patients experience DLT at dose level 2 and ≤ 2 patients experience DLT at dose level 1, the Data Safety Monitoring Board (DSMB) may opt to include additional 6 patients in dose level 2 of the run-in phase. Depending on the results, the DSMB may consider an additional dose level to be tested in 6 additional patients or terminate the trial. <u>Main part</u> A total of 146 evaluable patients are expected to be sufficient to detect a prolongation of the median EFS from 7 to 11.75 months with a power of 80% and a significance level of α=0.05. Under the assumption of loss to follow-up, or of alternate post-remission treatment (i.e. bone marrow transplantation), or protocol violation in up to 54 patients, total accrual to the phase II part of this trial is planned for 200 patients (100 per arm).
Sample size	Run-in-part: A maximum of evaluable 18 patients will be enrolled Main part: 200 patients will be enrolled (100 in each treatment group)
Trial duration	- First patient in: January 2nd, 2012 - Last patient in: January 2nd, 2014 - Recruitment: 2 years - Treatment: approx. 7 months - Follow up: 1 year - Trial duration: approx. 4 years - End of study: January 1st, 2016

Performance Status

ECOG		Karnofsky	
Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.