Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML (ETAL3-ASAP)

A phase-III study on the comparison of two treatment strategies for patients with high-risk acute myeloid leukemia by the **Study Alliance Leukemia** (SAL)

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Sponsor

DKMS gemeinnützige GmbH

Kressbach 1, 72072 Tübingen

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PROTOCOL SIGNATURE PAGE

"Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML"

Protocol of the DKMS gemeinnützige GmbH and the Studien-Allianz Leukämie (SAL)

By signing below, the sponsor agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by the Coordinating Investigator, prior to seeking approval from the Competent Authorities and/or Independent Ethics Committee.

This study will be conducted in accordance with current International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki, and local ethical and legal requirements.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALAT	Alanine Aminotransferase
AMG	Arzneimittelgesetz
AML	Acute Myeloid Leukemia
APL	Acute Promyelocytic Leukemia
ASAP	As Soon As Possible
ASAT	Aspartate Aminotransferase
ATG	AntiThymocyte Globulin
ATRA	All-Trans Retinoic Acid
bid	bis in die (twice daily)
BMDW	Bone Marrow Donors Worldwide
BMI	Body Mass Index
CBC	Complete Blood Count
CI	Confidence Interval
CIBTMR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Remission
CRF	Case Report Form
CT	Confirmatory Typing
CTP	Cytarabine Triphosphate
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical Trials Unit
DFS	Disease Free Survival
DISC	DISease Control (strategy)
DKMS	Deutsche Knochenmarkspenderdatei
DLCO	Diffusing Lung Capacity for Carbon Monoxide
DNA	Deoxyribonucleic Acid
EBMT	European Society for Blood and Marrow Transplantation
EC	Ethics Committee
ECG	Electrocardiogram / -ography
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
ELN	European LeukemiaNet
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ETAL	Evaluation of Transplantation in Acute Leukemia

FAS	Full Analysis Set
FHCRC	Fred Hutchinson Cancer Research Center
FISH	Fluorescence In Situ Hybridization
FLAG	Fludarabine + High-dose Cytarabine + G-CSF
FLAMSA	Induction therapy combined with conditioning regimen containing Fludarabine, Cytarabine, Amsacrine, Cyclophosphamide, Total body irradiation and ATG
FPFV	First Patient First Visit
FPI	First Patient In
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung (GCP guideline for Germany)
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GVHD	Graft-Versus-Host Disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCT	Hematopoietic Cell Transplantation
HDAC	High-Dose Cytarabine
HLA	Human Leucocyte Antigen
HR	High Risk
IF	Induction Failure
ISF	Investigator Site File
IT	Induction Chemotherapy
ITT	Intent to Treat
IUD	Intrauterine Device
i.v.	Intravenous
KKS	Koordinierungszentren für Klinische Studien
LDAC	Low-Dose Cytarabine
LDH	Lactate Dehydrogenase
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MAC	Myeloablative Conditioning
NA	Not Applicable
NCI	National Cancer Institutes (of the USA)
ND	Not Done
NRM	Non-Relapse Mortality
OS	Overall Survival
qd	quaque die (once a day)
PBSC	Peripheral Blood Stem Cells
p.o.	per os (orally)

PI	Principal Investigator
PIL	Patient Identification Log
PP	Per Protocol
RAEB	Refractory Anemia With Excess Blasts
RAEB-T	Refractory Anemia With Excess Blasts in Transmission
RIC	Reduced Intensity Conditioning
RIST	Remission Induction Strategy
RNA	Ribonucleic Acid
sAML	Secondary Acute Myeloide Leukemia
s.c.	subcutaneous[ly]
SAE	Serious Adverse Event
SAL	Studienallianz Leukämie
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
STR-PCR	Short Tandem Repeat Polymerase Chain Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
tAML	Therapy-Related Acute Myeloid Leukemia
TBI	Total Body Irradiation
TC	Treatment Choice
TDT	Time from Diagnosis to Treatment
TMF	Trial Master File
t-MN	Therapy-Related Myeloid Neoplasm
UD	Unrelated Donor
UDS	Unrelated Donor Search
ULN	Upper Limit Normal
VOD	Veno-Occlusive Disease
WBC	White Blood Cells
WHO	World Health Organization
Y	Years
ZKRD	Zentrales Knochenmarkspenderregister

1 Protocol Synopsis

1.1 Synopsis

SPONSOR	DKMS gemeinnützige GmbH 72072 Tübingen
COORDINATING INVESTIGATOR	Prof. Dr. med Johannes Schetelig Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus Fetscherstraße 74, 01307 Dresden [redacted]
TITLE OF STUDY	Evaluation of the impact of remission induction chemotherapy prior to allogeneic stem cell transplantation in relapsed and poor-response patients with AML
SHORT TITLE	ETAL3-ASAP
BACKGROUND	Patients with high-risk acute myeloid leukemia (AML) who relapsed or showed a poor response to induction chemotherapy have a dismal prognosis. For these patients, allogeneic transplantation is the recommended treatment. While allogeneic transplantation may be considered as the ultimate treatment concept, the treatment path to transplantation is not well defined. The traditional approach is to pursue a complete remission by means of aggressive reinduction chemotherapy prior to allogeneic transplantation. This approach is associated with potentially life-threatening toxicities and has limited efficacy. As a result, only some patients will reach allogeneic transplantation in complete remission. To reduce the number of patients who die or who are ineligible for transplantation due to the toxicity of aggressive induction

	chemotherapy, other bridging options have been explored. One promising alternative is to abstain from remission induction. Instead, disease control by means of less aggressive chemotherapy or simply monitoring leukemic proliferation can be considered. Based on the existing literature from uncontrolled phase II studies and retrospective analyses these two approaches may be considered to be comparable. Yet, direct comparisons between these two treatment strategies have not been performed. A randomized controlled trial is the only way to identify if there is non-inferiority of the less toxic approach, compared to the standard approach of remission induction by aggressive chemotherapy prior to allogeneic transplantation.
OBJECTIVES	The objective of this trial is to compare outcomes of two treatment strategies for patients with high-risk AML who failed to achieve or maintain a complete remission with standard therapy. Patients will be randomized between two strategies. The standard strategy is aimed at achieving a complete remission by aggressive salvage chemotherapy using high dose cytarabine and mitoxantrone, and is referred to as the Remission Induction Strategy arm or “RIST”. The alternative is a less toxic disease-control strategy of disease monitoring and, if necessary, low-dose cytarabine or mitoxantrone referred to as the Disease Control Strategy arm or “DISC” prior to allogeneic transplantation, which should be performed as soon as possible.
OUTCOME(S)	**Primary Endpoint** is disease-free survival on day 56 after allogeneic stem cell transplantation. This composite endpoint consists of two major components: i) To have received allogeneic HCT within 16 weeks after randomization and; ii) to be free of disease on 56 days after HCT. The endpoint can be assessed for all patients. **Secondary Endpoints**: Overall survival by treatment arm is the most important secondary endpoint. In addition, the rate of allogeneic stem cell transplantation, cumulative incidence of

	CR, and leukemia-free survival will be assessed by treatment arm. The treatment effect will be analysed in patients with relapsed and poor response AML. Further endpoints will be evaluated in pre-defined subgroups of patients.
INCLUSION AND EXCLUSION CRITERIA	**Inclusion criteria:** – Signed written informed consent. – Male and female patients of 18 to 75 years of age. – Diagnosis of AML according to WHO criteria. – Patient is fit for aggressive induction chemotherapy and transplantation by assessment of an experienced hematologist. – No known history of chronic pulmonary disease and absence of dyspnea. Otherwise, documented diffusion lung capacity for carbon monoxide (DLCO) ≥40% (adjusted for hemoglobin, if available) and FEV1/FVC ≥ 50%. – HLA-identical sibling. **or** HLA-compatible unrelated donor (≥9/10 antigens matched for HLA-A, -B, -C, -DRB1, and –DQB1) with completed confirmatory typing **or** Two unrelated donors with >90% probability of a 9/10 match for HLA-A, -B, -C, -DRB1, and –DRQB1, according to OptiMatch® list. – ***Relapse patients***: First AML relapse, defined as ≥5% bone marrow blasts and / or extramedullary AML manifestation. **or** ***Poor responders*** with ≥5% bone marrow blasts after the first cycle of induction therapy, and one of the following subtypes/risk groups of AML:

	AML that evolves from previously documented myelodysplastic syndrome (MDS) or after a Myeloproliferative Neoplasia (MPN) *or* Diagnosis of therapy-related myeloid neoplasm (t-MN) *or* Non favourable risk AML according to ELN-criteria. **Exclusion criteria:** – Acute promyelocytic leukemia (APL). – WBC count of ≥50 GPt/L at study inclusion. – For poor responder patients, the first cycle of induction therapy contained HDAC, defined as cytarabine at single-doses of >1g/ m^2. – Patient has received more than 440 mg/m^2 daunorubicin equivalents (see chapter 7.2 for definitions and worksheet for calculation). – Severe organ dysfunction, defined as any of the following: o Left ventricular ejection fraction <50%. o Patients who receive supplementary continuous oxygen. o Serum bilirubin >1.5 x ULN (if not considered Gilbert-Syndrome) or ASAT/ALAT >5 x ULN. o Estimated GFR <50 ml/min. – Treatment with any investigational drug within 10 days before study entry. – Uncontrolled infection at the time of enrollment. – History of allogeneic transplantation. – Manifestation of AML in the central nervous system. – Pregnant or breast-feeding women. – Men unable or unwilling to use adequate contraception

<table>
<tr><td></td><td>methods from start of study treatment to minimum of six months after the last dose of chemotherapy.

– Women of childbearing potential except those who fulfill the following criteria: Post-menopausal or post-operative or continuous and correct application of a contraception method with a Pearl Index <1% or sexual abstinence or vasectomy of the sexual partner.</td></tr>
<tr><td>INTERVENTIONS</td><td>All patients will be randomized 1:1 to either a remission-induction strategy (RIST) or a disease-control strategy (DISC).

→ Remission Induction Strategy (RIST arm):

The remission-induction strategy encompasses the administration of aggressive induction chemotherapy (HAM) and remission control after hematopoietic recovery. The induction chemotherapy has to start within 7 days from randomization as indicated in the following table:

For patients ≤60y:

<table>
<tr><th>Days</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Cytarabine i.v.
3 g/m^2 over 3h every 12 hours</td><td>X
X</td><td>X
X</td><td>X
X</td><td></td><td></td></tr>
<tr><td>Mitoxantrone i.v.
10 mg/m^2</td><td></td><td></td><td>X</td><td>X</td><td>X</td></tr>
</table>
For patients >60y:

<table>
<tr><th>Days</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th></tr>
<tr><td>Cytarabine i.v.
1 g/m^2 over 3h , every 12 hours</td><td>X
X</td><td>X
X</td><td>X
X</td><td></td><td></td></tr>
<tr><td>Mitoxantrone i.v.
10 mg/m^2</td><td></td><td></td><td>X</td><td>X</td><td>X</td></tr>
</table>
Once a complete remission has been confirmed within 35 days after start of induction treatment, or the disease has proven to</td></tr>
</table>

	be refractory to aggressive chemotherapy, the patient should be referred immediately to a transplant center and transplantation should be scheduled. → **Dis**ease **C**ontrol Strategy (DISC arm): The DISC arm aims at disease-monitoring and control until start of the conditioning regimen prior to transplantation. The aim is not to induce a remission but to prevent complications from AML with the least toxic approach. Disease-monitoring without anti-leukemic therapy ("Watch and wait") is the preferred approach except for those patients with rapidly proliferating AML (see definitions). Transplantation should be scheduled *as soon as possible*. Pharmacologic options aimed at disease-control in patients with rapidly proliferating AML comprise low-dose AraC (LDAC) or single-dose mitoxantrone. The choosen approach must be documented in the database within 3 days after randomization.Option A) Watch & wait **or** Option B) LDAC: cytarabine 20 mg/ m^2 s.c. once a day for 10 days **and / or** Option C) Mitoxantrone 10 mg/ m^2 i.v. given as single intravenous infusion In the event of prolonged donor search and delayed start of the conditioning regimen, LDAC may be repeated at monthly intervals up to maximum 3 cycles and mitoxantrone up to maximum 3 doses. Patients may be switched from one pharmacologic strategy to the other before the start of conditioning. In both study arms, the final remission assessment will be performed up to Day +56 post-transplantation, within a maximum of 24 weeks after randomization.

Duration of study and follow-up	Duration of study per patient: Up to 24 weeks Follow-up: from FPLV until 2 years after LPFV
STUDY TYPE	The proposed trial is an open, randomized, two-arm, multicenter phase-III trial. Stratification factors for randomization are disease status (relapse versus poor response AML), disease risk (high-risk versus other) and age (≤60 years versus >60 years).
STATISTICAL ANALYSIS	The primary endpoint of disease-free survival on Day 56 after HCT can be observed for all patients due to sufficient follow up. All patients who do not meet the criteria for this composite endpoint will be considered as failures. The endpoint will be interpreted as the success rate. The primary efficacy analysis will be done with the intent-to-treat and the per protocol population. The null hypothesis is H_0: pi2 - pi1 ≤ -0.05, where pi2 is the success rate in the DISC arm and pi1 is the success rate in the RIST arm. The non-inferiority margin is 5%. The null hypothesis will be tested by means of the test for non-inferiority of binomial trials described by Farrington and Manning. No interim analyses are projected. A hierarchical test-strategy will be applied. First, non-inferiority of disease-control versus remission-induction will be tested in the Full Analysis Set (FAS). If non-inferiority can be demonstrated in the FAS, non-inferiority will also be tested in the per protocol population at the same significance level. Secondary endpoints will be analysed in the FAS, the per-protocol population and further subgroups of patients. No formal adjustment for the significance level will be performed for analyses of secondary endpoints. The primary efficacy analysis will be supplemented by the multivariate analysis of overall survival in the FAS. For this purpose a Cox regression model will be fitted.
SAMPLE SIZE	At least 246 patients in the per protocol population, requiring 308 patients (154 in each arm) according to the initial study

	assumptions.
TRIAL DURATION	First patient in: Q3 2015 Last patient in: Q1 2022 Last patient, last visit: Q3 2022 End of follow-up: Q1 2024
PARTICIPATING CENTERS	15 centers – accounting for approximately 100 patients per year.

2 Flow chart

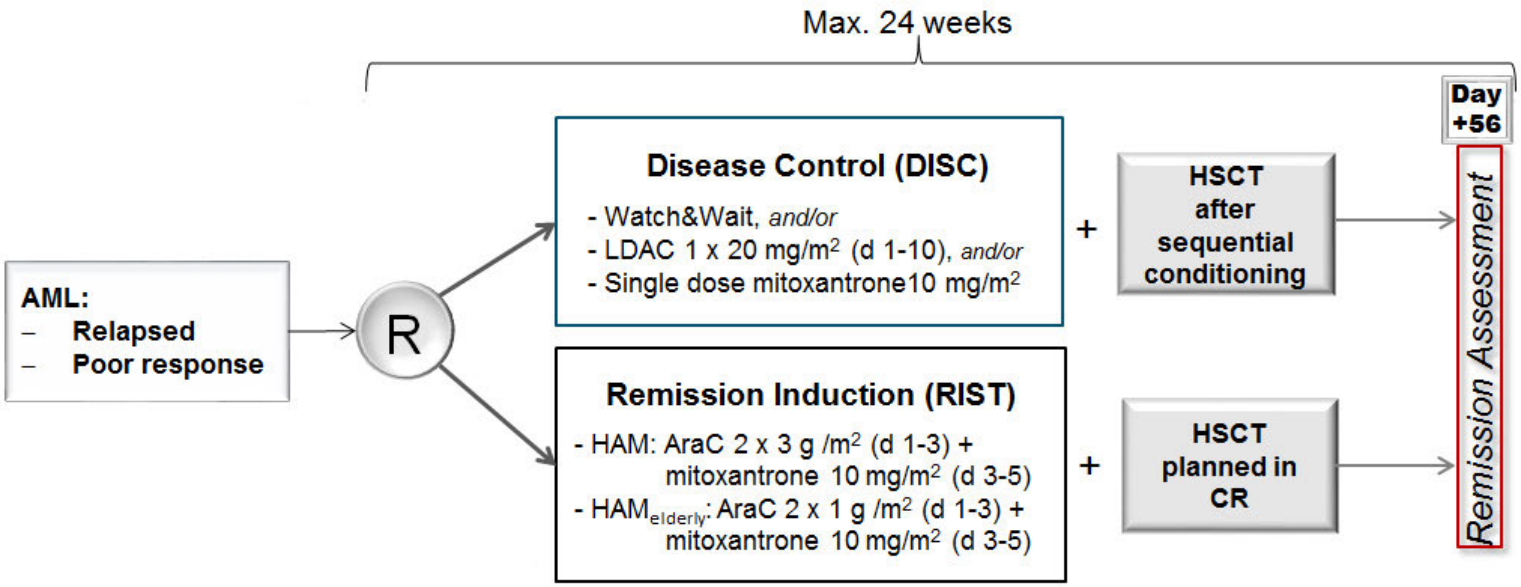

Figure 1. Trial flow chart.

3 Study Assessments

The tables below summarize the study assessments and their respective time schedules.

Table 1. Schedule of Study Visits for Remission Induction Strategy (RIST).

	Baseline	**Induction Treatment**	**Induction Response**	**Remission Assessment**	**Bridging Therapy**	**HCT**[9]	**Final Remission Assessment**	**Annual Follow Up**
	Clinical tests within two weeks prior to randomization, unless otherwise specified in a footnote	Within 7 days after randomisation	Within 21days(+/- 7 days) after start of induction treatment	Within 35 days after start of induction treatment		Within 7 days prior to conditioning	Up to day +56 latest within 24 weeks after randomization	Anually after randomization See Protocol section 9.2.6.
Inclusion/Exclusion criteria Worksheet	x							
Informed Consent	x							
Medical History	x							
AML History	x							
Physical Examination[1]	x[2]	x	x[2]	x[2]	x[2]	x[2]	x[2]	
ECG, ECHO	x[3]				x[3]	x[3]		
Pulmonary Function Test	x[3]				x[3]	x[3]		
HCT-CI Score	x				x	x		
Complete Blood Count	x	x	x	x	x	x	x	
Serum Chemistry[4]	x	x			x	x	x	
Infection Serologies[5]	x							
Bone Marrow Examination	x[6]		x[7]	x[8]		x[10]	x[6, 14,15]	
Central Laboratory	x[6,11]					x[11]	x[6, 11]	
Donor Search Status	x							
Study Treatment		x						
Adverse Events[12]		x	x	x	x	x	x	
Concomitant Medication[13]		x	x	x				

Abbreviations: ECG - Electrocardiogram; ECHO - Echocardiography, HCT-CI score - Hematopoietic Cell Transplantation Comorbidity Index, HCT - Hematopoietic Cell Transplantation.

[1] Also BMI (Body Mass Index) and ECOG.
[2] Detailed documentation of extramedullary manifestations
[3] Echocardiography with a semi-quantitative assessment of the left ventricular ejection fraction.
Baseline: ECHO, Pulmonary function test and ECG may date back up to 28 days, if no clinical signs suggest deterioration of patient's status since that investigation.
Bridging Therapy and HCT: a) ECHO required only if anthracyclines have been administered since last assessment or if clinical signs suggest deterioration of cardiac function; b) ECG required only if patient presents cardiac signs; c) Pulmonary Function Test required only if clinical signs suggest deterioration of pulmonary function.
[4] Analysis of: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH). At baseline and HCT also: Albumin, Ferritin and Fibrinogen (β-HCG pregnancy test for female with child bearing potential at baseline only).
[5] Analysis of: Infectious serology for HBV, HCV, CMV, EBV, HIV and Toxoplasma. Tests may date back up to 28 days, if no clinical signs occur since that investigation.
[6] For central review: at Baseline: one stained bone marrow smear performed from a bone marrow aspirate, done no more than 14 days prior to study randomisation; at Final remission assessment: one stained bone marrow smear
[7] See response criteria definitions in section 10.1.
[8] Remission assessment after induction based on morphological assessment and clinical criteria. Please refer to chapter 10.3 for response definitions
[9] Major characteristics of this procedure will be documented, e.g. final donor, conditioning regimen, GVHD prophylaxis, engraftment, VOD assessment, hospital discharge.
[10] If no bone marrow aspiration done within 14 days prior to start of conditioning regimen or peripheral blood counts are now compatible with CR after induction therapy but a CR after induction therapy had not been documented before.
[11] Ancillary Research: If patient signed informed consent for ancillary research: 5 ml heparinized bone marrow should be collected for central analysis at each time point. To circumvent additional intervention at baseline, stored unstained slides with bone marrow smears before baseline may be used instead or 20 mL of peripheral blood anticoagulated with EDTA which contains more than 10% myeloblasts
[12] Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after last dose of study treatment. Only adverse events Grade 4 and 5 will be documented until Final Remission Assessment.
[13] Concomitant Medication which is given to treat adverse events Grade ≥3 until Day 28 after last dose of study treatment.
[14] Assessment of overall chimerism of the aspirate is recommended in neutropenic or recovering patients.
[15] Bone Marrow Punction for Final Remission Assessment must be performed up to day +56 after HCT.

Table 2. Schedule of Study Visits for Disease Control Strategy (DISC).

	Baseline	**1st Approach Option A or B and/or C**	**2nd Approach Option B and/or C**	**3rd Approach Option B and/or C**	**Bridging Therapy**	**HCT[7]**	**Final Remission Assessment**	**Annual Follow Up**
	Clinical tests within two weeks prior to randomization, unless otherwise specified in a footnote	Within 3 days from randomization	(Optional)	(Optional)	(Optional)	Within 7 days prior to conditioning	Up to Day+ 56 after HCT, latest within 24 weeks after randomisation	Anually after randomization See Protocol section 9.2.6
Inclusion/Exclusion criteria worksheet	x							
Informed Consent	x							
Medical History	x							
AML History	x							
Physical Examination[1]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	
ECG, ECHO	x[3]				x[3]	x[3]		
Pulmonary Function Test	x[3]				x[3]	x[3]		
HCT-CI Score	x				x	x		
Complete Blood Count	x	x	x	x	x	x	x	
Serum Chemistry[4]	x	x	x	x	x	x	x	
Infection Serologies[5]	x							
Bone Marrow Examination	x[6]					x[8]	x[6,12]	
Central Laboratory	x[6,9]					x[9]	x[6,9,13]	
Donor Search Status	x							
Study Treatment		x	x	x				
Adverse Events[10]		x	x	x	x	x	x	
Concomitant Medication[11]		x	x	x				

Abbreviations: ECG - Electrocardiogram; ECHO - Echocardiography, HCT-CI score - Hematopoietic Cell Transplantation Comorbidity Index, HCT - Hematopoietic Cell Transplantation.

[1] Also BMI (Body Mass Index) and ECOG.
[2] Detailed documentation of extramedullary manifestations
[3] Echocardiography with a semi-quantitative assessment of the left ventricular ejection fraction.
Baseline: ECHO, Pulmonary function test and ECG may date back up to 28 days to baseline, if no clinical signs suggest deterioration of patient's status since that investigation
Bridging Therapy and HCT: a) ECHO required only if anthracyclines have been administered since last assessment or if clinical signs suggest deterioration of cardiac function; b) ECG required only if patient presents cardiac signs; c) Pulmonary Function Test required only if clinical signs suggest deterioration of pulmonary function.
[4] Analysis of: Creatinin, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH). At baseline and HCT also: Albumin, Ferritin and Fibrinogen. (β-HCG pregnancy test for female with child bearing potential at baseline only).
[5] Analysis of: Infectious serology for HBV, HCV, CMV, EBV, HIV and Toxoplasma. Tests may date back up to 28 days, if no clinical signs occur since that investigation.
[6] For central review: at Baseline: one stained bone marrow smear performed from a bone marrow aspirate done no more than 14 days prior to study enrollment; at Final remission assessment: one stained bone marrow smear.
[7] Major characteristics of this procedure will be documented, e.g. final donor, conditioning regimen, GVHD prophylaxis, engraftment, VOD assessment, hospital discharge.
[8] If no bone marrow aspiration is done within 14 days prior to start of conditioning regimen
[9] Ancillary Research: If patient signed informed consent for ancillary research: 5 ml heparinized bone marrow should be collected for central analysis at each time point. To circumvent additional intervention at baseline, stored unstained slides with bone marrow smears before baseline may be used instead or 20 mL of peripheral blood anticoagulated with EDTA which contains more than 10% myeloblasts
[10] Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after last dose of study treatment.Only adverse events Grade 4 and 5 will be documented until the end of the study. For watch & wait only: Adverse events CTCAE grade ≥3 will be documented until the start of subsequent anti-leukemic treatment (start of bridging therapy) or start of the conditioning regimen.
[11] Concomitant Medication which is given to treat adverse events Grade ≥3 until Day 28 after last dose of study treatment.
[12] Assessment of overall chimerism of the aspirate is recommended in neutropenic or recovering patients.
[13] Bone Marrow Punction for Final Remission Assessment must be performed up to day +56 after HCT.

4 Background and Study Rationale

4.1 Treatment of high-risk AML

Patients with high-risk acute myeloid leukemia (AML) have a dismal prognosis[1]. This is characterized by poor response to induction chemotherapy at early response assessment, and/or by relapse. For these patients, conventional chemotherapy remains unsatisfactory due to low response rates and high relapse rates[2,3]. Allogeneic transplantation is the standard of care as post-remission therapy for patients who finally achieve a complete remission, and also for patients whose AML turns out to be chemotherapy-refractory.

Many centers attempt to achieve a complete remission by means of aggressive salvage chemotherapy, prior to referring patients for allogeneic transplantation. Most of these aggressive salvage chemotherapies contain high-dose AraC and an anthracycline - often mitoxantrone or idarubicin. Use of this approach is justified by data which indicates that approximately 50% of patients who did not previously reach a CR after continuous infusion AraC, were able to achieve CR following dose escalation of AraC. In parallel, patients with a relapse also often achieve a second complete remission of AML after aggressive salvage chemotherapy, based on high-dose AraC in combination with an anthracycline, despite the fact that they had already received high-dose AraC as part of their previous post-remission therapy. Since aggressive salvage chemotherapy has limited efficacy and is associated with potentially life-threatening toxicities, only a certain fraction of these patients finally reach allogeneic transplantation, whereas other patients die as a result of complications from chemotherapy or refractory AML[4].

This topic has been discussed comprehensively in recently published reviews and subsequent correspondence[5,6]. Moreover, those patients who achieved a complete remission are at high risk of subsequent relapse while waiting for allogeneic transplantation. This second risk of failure is related to the complex and time-consuming process of transplant-coordination, which often includes a referral from a local hospital to a transplant clinic.

Since allogeneic transplantation is the essential part of the treatment of high-risk AML, and transplant procedures have been established for patients with and without residual AML, one important goal is to increase the percentage of patients who can finally take advantage of transplantation.

An alternative path to transplantation has been established in the last decade: In order to reduce the number of patients who are lost due to the excessive toxicity of salvage chemotherapy, other bridging options have been explored[7,8,9,10]. These approaches can be characterized as disease-control strategies, and aim at supportive care and prevention of tumour lysis and leukostasis. Since immediate treatment of AML is often not necessary, especially in patients with relapse or poor induction response, disease-monitoring is the basic approach. Some patients may need cytostatic drugs, such as cytarabine or mitoxantrone. If so, they are given at much lower doses compared to aggressive salvage chemotherapy.

This study addresses the question of whether an attempt made to induce a complete remission in high-risk AML patients is beneficial or harmful. Since outcome after transplantation is mainly the result of undefined selection processes, the only way to answer this question is to compare both approaches in a randomized controlled trial.

4.2 Risks and benefits of remission induction chemotherapy

Most protocols used for first aggressive salvage chemotherapy contain high-dose cytarabine. This drug has been the most effective agent in the treatment of AML for more than three decades now [11]. The cytotoxic effect of Ara-C depends on step-by-step phosphorylation to Ara-C-triphosphate (Ara-CTP). The rate-limiting enzyme that catalyzes the first step is the cytoplasmatic deoxycytidine kinase. Prompted by the observation that further increase of intracellular concentration of Ara-CTP can be achieved upon pre-treatment with fludarabine, combination protocols were developed[12]. However, significantly higher complete remission rates or a survival advantage of fludarabine-cytarabine combinations compared to cytarabine alone could not be demonstrated in two randomized controlled trials[13,14]. However, fludarabine-cytarabine combinations remain very popular in many AML centers of excellence, based on interpretation of point-estimates and secondary endpoint analyses which slightly favour the combination regimen.

Finally, different anthracyclines have been added. While daunorubicin is usually given during the first-line induction chemotherapy, most salvage regimens contain either idarubicin or mitoxantrone as alternative anthracyclines which are not cross-resistant.

Generally, aggressive salvage chemotherapies result in response rates between 40% and 60% in relapsed AML or poor induction response[11,14,15,16,17]. Direct randomized comparisons between the three most favoured regimens (FLAG-Ida, Mito-FLAG and HAM) do not exist. The efficacy and safety profiles of these regimens are assumed to be

comparable. Due to logistical reasons and quality management, only HAM will be used in this study.

HAM

Mitoxantrone has also been used in various combinations with high and intermediate-dose cytarabine (the HAM regimen), both with and without etoposide[18-20]. In one series of 47 patients with recurrent or refractory AML, the combination of mitoxantrone (5 mg/m^2 per day for five days) and intermediate-dose cytarabine (0.5 g/m^2 IV every 12 hours for six days) resulted in a complete remission rate of 62 percent, but the median duration of remission was only 3.7 months[21]. Ninety-six percent of those achieving complete remission (CR) eventually relapsed. Three patients ≥60 developed acute cerebellar toxicity.

Larson et al. performed a retrospective analysis on 78 high-risk AML patients treated with a combination of high-dose cytarabine and mitoxantrone from 2001 to 2008[22]. Overall response was 55% and induction death rate was 9%. Interestingly, the CR rate and risk of induction death of relapsed /refractory patients were equivalent to de novo AML patients within this series.

In a multivariate analysis of prognostic factors in 254 patients with refractory and relapsed acute myeloid leukemia undergoing HAM salvage therapy, the duration of the first remission was the only factor associated with time to treatment failure (P<0.0001), while disease-free survival was influenced by a short duration of the first CR of less than 6 months (P = 0.0001), WBC (P = 0.0018), blast count (P = 0.0037), and neutrophil count[23].

4.3 Disease-control prior to HCT

AML leads to bone marrow failure and related complications including severe infections, anemia, and bleeding. From a clinical point of view, AML is very heterogeneous. The clinical presentation may vary from moderate and well-tolerated cytopenias to highly proliferative states with extramedullary involvement that are sometimes complicated by severe coagulopathy, leukostasis, or metabolic disturbances requiring immediate therapeutic intervention.

Two large retrospective analyses have addressed the question of whether time to treatment, defined as time from diagnosis (TDT) to start of first-line intensive induction chemotherapy, is associated with the complete remission rate and overall survival[24,25]. No information is provided about structured disease-control measures.

Remarkably, in patients 60 years of age or older, TDT did not appear to affect CR or OS rates in both publications. Subgroups of older adults in whom delay had an impact could not be identified. In the publication from the US published by Sekeres et al, in patients below the age of 60 years, outcome appeared to worsen particularly with treatment delays of 5 days or greater, a delay that occurred in 41% of younger patients. The authors considered that the greater efficacy of Ara-C-based first-line induction chemotherapy in younger patients compared to older patients could explain the marked difference in the impact of the delay. If this explanation was correct, treatment delay should not impact on CR or OS in patients in whom first-line chemotherapy failed, i.e. the population selected for this protocol. In the publication from France published by Bertoli et al, TDT was not associated with early death rates, CR and OS.

Owing to the retrospective nature of these analyses, and hence the inability to know all the factors that entered into the decision to delay treatment, the results must be interpreted with caution. Reasons for treatment delay were probably concomitant disease, transport times from a tertiary care facility or a lack of health insurance coverage. These are factors which clearly affect survival. So it cannot be excluded that a long time from diagnosis to start of induction therapy is only a surrogate for other negative prognostic markers.

In summary, based on the current knowledge it appears to be safe to delay first-line treatment in AML. This should be even more applicable for patients who failed first-line therapy or present with relapsed AML. In this trial, patients will be observed. Furthermore, patients may optionally receive Low dose Ara-C (LDAC) or mitoxantrone which both have proven anti-leukemic activity.

Low dose Ara-C (LDAC)

The value of LDAC (defined as either 20 mg bid or 20 mg/ m^2 qd) has been demonstrated in several randomized controlled trials. So far, no alternative drug has proved to be superior in terms of safety and efficacy compared to a ten day schedule of LDAC in elderly or frail patients. Data on LDAC in young patients who are treated with curative intent do not exist.

A recent randomized comparison between Clofarabine (20mg/m^2 days 1-5, 4 courses) and LDAC (20 mg bid days 1-10, 4 courses) in a group of 406 patients with a median age of 74 years, showed equivalent OS for both regimens. Although Clofarabine doubled the remission rate when compared to LDAC, this was at the cost of more toxicities and supportive care. The day 30 mortality was 13% after LDAC compared to 18% after Clofarabine[26].

The UK LRF AML14 trial randomized 217 older patients who were unfit for intensive chemotherapy, to receive LDAC (20 mg bid days 1-10, 4 courses) or hydroxiurea with or without all-trans retinoic acid (ATRA). The schedule of Ara-C for 10 days was superior to supportive care in terms of better remission rate (18% vs. 1%; odds ratio [OR], 0.15; 95% confidence interval [95% CI], 0.06-0.37; P = .00006), better overall survival (OR, 0.60; 95% CI, 0.44-0.81; P = .0009) and duration of CR of 80 weeks vs. 10 weeks with no evidence of extra toxicity[27].

In a recent multi-center, randomized, open-label, phase III trial comparing the efficacy and safety of decitabine with treatment choice (TC), 485 older patients (lower age limit 64 years, median age 73 years) with newly diagnosed acute myeloid leukemia (AML) and poor- or intermediate-risk cytogenetics were enrolled. Patients were randomly assigned 1:1 to receive decitabine 20 mg/ m^2 per day as a 1-hour intravenous infusion for five consecutive days every 4 weeks or TC (app. 10% of patients received supportive care and 90% cytarabine 20 mg/ m^2 per day as a subcutaneous injection for 10 consecutive days every 4 weeks). The primary end point was overall survival (OS); the primary analysis showed a non-significant increase in median OS with decitabine versus TC. The CR rate was 18% with decitabine versus 8% with TC (p= .001). Adverse events were comparable for decitabine and cytarabine. Within 30 days after the first treatment, 9% of decitabine recipients and 8% of cytarabine recipients died [28-35].

Mitoxantrone

Mitoxantrone is an intravenous anthracenedione, structurally related to anthracycline antibiotics. It is active in AML cell lines resistant to daunorubicin and other alkylating agents[36]. Various treatment schedules, using mitoxantrone alone and in combination with other anti-leukemic agents, have been used in clinical trials[37]. Complete remission (CR) rates ranged from 14 to 44% in refractory AML and from 46 to 79% in relapsed patients. Although a superiority of mitoxantrone over anthracyclines has not been demonstrated in patients with newly diagnosed AML, mitoxantrone is recognized as a useful drug in first-line and salvage therapy[38]. It has demonstrated single-agent activity, even in patients who failed pre-treatment[39].

4.4 Donor search and HCT coordination

Once the indication for allogeneic HCT has been settled, donor search becomes a major task and eventually a factor which determines treatment. Allogeneic transplantation depends on the availability of an HLA compatible hematopoietic stem cell donor. By

Mendelian laws, siblings are HLA matched with 25% chance. Non-sibling relatives are matched with a much lower probability (<0.1%). Therefore, the chance to find a matched related donor almost exclusively depends on the number of siblings. With smaller families today compared to 40 years ago, the overall chance for a successful search within the family declines. Currently, matched related donors can be identified for about 20% of the patients in Germany. The remaining patients have to rely on Unrelated Donor Search (UDS) or alternative options for allogeneic transplantation.

Today, 13,800,000 donors are enrolled worldwide in bone marrow donor registries, and over 4,400,000 are registered at the German Bone Marrow Donor Center (DKMS gGmbH).

In a retrospective single center analysis on donor searches for Caucasian German patients, an HLA compatible unrelated donor (UD) (8/8) had been found for 29% (95% CI, 26% to 32%) of the patients within two weeks, 54% (95% CI, 51% to 58%) of patients within 4 weeks, and 61% (95% CI, 57% to 64%) of patients within 6 weeks [40]. In high risk diseases and high urgent indications for allogeneic transplantation, a partially mismatched UD (9/10) with one antigen or allele mismatch may be acceptable. The resulting probabilities of finding a matched or partially mismatched unrelated donor were 35% (95% CI, 32% to 39%), 66% (95% CI, 63% to 70%) and 75% (95% CI, 72% to 78%) at two, four, and six weeks respectively. After six weeks of UDS, the probability of finding a donor declined in that analysis.

The duration of the donor search process is determined by several institutions, the transplant center, and eventually the insurance company, the search unit, the registry and the donor center. In Germany, after failing a related donor search, the transplantation center assigns the unrelated donor search to a Search Coordinator (SC). A guarantee that the health insurance company will cover the expenses for the donor search has to be obtained. In patients above the age of 69 years a positive vote from the “clearing agency” is needed. Usually, a first HLA matching program is run on the data of the Bone Marrow Donors Worldwide (BMDW) Match Program by the SC. The resulting list of possibly matching donors is used to contact national search centers - in Germany the Zentrales Knochenmarkspender-Register Deutschland (ZKRD) - giving rise to a second, national donor list. Incomplete HLA phenotype information of potentially matching donors needs to be accomplished - depending on the quality of baseline HLA-typing at registration of that specific donor. This request is communicated via the national search registry to the corresponding donor center. Typing may be done from stocked samples or from fresh blood samples or buccal swabs the donor has to be asked to provide. The results are communicated to the donor’s center which commissioned the typing. Then the information

is passed over the national search registry to the SC. For Confirmatory Typing (CT), the same channels are used to contact the donor and provide him or her with a blood extraction kit. A blood sample is taken at his family doctor and directly sent back to the SC via a messenger to get the CT from the same laboratory as the patient's initial typing. Only after this obligatory step, a donor may be decided on as "identified" and be called for work-up. After CT, a careful medical check has to confirm the ability of the donor to donate either Bone Marrow (BM) or Peripheral Blood Stem Cells (PBSC). In the case of medical contraindications, an alternative donor has to be searched for.

More recently, Urgent Combined CT and Work-up (UCCW) has been established as an expedited search process in Germany. Pre-requisites for this process are that the patients have been typed at high-resolution for 5 loci, the potential donor has the same nationality with the patient, high-resolution data on the donor HLA-type is available, and the OptiMatch probability for a match is 90% or higher.

Current software provided by donor registries allows the estimation of matching probabilities for donors listed on the BMDW-report. Since only patients may be recruited who have at least one matched unrelated donor with an 8/8 matching probability of >90% and two more back-up donors with an 9/10 matching probability of >90%, it is expected that the median time to donor identification at the CT-level will be two weeks. The expected median time to transplantation can be less than 5 weeks in the population selected for this clinical trial.

Transplant coordination is further complicated by the clinical course. With the aim to achieve a complete remission, the timing of allogeneic transplantation is conditional to a number of assumptions on hematopoietic reconstitution and physical recovery of the patient from aggressive salvage chemotherapy. If this strategy fails – which happens frequently due to the limited efficacy and toxicity of salvage chemotherapy – optimal timing of allogeneic transplantation is compromised.

During the last decade, a variety of preparative regimens has been established for patients with various levels of residual disease and different clinical conditions. Preparative regimens are available for patients with and without residual morphological disease as for patients in CR or aplasia after chemotherapy. So far, superiority of one conditioning regimen over the other has never been demonstrated with proper methodology in a randomized controlled trial. As a result, a variety of different regimens which are similar with respect to major outcomes has been established.[7,8,41-45].

4.5 Risk-benefit assessment

Two aspects deserve consideration: risks and potential benefits associated with intensive induction chemotherapy, and risks and benefits associated with the omission of this treatment.

With respect to intensive induction chemotherapy, Day 30 mortality is around 10% in the selected population[14,22,46-49]. Major causes of death are sepsis and bleeding episodes. The frequency of non-lethal severe complications which prevent subsequent treatment, especially allogeneic HCT, is not a standard endpoint which is reported for clinical trials. This rate ranges between 5% and 20% depending on the aggressiveness of the pharmacologic approach.

The success rate of intensive induction chemotherapy in terms of a complete remission is around 50%. When compared to patients with residual morphologic disease, patients who achieve and maintain a remission may have an advantage at the time of transplantation which may translate into better long-term disease control; this advantage is uncertain, however. For example, the value of post-remission chemotherapy (treatment given to further reduce the amount of residual leukemic cells) is questionable[50,51]. In a CIBTMR study, outcomes after reduced-intensity or non-myeloablative conditioning were compared based on exposure to cytarabine post remission chemotherapy[52]. Multivariate regression analyses confirmed no effect of consolidation on relapse, disease-free survival and survival. Before reduced-intensity or non-myeloablative conditioning HCT, these data suggest that pre-HCT consolidation cytarabine does not significantly alter outcomes. Moreover, for patients with RAEB II (Refractory Anemia with Excess Blasts) or secondary AML the value of induction chemotherapy prior to allogeneic HCT is questionable. Data from 125 patients with advanced MDS and tAML who received transplants from HLA-identical related or unrelated donors after preparation with myeloablative conditioning regimens were reviewed at the FHCRC[53]. Thirty-three patients (3 with RAEB, 6 with RAEB-T, and 24 with tAML) received induction chemotherapy before transplantation, and 92 patients (62 with RAEB, 22 with RAEB-T, and 8 with tAML) did not. Seventy-six patients were conditioned with oral busulfan 16 mg/kg, which was adjusted to achieve steady-state plasma concentrations of 800 to 900 ng/mL, plus cyclophosphamide 2 x 60 mg/kg, and 49 patients received busulfan 7 mg/kg (without dose adjustment) and total body irradiation 6 x 200 cGy given over 3 days. There was no evidence of a benefit in post transplantation outcome associated with prior IC, neither for patients with RAEB/RAEB-T nor for those with tAML, with either conditioning regimen.

Patients who fail to achieve a remission and those who relapse prior to the subsequent treatment may have a disadvantage from accumulation of toxicity caused by intensive induction chemotherapy.

With respect to the watch and wait strategy of experimental treatment, limited or no treatment-related risk exists. If the investigator decides to stop the watch and wait strategy and to start a low-toxicity bridging therapy, treatment-related mortality will still remain very low, because no aggressive attempt is made to reduce the leukemic burden. In turn, complications may directly be linked to a poorly controlled leukemia. Patients will mainly remain at an elevated risk of infection due to direct (e.g. neutropenia) and indirect effects (compromised function of the immune system) of the leukemia. Furthermore, patients can develop complications from progressive leukemia, e.g. extramedullary disease or leukostasis.

The proliferative potential of an individual leukemia cannot be reliably predicted. If the leukemia turns out to be highly proliferative during the watch and wait period, aggressive induction chemotherapy may become necessary to prevent subsequent complications. According to clinical experience this will happen in approximately 5% of patients. These patients may not benefit from the initial watch and wait approach. As a safety measure, patients with WBC-counts of ≥50 GPt/L will be excluded from this protocol[24,25].

If the leukemia turns out to be smoldering, however, the patients may benefit from the watch and wait strategy because they circumvent treatment-related mortality of the aggressive induction chemotherapy and severe complications which prevent the subsequent treatment.

4.6 Why is randomization needed?

Whether there is an effect of the amount of residual leukemic cells at the time of transplantation on the outcome after transplantation cannot be answered, because data from randomized trials do not exist. Although data from retrospective studies is available which describes that the level of minimal residual disease is associated with outcome after allogeneic transplantation, this data should not be misinterpreted as evidence for the value of induction chemotherapy. Retrospective data are subject to selection bias in such a way that those patients with least aggressive disease exhibit the lowest level of minimal residual disease at the time of transplantation, whereas patients with higher levels of residual disease, or even relapse after the same treatment, by nature have more aggressive disease. This is one example of a common mistake, wherein an association

observed in epidemiologic research is interpreted as causal relationship. The question whether it is beneficial to attempt to achieve a CR prior to HCT in high-risk AML can only be addressed in a prospective randomized trial. This question will be addressed in the ETAL3-ASAP trial.

5 Study Design and Objectives

The aim of this trial is to compare two treatment strategies: The research question is whether an attempt to achieve a CR by intensive induction chemotherapy in patients with relapsed AML or poor response AML is beneficial or harmful.

On one hand, registry data suggest that long-term survival is better in patients who were transplanted in complete remission, compared to patients who were transplanted with residual AML. On the other hand, extensive data have been published in recent years, where sequential treatment approaches without documented complete remission prior to HCT have been very successful. Due to complex selection effects, the overall impact of these strategies on the average treatment success cannot be assessed from the literature. Whether a CR should be attempted prior to HCT in this patient population is a crucial question. This question affects daily clinical practice. The results of this study are potentially practice-changing.

5.1 Testing for non-inferiority

The objective of this trial is to compare two treatment strategies in patients with high-risk AML who failed to achieve or maintain a complete remission with standard therapy. Patients will be randomized between the standard strategy aiming at achieving a CR by aggressive salvage chemotherapy, and a less toxic disease-control strategy prior to transplantation. The sample size of this study has been calculated in order to demonstrate non-inferiority of the less toxic treatment strategy. According to the basic principle of “First, do no harm”, the demonstration of the non-inferiority of the less toxic treatment strategy should be sufficient to change clinical practice. If the assumptions for this trial hold, the use of aggressive chemotherapy prior to HCT could be limited and repetitive periods of hospitalization could potentially be prevented.

5.2 Blinding

The study will be open and conducted at multiple centers. Blinding of the study treatment is impossible due to large differences between the two treatment schedules. In order to rule out a potential observation bias, all marrow aspirates of the final remission assessment will be analysed centrally , and slides will be reviewed by an independent experienced morphologist in a blinded fashion.

5.3 Choice of endpoints

According to the scientific guidelines on clinical trials in cancer from the European Medicines Agency (EMEA)(CPMP/EWP/205/95/Rev.4), the most relevant endpoint in AML is overall survival (OS). The complete remission rate is also broadly accepted as a standard primary outcome measure for phase III trials in AML, since achievement of complete remission has been linked in multiple trials to increased overall survival.

In this specific study, two different strategies for bringing patients to allogeneic HCT are compared. Both strategies will lead to long-term disease control in a certain fraction of patients. Importantly, allogeneic HCT is the most effective treatment in the study population. The fraction of patients who proceed to an allogeneic HCT can thus be regarded as a safety endpoint which reflects the toxicity of the bridging treatment. Transplantation itself, however, does not per se imply disease eradication. Thus disease-free survival at Day 56 after HCT has been selected as the primary endpoint, since a complete remission after HCT can be interpreted as a successfully completed treatment.

The comparison of disease-free survival after HCT at Day 56, according to the intent-to-treat principle and in the per-protocol population, will be complemented by analyses of overall survival by intent-to-treat based on observational data.

5.4 Primary Endpoint

The primary endpoint is disease-free survival on Day 56 after allogeneic HCT.

The endpoint consists of two components:

- Patients must have received allogeneic HCT.
- Patients have to be free of disease at Day 56 after HCT.

This endpoint is a composite endpoint reflecting treatment success. Patients who do not have a confirmed complete remission by Day 56 after HCT, and patients with early relapse before Day 56 after HCT, will be counted as failures. Also, patients who have not been transplanted within 16 weeks from randomization will be counted as failures.

5.5 Secondary Endpoints

Covariate adjustment for disease-, patient- and donation-related risk will be considered for all secondary analyses. Overall survival is considered as a major secondary outcome to test for long-term consequences of the initial treatment decision. Information on the follow-up of patients beyond the final remission assessment is not part of the clinical trial, but will be collected within an observational study.

The following endpoints will be analysed according to the intent-to-treat:

- Effect of study treatment on overall survival and overall survival at the following time-points: 4 weeks, 8 weeks, and 24 weeks from randomization.
- Rate of allogeneic transplantation at 4 weeks, 8 weeks, and 16 weeks from randomization.
- Incidence of CR at 4 weeks, 8 weeks, and 24 weeks from randomization.
- Leukemia-free survival.

The following endpoints will be compared in per-protocol treated patients according to treatment arm:

- Overall Survival after HCT.
- Event-Free Survival after HCT.
- Leukemia-Free Survival calculated in CR-patients from final remission assessment after HCT.

Furthermore, the following analyses will be performed exclusively in the Remission-Induction Strategy (RIST) arm, to describe the sequence of events under standard treatment:

- Complete remission-rate after induction chemotherapy.
- Relapse prior to transplantation in patients who achieved a CR.

Further, analyses will be performed to describe bottle-necks during donor search and

activation:

- HLA-compatible donor availability at 4 weeks, 8 weeks, and 16 weeks from randomization.
- Final Matched Donor Clearance at 4 weeks, 8 weeks, and 16 weeks from randomization.

6 Time schedule

Table 3. Time schedule

First Patient First Visit (FPFV):	Q3 2015
Last Patient Last Visit (LPLV):	Q3 2022
Report on Confirmatory Analysis:	Q3 2023
Report on Long-Term Outcome:	Q1 2025

7 Study population

Patients will be enrolled in two strata defined by their AML treatment status (poor responders and relapsed). The unifying characteristic of both patient groups is that the AML responded poorly to chemotherapy. In the relapsed patient group, relapse itself serves as an indicator that chemotherapy was not able to eradicate the disease, whereas in the group of poor-responders to induction chemotherapy, the poor response indicates limited efficacy of chemotherapy.

7.1 Inclusion criteria

Eligible patients must fulfill all of the following criteria:

- Signed written informed consent.
- Male and female patients of 18 to 75 years of age.

- Diagnosis of AML according to WHO criteria.

- No known history of chronic pulmonary disease and absence of dyspnea. Otherwise, documented diffusion lung capacity for carbon monoxide (DLCO) ≥40% (adjusted for hemoglobin, if available) and FEV1/FVC ≥ 50%.

- Patient is fit for aggressive induction chemotherapy and transplantation by assessment of an experienced hematologist.

- HLA-identical sibling.

  or

  HLA-compatible (≥9/10 antigens matched for HLA-A, -B, -C, -DRB1, and –DQB1) unrelated donor with completed confirmatory typing.

  or

  Two unrelated donors with >90% probability of a 9/10 match for HLA-A, -B, -C, -DRB1, and –DRQB1, according to OptiMatch® list.

- ***Relapse patients***:

  First AML relapse, defined as ≥5% bone marrow blasts and / or extramedullary AML manifestation.

  or

  Poor responders with ≥5% bone marrow blasts after the first cycle of induction therapy and one of the following subtypes/risk groups of AML:

  AML that evolves from previously documented myelodysplastic syndrome (MDS) or after a Myeloproliferative Neoplasia (MPN)

  or

  Diagnosis of therapy-related myeloid neoplasm (t-MN)

  or

  Non favourable risk AML according to ELN-criteria.

7.2 Exclusion criteria

- Acute promyelocytic leukemia (APL).
- WBC count of ≥50 GPt/L at study inclusion.
- For poor-responder patients, the first cycle of induction therapy contained High Dose Cytarabine (HDAC), defined as bolus cytarabine at single-doses of >1g/m^2.
- Patient has received more than 440 mg/m^2 daunorubicin equivalents. The cumulative dose is calculated by summing up isotoxic daunorubicin-equivalents for daunorubicin, doxorubicin, epirubicin, idarubicin and mitoxantrone. The conversion factors are derived from the comparison of the respective maximum doses. The conversion factor is 1 for daunorubicin, 1 for doxorubicin, 0.6 for epirubicin, 4.6 for idarubicin, and 2.7 for mitoxantrone (see worksheet for calculation).
- Severe organ dysfunction, defined as any of the following:
  - Left ventricular ejection fraction <50%.
  - Patients who receive supplementary continuous oxygen.
  - Serum bilirubin >1.5 x ULN (if not considered Gilbert-Syndrome) or ASAT/ALAT >5 x ULN.
  - Estimated Glomerular Filtration Rate (GFR) < 50 ml/min, where:

    Estimated GFR (ml/min/1.73 m^2) = 186x (Serum Creatinine)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if patient is female) x (1.212 if patient is black)
- Treatment with any investigational drug within 10 days before study entry.
- Uncontrolled infection at the time of enrollment.
- History of allogeneic transplantation.
- Manifestation of AML in the Central Nervous System (CNS).
- Pregnant or breastfeeding women.
- Men unable or unwilling to use adequate contraception methods from enrollment to a minimum of six months after the last dose of chemotherapy. Before contraception methods can be stopped a medical doctor should be consulted.

- Women of childbearing potential except those who fulfill the following criteria:
  - Post-menopausal (12 month of natural amenorrhoea or 6 months of amenorrhoea with Serum Follicle Stimulating Hormone (FSH) > 40 U/ml) or;
  - Postoperative (6 weeks after bilateral ovariectomy with or without hysterectomy) or;
  - Continuous and correct application of a contraception method with a Pearl Index <1% (e.g. implants, depots, oral contraceptives, intrauterine device – IUD) or;
  - Sexual abstinence or;
  - Vasectomy of the sexual partner.

  Before contraception methods can be stopped, a medical doctor should be consulted.

8 Treatment plan

The goal of this study is to test the value of aggressive salvage chemotherapy aiming at the achievement of a complete remission, prior to allogeneic HCT in the specific study population. The trial tests the hypothesis that a less toxic disease-control strategy is not inferior, compared to aggressive chemotherapy attempting to achieve a CR prior to an allogeneic HCT with respect to the CR-rate after allogeneic transplantation.

8.1 Investigational drugs

8.1.1 Cytarabine

8.1.1.1 Characteristics

Cytarabine belongs to the group of chemotherapeutic agents called antimetabolites. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Cytarabine is not active orally.

8.1.1.2 Drug formulation, availability and preparation

Cytarabine is commercially available as ARA-cell® (cellpharm) in vials / bottles as 40 mg /100 mg/ 1000 mg / 4000 mg / 5000 mg /10.000 mg sterile solution (2 ml/5 ml/20 ml/80 ml/ 50 ml/ 100 ml) for preparation of diluted infusion solution. Cytarabine powder is reconstituted with sterile water for injection or 0.9% sodium chloride for injection. Solutions reconstituted with bacteriostat should not be used for IV administration of high dose cytarabine (> 1 g/m^2), as are used in this study. Solutions for parenteral administration should be reconstituted to a concentration of 100 mg/ml. Reconstituted solutions are further diluted in D5W (dextrose 5% water) or 0.9% sodium chloride for IV infusion. Intact vials should be stored at room temperature 15-30°C (59 to 86°F). Solutions reconstituted with bacteriostatic diluents for infusion are stable for 8 days at room temperature.

In this trial, cytarabine is administered as a continuous infusion to prevent nausea and vomiting. The infusion should not be interrupted for the delivery of blood products, antibiotics, etc. Please refer to protocol section 8.2 und 8.3 for detailed drug dosage and administration.

8.1.1.3 Toxicities

A cytarabine syndrome has been reported to occur in patients. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, the use of corticosteroids should be considered as well as continuation of therapy with cytarabine.

Like other cytotoxic drugs, cytarabine may induce anemia, leukopenia, thrombocytopenia and hyperuricemia secondary to rapid lysis of neoplastic cells. Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

Severe and at times fatal central nervous system, gastrointestinal and pulmonary toxicity has been reported following high dose schedules of cytarabine. These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with local corticosteroid eye drops; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, pulmonary edema, and liver damage with hyperbilirubinemia. Rarely, severe skin rash, leading to desquamation has been reported.

The most common adverse reactions reported with cytarabine (“usual dosage” e.g., ≤ 200 mg/m^2/day) include hematologic, gastrointestinal, dermatologic, and hepatic reactions. Myelosuppression includes neutropenia, thrombocytopenia and anemia. Cytarabine is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in >10% of patients receiving cytarabine. Alopecia is common. Rash, including hand-foot syndrome, is reported also. Mild jaundice and elevated transaminase levels also are reported in >10% of patients.

Dose-reduction of cytarabine for patients with liver or hepatic insufficiency is recommended if administered in high doses in order to decrease the risk of neurotoxicity.

Please refer to the prescription information for more detailed information on cytarabine.

8.1.2 Mitoxantrone

8.1.2.1 Characteristics

Mitoxantrone is a synthetic anthracenedione that is structurally similar to doxorubicin and daunorubicin. It was synthesized with the goal to reduce anthracycline side effects, particularly cardiotoxicity. Mitoxantrone inhibits DNA repair by inhibiting topoisomerase II which results in fragmentation of DNA. Mitoxantrone is an immunosuppressive agent that may also generate free radicals, inhibit protein kinase C, cause electrostatic DNA cross-links, and induce apoptosis. Although maximally cytotoxic in the S-phase, mitoxantrone is not cell cycle phase-specific. Cross-resistance with anthracyclines has been demonstrated.

Oral absorption is poor and it is distributed extensively. It binds to proteins in >95%, and it is eliminated via urine (6-11%; 65% unchanged) and feces (25%; 65% unchanged).

8.1.2.2 Drug formulation, availability and administration

Mitoxantrone is available as a dark blue, aqueous concentrate for solution for intravenous infusion. Each 1ml contains mitoxantrone hydrochloride equivalent to 2.0mg mitoxantrone. After reconstitution, the solution is stable at 25 °C for maximum 4 days.

The required volume of Mitoxantrone sterile concentrate should be diluted to at least 50 ml in either sodium chloride 0.9% or glucose 5% infusion solutions.

The resulting solution should be administered slowly via the tubing of a freely running intravenous infusion of the above fluids. Mitoxantrone should not be mixed with other drugs in the same infusion.

If possible, a well-placed central intravenous line should be used. Peripheral veins over joints or in extremities with compromised venous or lymphatic drainage should be avoided. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes or eyes. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein. During intravenous administration of mitoxantrone, extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

8.1.2.3 Special warnings

Mitoxantrone is contraindicated in patients who have demonstrated prior hypersensitivity to mitoxantrone hydrochloride, other anthracylines or any of its components.

MITOXANTRONE SHOULD NOT BE ADMINISTERED SUBCUTANEOUSLY.

Cardiotoxicity risk increases with cumulative anthracyclines dose and may occur whether or not cardiac risk factors are present. Presence or history of cardiovascular disease, radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or use of other cardiotoxic drugs may increase this risk. Cumulative dose recommendation for minimizing the occurrence of cardiomyopathy is 200 mg/m^2 in patients without cardiac risks factors, and no prior anthracycline exposure. If previous anthracycline therapies are documented, dosage reduction must be considered.

Careful supervision is recommended when treating patients with hepatic insufficiency. In patients with hepatic impairment (bilirubin >3,5 mg/dl) the initial dose must be reduced based on clinical judgement.

No dose reduction recommendations have been established in the case of mild renal insufficiency.

Full blood counts should be undertaken serially during a course of treatment. Dosage adjustments may be necessary based on these counts (see prescription information).

8.1.2.4 Toxicities

Common side effects when administering mitoxantrone are decreased left ventricular ejection fraction, ECG changes, acute arrhythmia, leucopenia and thrombocytopenia. Undesirable non-specific neurological effects such as somnolence, neuritis, confusion, convulsion, anxiety and mild paresthesia have been reported.

Alopecia (11 %), diarrhea (9-13%), fever, nausea or vomiting (8%), stomatitis/mucositis (9-29%) and hepatitis (8%) are also frequent.

Please refer to the prescription information for more detailed information on mitoxantrone.

8.2 Remission-Induction Strategy (RIST)

Intensive induction chemotherapy with the goal to achieve a CR is considered to be standard in patients with relapsed AML or poor early treatment response prior to allogeneic HCT (see www.sal-aml.org or www.dgho-onkopedia.de)[3,54,55]. In the absence of randomized controlled trials demonstrating superiority of one salvage regimen over the other, different induction chemotherapies are currently used. Generally, the administration of cytarabine for 3-5 days at intermediate (1 g/m^2) or high (3 g/m^2) dose levels (HDAC) is considered to be the backbone of salvage chemotherapy. HDAC is usually combined according to local practice with different anthracyclines and/or fludarabine.

Three regimens, FLAG-Ida, HAM and MitoFLAG are most frequently used in Germany.. High-dose Ara-C in combination with mitoxantrone (HAM) contains only drugs which are approved for the treatment of AML. A convenient dosing schedule for elderly patients is established. For these reasons HAM will be given as remission-induction chemotherapy.

Strict intravenous administration of Mitoxantrone via a central intravenous line or confirmed intravenous peripheral access must be ensured due to the toxic reaction of paravasates.

With respect to potential cardiotoxicity of mitoxantrone, a cumulative dose of 30 mg/m^2 mitoxantrone represents approximately 15% of the maximum tolerable cumulative dose. Three single doses of mitoxantrone 10 mg/m^2 can thus be tolerated in patients who received a maximum of 80% of the maximum cumulative anthracycline dose during their life-time.

Dose-reduction of cytarabine for patients with liver or hepatic insufficiency is recommended if administrated in high doses in order to decrease the risk of neurotoxicity.

Generally, administration of antiemetics, adequate hydration and monitoring for tumor lysis is indicated. Further, in the context of HDAC therapy prophylaxis of conjunctivitis is mandatory. The administration of G-CSF is not recommended.

Table 4. HAM regimen

For patients ≤60y

Days	**1**	**2**	**3**	**4**	**5**
Cytarabine i.v. 3 g/m^2 over 3h every 12 hours	X X	X X	X X		
Mitoxantrone i.v. 10 mg/m^2			X	X	X

For patients >60y

Days	**1**	**2**	**3**	**4**	**5**
Cytarabine i.v. 1 g/m^2 over 3h , every 12 hours	X X	X X	X X		
Mitoxantrone i.v. 10 mg/m^2			X	X	X

8.2.1 Evaluation of remission induction

Early induction response (see definitions in chapter 10.1) should be assessed by a bone marrow aspirate or histology within 21 days (+/- 7 days) after start of induction treatment.

Patients with a *morphologic leukemia-free state* at the early response assessment will have a subsequent remission assessment. This remission assessment must be performed within 35 days after start of induction therapy, to confirm a complete remission. If at the time of the early induction response assessment the patient has already experienced hematological recovery, this will be considered the remission assessment and

documented in the CRF accordingly. A further bone marrow examination is not required in this case.

Patients with a *moderate early reponse* may be given a further response evaluation within one week in order to exclude the possibility of increasing bone marrow blast counts.

- Patients who have stable or decreasing blast counts will have a remission assessment within 35 days after start of induction therapy.
- Patients found to have increasing blast counts at this further assessment should be considered to be experiencing early induction failure.

Patients who show *no response* at early response assessment will be considered as having early induction failure.

Patients with early induction failure and patients who failed to achieve a complete remission should be treated according to investigator's discretion while considering the individual treatment history, comorbidity and physical performance of the patient. Generally, these patients should not be subject to additional attempts to induce a complete remission with aggressive chemotherapy. Allogeneic transplantation should be scheduled without delay.

Patients who achieve a complete remission should be scheduled for allogeneic transplantation in complete remission without delay.

8.3 Disease-Control Strategy (DISC)

A second standard approach prior to a planned allogeneic HCT is not to achieve a CR prior to allogeneic HCT, but to simply monitor the disease or to stop proliferation by low-dose cytarabine. Allogeneic transplantation should be scheduled as soon as possible in order to keep the time covered by the disease-control strategy as short as possible. Ideally, patients should be referred to a transplant center immediately. If the patient has been enrolled at a trial site which does not perform allogeneic HCT, the transplant center should be informed about the necessity to proceed with HCT as soon as possible.

The goal is to avoid toxicities from aggressive salvage chemotherapy which could turn out to become a contraindication against transplantation.

Three possible options are given in the DISC arm to treat randomized patients until allogeneic HCT:

Option A – Watch & wait: Monitoring consists of WBC counts twice weekly (e.g. on Mondays and Fridays), requests for symptoms, and regular physical examinations. Based on these results, criteria for the start of an anti-proliferative treatment with low-dose cytarabine (Option B) and/ or single-dose mitoxantrone (Option C) have to be checked on a regular basis.

Option B – Low-dose AraC (LDAC): The option here is to give anti-proliferative treatment with low-dose cytarabine. The dosing schedule has been established by multiple randomized controlled trials in elderly and frail AML patients. This treatment is considered to cause only very limited non-hematologic toxicity. Generally, administration of antiemetics, adequate hydration and monitoring for tumor lysis is indicated. The administration of G-CSF is not recommended. In the event of insufficient anti-proliferative activity of LDAC, patients may switch from Option B to Option C or Option C may be given simultaneously with Option B (in this case, it would be considered as a single visit in the study assessment schedule in Chapter 3).

Table 5. Treatment B: Low-dose Ara-C

Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Cytarabine 20 mg/m^2 s.c. once per day	X	X	X	X	X	X	X	X	X	X

Monitoring consists of blood checks twice weekly (e.g. on Mondays and Fridays), requests for symptoms, and regular physical examinations. The laboratory safety tests for the patient consist of WBC, creatinine, ASAT, ALAT, bilirubin and C - reactive protein checks.

Due to the low dose of cytarabine contained in this regimen, patients do not need dose adjustment.

Option C – Mitoxantrone: This is considered to have a better anti-proliferative activity than LDAC, and causes very limited non-hematologic toxicity. Option C may thus be given alone or simultaneously with Option B if Option B is not sufficient for disease-control.

With respect to potential cardiotoxicity of mitoxantrone a cumulative dose of 30 mg/m^2 mitoxantrone represents approximately 15% of the maximum tolerable cumulative dose.

Three single doses of mitoxantrone 10 mg/m^2 can thus be tolerated in patients who received a maximum of 80% of the maximum cumulative anthracycline dose during their life-time.

Generally, administration of antiemetics, adequate hydration and monitoring for tumor lysis is indicated. The administration of G-CSF is not recommended.

The recommended dose of mitoxantrone used as a single agent is 10mg/m^2 of body surface area. A complete blood count, kidney and liver function tests should be obtained prior to each course of mitoxantrone in order to reduce the starting dose if necessary. If values before the start of each treatment are worse than those described in the eligibility criteria, the investigator should decide together with the Coordinating Investigator about the starting dose for that patient.

A second and third dose may be administered according to the investigator's judgement. Reduction of the initial dose in the second and third administration should be evaluated for each individual patient, on the basis of the clinical assessment (see section 8.1.2 and prescription information).

Table 6. Treatment C: Mitoxantrone

Days	**1**	**Up to 3 doses**
Mitoxantrone 10 mg/ m^2 i.v.	X	(optional) X

Monitoring consists of blood checks twice weekly (e.g. on Mondays and Fridays), requests for symptoms, and regular physical examinations. The safety laboratory consists of WBC, creatinine, ASAT, ALAT, bilirubin and C - reactive protein.

Strict intravenous administration of mitoxantrone via a central intravenous line or confirmed intravenous peripheral access must be ensured due to the toxic reaction of paravasates.

For further information please refer to the prescription information.

8.4 Donor search

At the time of registration, patients would have either:

- An HLA-identical sibling.

or

- An HLA-compatible (≥9/10 antigens matched for HLA-A, -B, -C, -DRB1, and –DQB1) unrelated donor with completed confirmatory typing.

or

- A first report on unrelated donor search resulting in two unrelated donors with >90% probability of a 9/10 match for HLA-A, -B, -C, -DRB1, and –DRQB1, according to OptiMatch® list.

The search unit should be informed immediately about the study participation of the patient by the transplant coordinator to allow for reports on the progress of unrelated donor search. The search criteria should be set in such a way that worldwide unrelated donor search accepting one split-mismatch can be conducted.

If an HLA-identical sibling fails to be cleared during final work-up, an unrelated donor search should be initiated immediately.

8.4.1 HLA typing

HLA typing has to be performed using DNA-based methods both for related and unrelated donor search.

For HLA-identical siblings, intermediate resolution typing of HLA-A, -B, -C and DRB1 are acceptable. Intermediate resolution typing defines alleles in groups of related families historically defined as antigens by allogeneic antisera. Results are reported as two digits (e.g., A*02, B*15, or DRB1*04).

For unrelated donor search, high-resolution typing of HLA-A, -B, -C, DRB1 and DQB1 of donor and recipient are mandatory. High resolution typing is required to define individual alleles. High resolution data are reported with four or more digits (e.g., A*0201, A*0205, B*1504, or DRB1*0401).

8.4.2 HLA matching requirements

Matched siblings or unrelated volunteers who are matched at the allele level with the patient for HLA-A, -B, -C and -DRB1 are considered as donors.

In line with national guidelines accounting for the poor prognosis of patients under conventional treatment, one antigen or allele mismatch is considered acceptable[56]. If no matched unrelated donor can be identified during confirmatory typing, a partially matched unrelated donor should be activated. A second mismatch at the DQB1 locus must be

avoided in donor – recipient pairs who have one mismatch at HLA-A, -B, -C and -DRB1. Uni-directional HLA mismatches in either direction (host versus graft (HvG) and graft versus host (GvH) are counted equally. Patient and donor pairs which are homozygous for one locus are considered to have a two-allele mismatch, implying that this type of mismatch renders the donor ineligible for the purposes of this study.

8.4.3 Donor selection

CMV status should be matched if several HLA-compatible donors are available (i.e. CMV seropositive donors should be selected for CMV seropositive patients and CMV negative donors should be selected for CMV negative patients).

For male recipients male donors are considered to be superior compared to female donors. For female patients donors of both genders are considered equal.

8.5 Patient registration

8.5.1 Registration

No central screening process will be implemented. Slides of the bone marrow aspirates for the morphological diagnosis of relapse, or poor induction response have to be made available for central review however.

Only patients who gave their informed consent prior to registration can be enrolled. Patient information and informed consent covers the study treatment and observation until the primary endpoint has been reached. Informed consent includes pseudonymized reports on donor search to be provided from the donor search unit to the study center. Furthermore, patients will be asked to allow for permission to collect observational data on the disease status and last follow-up after the primary endpoint has been reached for a maximum period of 5 years.

Only patients who fulfill all eligibility criteria can be enrolled in the trial. Registration onto the study will be done electronically. After providing demographic data, eligibility data, and information relevant for stratification, the center receives the study ID and the result of randomization directly from the trial database.

8.5.2 Randomization and stratification

Randomisation will be implemented by an independent institution. A computer generated randomization list will be used. Block-randomization will be used.

Patients will be stratified by disease status (relapse versus poor response AML), disease risk (high-risk versus other) and age (≤60 years versus >60 years).High risk AML is defined as any of the following or combinations thereof:

- Adverse risk AML according to ELN-criteria (Döhner et al., 2010).
- AML that evolves from previously documented myelodysplastic syndrome (MDS) or from previously documented myeloproliferative neoplasms (MPN).
- Diagnosis of therapy-related myeloid neoplasm (t-MN).

In previous protocol versions, the stratum “poor response AML, intermediate disease risk and age ≤60 years” was not part of the inclusion criteria. This stratum will be included starting from protocol version 5.0. For this stratum, a second independent randomization list will be generated by a computer and by using block-randomization. The generated list will be combined with the current list and imported into the Database. This procedure ensures the balance between both treatment arms with respect to the three stratification parameters.

8.6 Concomitant treatment

8.6.1 Transfusion support for study subjects

No study-specific recommendations with respect to transfusion support are implemented for this study. The local institutional guidelines should be used for all decisions with this respect. All blood products are to be irradiated and leukocyte-reduced according to each institution’s guidelines. Also, Cytomegalovirus (CMV)-negative patients should receive CMV-negative blood products according to each institution’s guidelines.

8.6.2 Prophylaxis and treatment of Infections

The use of prophylactic antibacterial and antiviral agents is recommended according to each local institution’s guidelines. Antibiotic prophylaxis with fluorochinolones has proven value and its use is supported in the treatment recommendations of the SAL[57]. It should therefore be considered. Primary prophylaxis with posaconazole is recommended during neutropenia according to current guidelines[58,59].

8.6.2.1 Treatment of neutropenic Fever

Fever in neutropenic patients generally needs prompt action. Diagnostic procedures and therapeutic measures should be in accordance with national and local institutional guidelines[60-62]. If fever occurs during or soon after chemotherapy, the patient should be

carefully evaluated for the focus of infection. Samples for microbiological investigations should be obtained from potential sites of an infection. Urine and blood should be cultured for bacteria. To the extent possible, use of nephrotoxic (e.g., vancomycin, amphotericin B, aminoglycosides, etc.) agents should be minimized since a good renal function renders pharmacologic immunosuppression after transplantation much easier than for patients with impaired renal function.

8.7 Duration of Study Treatment

The goal of the study is to analyse the impact of striving for a complete remission prior to transplantation in patients with relapsed or poor responding AML. This question arises after the indication for allogeneic transplantation has been defined and a provisional donor search has been initiated. The impact of the decision about a remission-induction versus a disease-control strategy on the outcome after transplantation will be assessed. Only the randomization between aggressive salvage chemotherapy, aimed at achieving remission, and a disease-control strategy -based on disease monitoring or low toxic anti-proliferative medication - defines the study treatment. The study treatment ends with a failure of this strategy or with the beginning of a subsequent treatment.

The end of study treatment is defined by the first of the following events which occurs:

- Death.
- The study treatment ends in the remission induction strategy (RIST) arm:
    - After last dose of HAM.
- In the disease control strategy (DISC) arm, study treatment ends:
    - If only Option A (Watch and Wait) is followed: Treatment ends at start of conditioning or start of bridging therapy.
    - If Option B (LDAC) and / or C (Mitoxantrone) is followed: Treatment ends with the last dose of LDAC or Mitoxantrone whichever is given last.

8.7.1 Treatment after failure of the study intervention

For both strategies, the attempt to achieve a CR and disease-control, are subject to high rates of treatment failure. Chemotherapy after failure of either the remission-induction or disease-control strategy is no longer part of the study intervention. The treatment has to be

tailored individually according to comorbidity at that time. Since allogeneic HCT represents the only curative option, this ultimate goal should be kept whenever possible.

For patients who failed aggressive remission induction chemotherapy, no standard treatment option exists. One consensus approach is that these patients should not be subject to additional attempts to induce a CR with aggressive chemotherapy. Based on standard practice in most centers, low toxic bridging measures analogous to the disease-control strategy of this protocol and allogeneic HCT are recommended as soon as possible.

This applies also for patients with whom the disease-control strategy fails, and who may need alternative anti-proliferative medication or aggressive salvage chemotherapy.

Different options of bridging options are shown in the Table below:

Table 7. Further bridging strategies after failure of study treatment

Azacitidine s.c.	Azacitidine is approved for the treatment of AML with ≤30% blasts and multi-lineage dysplasia, among others. The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle). Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle. For dose-adjustment instructions, please refer to the prescription information.
Decitabine i.v.	Decitabine is indicated for the treatment of adult patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, and who are not candidates for standard induction chemotherapy. In a treatment cycle, decitabine is administered at a dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle). The total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2. If a dose is missed, treatment should be resumed as soon as possible. The cycle should be repeated every 4 weeks depending on

	the patient's clinical response and observed toxicity. Studies in patients with hepatic impairment have not been conducted. The need for dose adjustment in patients with hepatic and renal impairment has not been evaluated. If worsening hepatic or renal function occurs, patients should be carefully monitored.

Study-specific criteria for the immediate start of anti-leukemic treatment are provided in Chapter 11.2. Again, allogeneic transplantation should be organized as soon as possible for these patients.

8.7.2 Subsequent Allogeneic Transplantation

Patients with high-risk AML should receive allogeneic HCT as remission-induction or post-remission therapy. Since the availability of a stem cell donor is a pre-requisite for study inclusion, it can be expected that an attempt is made in all patients to schedule allogeneic transplantation, unless acquired comorbidities during induction chemotherapy define contra-indications. Conditioning and allogeneic HCT have to be performed according to local standards since they are not part of the trial invervention. Experimental approaches are not allowed prior to the final response assessment unless the patient has been excluded from the trial.

At the time of transplantation all patients have residual AML cells in their body – this premise constitutes the indication for transplantation. Morphologically, remission status can be classified as follows: patients have morphologically residual AML cells in the bone marrow or blood, or a morphologically leukemia-free state, or a complete remission (see 10.3.1). Different conditioning regimens are recommended for these situations. Further, age and comorbiditieshave to be considered when selecting the conditioning regimen on an individual basis[63,64]. Although several randomized controlled trials have been conducted during the last two decades with the goal to demonstrate superiority of one conditioning regimen over the other, none of these trials conclusively demonstrated a survival advantage by selecting a specific regimen[65-76].

8.7.2.1 AML in complete remission

A variety of different regimens have been applied for conditioning and GVHD-prophylaxis in complete remission.

Busilvex/Cyclophosphamide may be regarded as the historical standard for myeloablative conditioning in young and fit patients with AML[71,73,77-79].

Table 8. Busilvex/Cyclophosphamide

Day -7 → -4	Busilvex 3.2mg/kg i.v
Day -3 → -2	Cyclophosphamide 60mg/kg i.v.
Day -3 → -1	ATG Fresenius 10-20mg/kg for UD
Day 0	Allogeneic HCT
Start on Day -1	Cyclosporine 3 mg/kg/d i.v.
Day +1, +3, +6	Methotrexate 10 mg/m^2 *i.v.*

Fludarabine-Total Body Irradiation (TBI) 8 Gy is a reduced-intensity conditioning regimen for which safety and eficacy has been demonstrated in large randomized studies up to a patient age of 66 years[51,74]. Bornhäuser et al demonstrated that overall survival and event-free survival are comparable after Fludarabine / 8 Gy TBI compared to Cyclophosphamide / 12 Gy TBI. They showed that the advantage of a somewhat better leukemia-control with the higher irradiation dose was offset by higher non-relapse mortality.

The use of lower-dose, irradiation-based preparative regimens has allowed older and medically unfit patients to undergo allogeneic HCT. Doses of 12 Gy present intolerable non-relapse mortality (NRM) for these patients, and doses of ≤2 Gy TBI, though less treatment-related toxicitiy, may not guarantee anti-leukemic activity in the long term (Clift blood 1998 Niederwieser blood 2003).

Stelljes et al reported data on 71 patients, traditionally considered ineligible for HCT, who were enrolled in a multicenter phase II study[44]. Using 8 Gy fractionated total body irradiation and fludarabine (120 mg/m^2) as a reduced intensity conditioning regimen, 2-year probabilities of survival for patients who received a transplant in CR and non-CR were 81% and 21%, respectively. Relapse-free survival rates were 78% and 16%.

Table 9. Fludarabine-TBI 8Gy

Day -6 → -3	Fludarabine 30 mg/m^2 i.v.
Day -3 → -2	TBI 2x2 Gy
Day -3 → -1	ATG Fresenius 10mg/kg for UD
Day 0	Allogeneic HCT

Start on Day -1	Cyclosporine A 3mg/kg/d i.v.
Day +1, +3, +6	Methotrexate 10 mg/m^2 ~~p.o.~~ *i.v.*

Busulfan/Fludarabine (Bu/Flu) is a reduced-intensity conditioning regimen which has been administered in multiple phase II trials[43,80,81]. Several phase II studies have shown that combination treatments consisting of oral or intravenous busulfan (less than 9 mg/kg) plus fludarabine (120-180 mg/m^2) are associated with low incidence of NRM [82,83,84]. Ho et al. published results using fludarabine (180 mg/m^2) and oral busulfan (8 mg/kg) with ATG undergoing HCT after relapse. Leukemia-free survival was 57% at 2 years[85]. In another study reported by Mohty et al, 4-year probability of survival of patients with AML was 42%[86,87]. Ample registry data are available on the safety and efficacy of reduced-intensity conditioning regimens of that type in patients at advanced age[76].

Table 10. Busulfan/Fludarabine

Day -6 → -2	Fludarabine 30 mg/m^2 i.v.
Day -3 → -2	Busilvex 3,2mg/kg
Day -3 → -1	ATG Fresenius 10mg/kg for UD
Day 0	Allogeneic HCT
Start on Day -1	Cyclosporine A 3 mg/kg/d i.v.
Day +1, +3,+ 6	Methotrexate 10 mg/m^2 ~~p.o.~~ *i.v.*

8.7.2.2 Morphologically leukemia-free state

In a morphologically leukemia-free state, residual blasts cannot be detected by means of morphologically assessing the marrow aspirate. However, residual disease below this level of detection must be assumed. Since patients are not in CR and thus are cytopenic, a lower conditioning intensity is appropriate, especially in elderly patients. Again, no formal comparisons of different approaches exist for this specific setting. A standard approach is the combination of fludarabine and melphalan (Flu/Mel), which has been used in specifically this situation[88,89]. As part of a prospective clinical trial, patients with high-risk AML received melphalan (100-150 mg/m^2) and fludarabine (155 mg/m^2) as reduced-intensity conditioning regimen. Stölzel et al reported single-center data for this approach[90]. The authors reported on a retrospective, single-center cohort analysis in a study population comprising 95 patients

with a median age of 52 years (range, 17–71 years). A morphological CR was documented in 82 patients (86%) after allogeneic HCT. Seven patients failed to achieve a CR because of progressive AML or because they died of complications before a CR could be documented. Two-year post transplantation overall survival (OS) for patients with primary refractory AML, patients with high-risk AML according to cytogenetic and molecular risk, and for patients with relapsed AML, were 59% (95% CI, 45%-73%), 67% (95% CI, 45-88%) and 37% (95% CI, 19-54%), respectively.

Flu/Mel is a standard reduced-intensity preparative regimen, consisting of melphalan (100-140mg/m^2) and fludarabine (125mg/m^2) which was first evaluated for allogeneic HCT in 78 patients who had a variety of hematologic malignancies, and were considered poor candidates for conventional myeloablative therapies because of age or comorbidity. NRM at day 100 was 37,4%. RFS was 49% for patients with untreated first relapse or in a second or later remission[41]. Estey reported a significant survival advantage for AML patients in CR1 above 55 years who received FluMel allogeneic HCT compared to matched pairs in a retrospective case control study[91].

Table 11. Fludarabine/Melphalan

Day -6 → -2	Fludarabine 30 mg/m^2
Day -5 → -2	ATG Fresenius 10 mg/kg
Day -2	Melphalan 140 mg/m^2
Day 0	Allogeneic HCT
Start on Day -1	Cyclosporine A 3 mg/kg/d i.v.
Start on Day +1	Mycophenolate Mofetil 2x15 mg/kg p.o.

Bu/Flu or Flu/TBI-8 Gy (see above), may also be administered according to local practice. Myeloablative regimens should be avoided due to excessive toxicity in patients with pancytopenia early after salvage chemotherapy.

8.7.2.3 AML with morphologically residual disease

A variety of highly-effective conditioning strategies has been published, and some are part of routine practice for patients with relapsed or refractory AML. These regimens should be used for patients with morphologically residual disease. With respect to the age of the patients in this study a variant of this regimen for elderly people should be used.

FLAMSA-RIC is an intensive well-established conditioning regimen which has been administered in exactly this indication for more than a decade now[7,8,92]. For elderly patients or patients with relevant comorbidity, a variant of this regimen which contains 1 g/m^2 cytarabine instead of 2 g/m^2 may be used.

Table 12. FLAMSA RIC

Day -12 → - 9	FLAMSA (fludarabine 25 mg/m^2, amsacrine 100mg/m^2, cytarabine 2 g/m^2 (4h after fludarabine)
Day -5 → - 4	Busilvex 3,2 mg/kg i.v.
Day -3 →- 2	Fludarabine 25 mg/m^2 i.v
Day -3 → - 1	ATG Fresenius 10 (SIB) 20 (UD) mg/kg
Start on Day -1	Cyclosporine A 3 mg/kg/d i.v.
Day 0	Allogeneic HCT
Start on Day +1	Mycophenolate Mofetil 2 x15 mg/kg p.o.

A related approach has been evaluated in a large multicenter trial in AML, the AML 2003 study[10,88,90]. Since the dose-intensity is lower compared to the tight FLAMSA-RIC schedule the toxicity of this regimen may be considered to be lower. A formal comparison between different approaches for conditioning in this setting has never been conducted.

Table 13. AML 2003

Day -21 → 17	Mito-FLAG: *Days -21→-17*: Fludarabine 15 mg/m^2 i.v over 30 min/12h and cytarabine1 g/m^2 over 1h/12h (4h after fludarabine) *Days -21, -19 and -17*: Mitoxantrone 10 mg/m^2
Day -6 → -2	Fludarabine 30 mg/m^2 i.v.
Day -5 →-2	ATG Fresenius 10 mg/kg
Day -2	Melphalan 150 mg/m^2 i.v.
Start on Day -1	Cyclosporine A 3 mg/kg/d i.v.
Day 0	Allogeneic HCT

Start on Day +1	Mycophenolate Mofetil 2 x15 mg/kg p.o.

A third standard regimen is the sequential treatment with high-dose melphalan and subsequent reduced-intensity conditioning with Flu-TBI 8 Gy in many centers across Germany[9]. The main advantage of this regimen is that it is especially appropriate in patients who recently failed an HDAC-containing regimen, because melphalan is used in this regimen for immediate leukemia control.

Table 14. Melphalan/Fludarabine/TBI

Day -11	Melphalan 140 mg/m^2 i.v.
Day -5 → - 2	Fludarabine 25 mg/m^2 i.v
Day -4 →- 2	ATG Fresenius (day -4: 5 mg/kg, day -3: 15 mg/kg, day -2 20 mg/kg)
Day -1, 0	TBI 2 x 2 Gy
Day -1→1	Cyclosporine A 3 mg/kg/d i.v.
Day 0	Allogeneic HCT
Day 1	Mycophenolate Mofetil 2 x15 mg/kg p.o.

8.7.2.4 Procedural aspects of allogeneic transplantation (Graft source, GVHD and Infection-prophylaxis, Transfusion support)

Local institutional guidelines and Standard Operating Procedures (SOP) retain their validity for all study subjects with respect to allogeneic HCT. Furthermore, published EBMT (European Group for Blood and Marrow Transplantation) guidelines should serve as a resource of knowledge on these topics[93]. No study-specific recommendations exist for this part of the subsequent treatment. Specifically, this rule covers the selected graft source, graft versus host disease (GVHD) prophylaxis and treatment, infectious prophylaxis and treatment, taper of immunosuppression, transfusion support and transplant-specific follow-up procedures.

8.8 Compliance

Compliance with the study protocol will be monitored during the conduct of the trial. Protocol deviations will be captured in the monitoring reports. The protocol deviations will

be categorized according to their severity with respect to patient safety and integrity of the trial. Protocol deviations may lead to exclusion of a patient from the per protocol population.

8.9 Withdrawal of individual patients from the study

Participation in the trial is voluntary. Patients have the right to withdraw from the trial at any time, for any reason and without any consequences for further medical treatment. Furthermore, the investigator has the right to terminate the participation of any subject at any time, if this is in the patient's best interest. The reason and circumstances for trial discontinuation should be documented in the patient's Case Record/Report Form (CRF).

Reasons for trial discontinuation might be:

- Occurrence of concomitant disease.
- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment per the investigator's judgment.
- The patient is not able to comply with the protocol requirements.
- Withdrawal of consent for personal reasons.

Any subject who discontinues participation should undergo a final examination if possible. The result of the final examination will be documented in the CRF.

8.10 Premature discontinuation of the clinical trial

The Sponsor has the right to discontinue the trial due to relevant medical or administrative reasons. Patients who are under trial treatment will undergo a final visit which has to be defined in the event of a premature discontinuation of the clinical trial. Further treatment has to be delivered in an individualized way complying with the extant standards. Possible reasons for discontinuation by the sponsor are:

- Severe shortfall in patient-recruitment defined by less than 50% of the target recruitment at the end of the second year.
- Unforeseen circumstances at the trial sites that make the continuation of the trial impossible.
- New scientific knowledge that changes the risk-benefit assessment of the trial.

The coordinating investigator will decide on trial discontinuation together with the protocol committee in cooperation with the sponsor.

9 Study assessments

The trial aims to compare two strategies prior to allogeneic HCT in high-risk AML, remission induction by aggressive salvage chemotherapy compared to disease-control by monitoring and low-toxic chemotherapy. The clinical course of the patient will be assessed and reported by the study physician. Independently of the clinical course, the progress of unrelated donor search processes will be reported by the search coordinator in the search unit.

9.1 Baseline and Randomisation

The patient must have signed to confirm informed consent prior to registration. Registration itself will be done electronically with the trial database. Immediately after entry of baseline information into the database, a trial ID and the result of randomization will be provided automatically.

The following evaluations should be carefully reviewed to determine the patient's eligibility for the trial prior to trial inclusion. All investigations are clinical standard diagnostic procedures, recommended in diagnostic and treatment guidelines (see Appendix and Onkopedia)[94,95].

1. Information on all inclusion and exclusion criteria, to be documented on the worksheet "Checkliste Ein- und Ausschlusskriterien".

2. Signed written informed consent.

3. Medical history.

4. AML History.

5. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.

6. 12-lead Electrocardiogram (ECG). The investigation may date back up to 28 days, if no clinical signs suggest deterioration of patient's status since that investigation.

7. Echocardiography with a semi-quantitative assessment of the left ventricular ejection fraction. The investigation may date back up to 28 days, if no clinical signs suggest deterioration of patient's cardiac status since that investigation.

8. Assessment of lung function by spirometry. The investigation may date back up to 28 days, if no clinical signs suggest deterioration of patient's status since that investigation.

9. Assessment of HCT-CI score.

10. Complete Blood Count with microscopic differential.

11. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH), Albumin, Ferritin, Fibrinogen and ß-HCG (for women of childbearing potential only).

12. Infectious serology for HBV, HCV, CMV, EBV, HIV and, Toxoplasma. Analysis of: Infectious serology may date back up to 28 days, if no clinical signs occur since that investigation.

13. Results from a bone marrow aspirate or histology at relapse/poor response to induction chemotherapy dating back no more than 14 days. For central review, one stained bone marrow smear from this aspiration should be sent.

14. Ancillary Research: If patient signed informed consent for ancillary research: 5 ml heparinized bone marrow should be collected for central analysis. To circumvent additional intervention at baseline, stored unstained slides with bone marrow smears before baseline may be used instead or 20 mL of peripheral blood anticoagulated with EDTA which contains more than 10% myeloblasts.

15. Donor search status (HLA-report from HLA-identical sibling or Matching-list with OptiMatch probabilities).

All hematology, blood chemistries, and bone marrow examinations are to be performed under the auspices of the local laboratories at the investigational site.

9.2 Medical assessments

The timeline for clinical assessments is calculated from the day of randomization.

9.2.1 Remission induction strategy (RIST)

9.2.1.1 Remission-Induction Chemotherapy

Remission Induction Chemotherapy should start within 7 days after randomisation. This visit covers the complete chemotherapy regimen.

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.

2. Complete Blood Count with microscopic differential

3. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH).

4. Study Treatment.

5. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment.

6. Concomitant medication given to treat adverse events Grade ≥3 occurring until day 28 after last dose of study treatment.

9.2.1.2 Induction Response

Induction response should be assessed by a bone marrow aspirate or histology within 21 days (+/- 7 days) after start of induction treatment. If at the time of the induction response assessment the patient has already experienced hematological recovery, this will be considered the remission assessment and documented in the CRF accordingly.

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.

2. Complete Blood Count with microscopic differential.

3. Bone marrow aspirate or histology. Remission assessment based on locally conducted morphological assessment and clinical criteria. Please refer to chapter 10.1 for response definitions.

4. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment.

5. Concomitant medication given to treat adverse events Grade ≥3 until Day 28 after the last dose of study treatment.

9.2.1.3 Remission Assessment

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.

2. Complete Blood Count with microscopic differential.

3. Bone marrow aspirate or histology. Remission assessment based on locally conducted morphological assessment and clinical criteria. Please refer to chapter 10.3 for response definisions.

4. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment. Adverse events Grade 4 and 5 will be further documented until end of trial (final remission assessment until Day 56 after HCT).

5. Concomitant medication given to treat adverse events Grade 3 and 4 until Day 28 after the last dose of study treatment.

9.2.2 Disease Control Strategy (DISC)

The chosen approach must be documented in the CRF within 3 days after randomization.

9.2.2.1 First Approach

1. Physical examination: ECOG.

2. Complete Blood Count with microscopic differential.

3. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH).

4. Study treatment.

5. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment.

6. Concomitant medication which is given to treat adverse events Grade ≥3 until Day 28 after the last dose of study treatment.

7. If only Option A (watch and wait) is followed, adverse events CTCAE grade ≥3 will be documented until the start of subsequent anti-leukemic treatment (start of bridging therapy), or the start of the conditioning regimen.

9.2.2.2 Second Approach

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.
2. Complete Blood Count with microscopic differential.
3. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH).
4. Study treatment.
5. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment.
6. Concomitant medication which is given to treat adverse events Grade ≥3 until Day 28 after the last dose of study treatment.

9.2.2.3 Third Approach

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.
2. Complete Blood Count with microscopic differential.
3. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH)
4. Study treatment.
5. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment.
6. Concomitant medication which is given to treat adverse events Grade 3 and 4 until Day 28 after the last dose of study treatment.

9.2.3 Bridging Therapy

This visit shall be completed at the start of the bridging regimen. Bridging therapy is defined any treatment aiming at disease control or remission induction which is neither study treatment nor part of a (sequential) conditioning regimen.

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.
2. 12-lead ECG if patient presents cardiac signs.
3. Echocardiography if anthracyclines have been administered since last assessment, or if clinical signs suggest deterioration of cardiac function.
4. Assessment of lung function by spirometry if clinical signs suggest deterioration of pulmonary function.
5. Assessment of HCT-CI score.
6. Complete Blood Count with microscopic differential.
7. Serum Chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH).
8. Adverse events Grade ≥3 NCI CTCAE Version 3.0 will be documented until Day 28 after the last dose of study treatment, even if any bridging therapy has started before that time point.
9. Adverse events Grade 4 and 5 and will be documented until end of trial (final remission assessment until Day +56 after HCT).

9.2.4 Transplant Report (HCT)

This report has to be completed after the patient has been discharged from hospital after allogeneic HCT. The following information will be collected retrospectively:

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG within 7 days prior to conditioning.
2. 12-lead ECG within 7 days prior to conditioning if patient presents cardiac signs. .
3. Echocardiography, if anthracyclines have been administered since last assessment or if clinical signs suggest deterioration of cardiac function.

4. Assessment of lung function by spirometry if clinical signs suggest deterioration of pulmonary function.

5. Assessment of HCT-CI score.

6. Complete Blood Count.

7. Serum chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH), Albumin, Ferritin and Fibrinogen .

8. Bone marrow aspiration within 14 days prior to start of conditioning regimen.

   Only for RIST strategy: or peripheral blood counts are now compatible with CR after induction therapy but a CR after induction therapy had not been documented before.

9. Final donor (CMV, gender donor and patient).

10. Conditioning regimen.

11. GVHD prophylaxis.

12. Veno Occlusive Disease (VOD) assessment.

13. Neutrophil and platelet engraftment.

14. Ancillary Research: If patient signed informed consent for ancillary research: 5 ml heparinized bone marrow should be collected for central analysis.

15. Hospital discharge.

16. Adverse events Grade 4 and 5 will be documented until end of trial (final remission assessment until Day +56 after HCT).

9.2.5 Final Remission Assessment

Final Remission Assessment has to be performed up to Day +56 after allogeneic transplantation, latest within 24 weeks after randomization.

1. Physical examination. Detailed documentation of extramedullary manifestations, also BMI (Body Mass Index) and ECOG.

2. Complete Blood Count with microscopic differential.

3. Serum Chemistry: Creatinine, Uric Acid, Urea, Aspartate Aminotransferase (ASAT), Alanine Aminotransferase (ALAT), Gamma Glutamyl Transpeptidase (GGT), total Bilirubin, Lactate Dehydrogenase (LDH).

4. Bone marrow aspirate or histology. Remission assessment based on morphological assessment and clinical criteria according to Döhner et al., 2010; locally. Assessment of overall chimerism of the aspirate is recommended in neutropenic or recovering patients.

   For central review, one stained bone marrow smear from this aspiration should be sent to the central laboratory.

5. Ancillary Research: If patient signed informed consent for ancillary research: 5 ml heparinized bone marrow should be collected for central analysis.

6. Adverse events Grade 4 and 5 will be documented end of trial (final remission assessment until Day +56 after HCT).

9.2.6 Annual Follow-up Report

This report shall be completed annually for all patients until the last patient has passed the two-year landmark from randomization (longest follow-up period for the first patient and shortest – two years - for the last patient randomized).

1. Survival

2. ECOG performance status.

3. Remission status of AML.

4. GVHD assessment, if applicable.

5. Ongoing immunosuppressive treatment, if applicable.

9.3 Donor Search Reports

Knowledge about the parallel donor search process is important in order to check information on the treatment-history. Substantial delays during donor search might prompt additional chemotherapy in order to maintain a complete remission in the remission induction strategy arm (RIST arm) or an additional management strategy in the disease-control strategy arm (DISC arm).

The baseline report on donor search will cover information on:

1. Related donor search (number and availability of siblings and dates of HLA typing)
2. Start of unrelated donor search (date of submission of donor search by search coordinator and eventually date of clearance of donor search) and information on search criteria.

Follow up reports will be generated on a bi-weekly basis until transplantation. These reports cover the following information:

1. Status of related donor search until final related donor clearance.
2. Status of unrelated donor search until confirmatory typing has been received.
3. Status of donor activation until final donor clearance.

Information on the search status is collected for each donor for whom a confirmatory typing has been requested.

9.4 Concomitant Medication

Throughout the study treatment period, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care or prevent and treat infections. Please refer to protocol section 8.6 for details. Any anti-leukemic treatment, other than the study medication described in protocol Chapter 8 is NOT allowed during the study treatment duration (see protocol section 8.7). The use of G-CSF is not recommended.

9.5 Ancillary Research

Information on minimal residual disease is instrumental for the comparison of treatment efficacy and prognostication. In order to complement the clinical information on the course of AML, samples of peripheral blood or bone marrow will be collected throughout the conduct of the trial. Three main research questions will be addressed:

1) Is the residual disease load at final remission assessement in the RIST arm significantly different to the DISC arm?
2) How frequently can minimal residual disease be detected prior to the start of the conditioning regimen in patients who achieved a CR in the RIST arm?

3) Does the level of residual disease prior to the start of the conditioning regimen predict outcome in terms of CR-achievement and overall survival independently from the study arm and the conditioning regimen?

Samples will be collected at three time-points: baseline, prior to the start of the conditioning regimen, and at final remission assessment. Given an optimal course of the treatment, one interim bone marrow assessment will be done after remission induction chemotherapy or prior to the start of the conditioning regimen. Since additional diagnostic procedures for the collection of patient material should be avoided and it is impossible to foresee the results, samples from all interim bone marrow assessments should be collected and be shipped to the Labor SAL-Biobank / Haus 65, Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus in Dresden.

The type of material may vary depending on the time point. Optimally, 5 ml of heparinized bone marrow should be collected for central analysis at each time point. In order to facilitate testing for minimal residual disease the diagnostic sample harboring leukemic cells is of crucial importance. Yet, many patients will have had a bone marrow aspiration prior to study enrollment and an additional assessment cannot be justified in these patients. In order to circumvent an additional intervention, stored slides with bone marrow smears from this very time-point may be used instead. Alternatively, 20 mL of peripheral blood anticoagulated with EDTA or Li heparin which contains more than 10% myeloblasts may be suitable as base-line sample.

The samples will be used for prognostication based on mutations in significantly mutated genes in leukemia and for the description of courses of minimal residual disease. Mutations will be diagnosed using molecular genetic techniques.

10 Definitions

10.1 Induction early response assessment

The first response assessment has to be performed in all patients in the remission induction strategy (RIST arm) regardless whether the peripheral cell counts meet criteria for a complete remission. In patients with imminent hematologic recovery, a repeat marrow aspiration must be performed by day 35. If marrow aspiration fails (dry tap) a bone marrow biopsy should be performed in order to guide subsequent therapy.

10.1.1 Morphologic Leukemia-free State

This response category is defined by <5% leukemic blasts in the bone marrow, absence of blasts with Auer rods, and absence of extramedullary disease. No hematologic recovery is required.

10.1.2 Moderate response

A moderate response is defined by:

- a decrease of bone marrow blast percentage to a value between 5% and 25%, and decrease of the pre-treatment bone marrow blast percentage by at least 50% (e.g. from 40% to 20%).
- clearance of myeloblasts from the peripheral blood, and
- absence of extramedullary disease.

In patients with imminent hematologic recovery, up to 5% circulating blasts are consistent with a moderate response. The criteria for a morphologic leukemia-free state are not met.

10.1.3 No response (resistant disease)

If criteria for a morphologic leukemia-free state or moderate response are not fulfilled, failure of remission induction has to be documented.

10.2 Criteria for immediate start of anti-leukemic treatment

Standard criteria for the need of anti-leukemic treatment in patients with AML-relapse or poor-response AML do not exist. A treatment delay is not unequivocally associated with worse CR-rate or higher mortality[25,24].

For this study the following criteria for immediate start of anti-leukemic therapy comprise:

- White Blood Cell (WBC)-count >50 GPt/L.
- Spontaneous leukocyte doubling-time of less than 7 days in combination with >10% myeloblasts in the peripheral blood referring to reference WBC-count of >10 GPt/L.
- Clinical apparent extramedullary manifestation of AML.

10.3 Remission assessment after induction chemotherapy

The remission status will be assessed after partial or complete recovery of neutrophil and platelet counts. It must be performed by Day 35 from start of induction therapy.

10.3.1 Complete Remission (CR)

Complete remission (CR) is achieved when the bone marrow blasts are below 5%. Additional criteria are the absence of blasts with Auer rods, absence of extramedullary disease and hematopoietic recovery defined by an absolute neutrophil count (ANC) >1 /nL (1,000/µL) and a platelet count >100 /nL (100,000/µL).

10.3.2 CR with incomplete recovery (CRi)

Complete remission with incomplete recovery (CRi) is defined by CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/µL)] or thrombocytopenia [<100 x 10^9/L (100,000/µL)].

Generally, in patients with low blast counts (<20% marrow blasts) at remission assessment – especially during hematopoietic recovery - a repeat bone marrow aspirate can be performed within a time-frame of two weeks, to confirm complete remission.

10.4 Final Remission assessment

Final remission status will be assessed until Day +56 after HSCT, latest within 24 weeks after randomization.

10.4.1 Complete Remission (CR)

Complete remission (CR) is achieved, when the bone marrow blasts are below 5%. Additional criteria are the absence of blasts with Auer rods, absence of extramedullary disease and hematopoietic recovery defined by an absolute neutrophil count >1 /nL (1,000/µL) and a platelet count >100 /nL (100,000/µL).

10.4.2 CR with incomplete recovery (CRi)

Complete remission with incomplete recovery (CRi) is defined by CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/µL)] or thrombocytopenia [<100 x 10^9/L (100,000/µL)].

10.4.3 Complete remission by chimerism (CRchim)

Complete remission by chimerism (CR chim) is defined as a >95% overall donor chimerism assessed by STR-PCR (Short Tandem Repeat Polymerase Chain Reaction) in bone marrow and absence of extramedullary disease together with an absolute neutrophil count >0.5 /nL (500/µL).

Generally, in patients with low blast counts (<20% marrow blasts) at remission assessment, especially during hematopoietic recovery, a repeat bone marrow aspirate can be performed within two weeks to confirm complete remission.

10.5 Definition of failure and relapse

10.5.1 Remission induction failure

Patients who do not achieve a complete remission (CR or CR_i) as defined in chapter 10.3 will be considered as remission induction failures.

10.5.2 Final remission assessment

Patients who do not achieve a complete remission (CR, CR_i or CRchim) as defined in chapter 10.4 will be considered as treatment failures.

10.5.3 Relapse

Hematological relapse is defined for patients whose best response was a CRi or CR. In this group of patients, the detection of ≥5% bone marrow blasts, or the re-appearance of leukemic cells in the peripheral blood, or development of extramedullary disease is defined as hematological relapse.

Molecular relapse can only be defined in patients with a molecular marker suitable for minimal residual disease, for whom disappearance of the molecular marker was shown in two subsequent samples. The reappearance of the molecular marker in two subsequent samples with an assay of same sensitivity is considered as molecular relapse. In this context, the date of the first of two subsequent samples is considered as the date of molecular relapse.

For the evaluation of leukemia-free survival, both hematological and molecular relapses are considered.

10.6 Time-dependent endpoints

10.6.1 HLA-compatible Donor Availability

Availability of an HLA-compatible donor is critical for patients who are in need of an allogeneic transplantation. HLA-compatibility has to be confirmed by confirmatory HLA typing. The cumulative incidence of donor availability shall be assessed in patients for whom an unrelated donor search has been activated. Donor availability, death before donor availability, and transplantation from alternative donors will be considered as

competing time-dependent events. In this context, the event of donor availability is defined by the date of receipt of confirmatory typing of an HLA-allele matched unrelated donor for HLA-A, -B, -C and –DRB1. Patients for whom no HLA-compatible donor can be confirmed by confirmatory typing are censored at the 24 weeks landmark from randomization. Patients who receive allogeneic transplantation from alternative donors (haplo-identical donors,or cord blood) are considered to have experienced a competing event at the date of transplantation.

10.6.2 Final Matched Donor Clearance

For all patients for whom a donor has been activated, the final step in transplantation coordination is the final donor clearance based on the medical evaluation of the donor. Final matched donor clearance, death before donor clearance, and transplantation from alternative donors are considered as competing time-dependent events. The event is defined by the date of final donor clearance for an HLA-identical or HLA-compatible donor referring to HLA-A, -B, -C and –DRB1. Patients for whom no HLA-compatible donor can be finally cleared are censored at the six month landmark from randomization. Patients who receive allogeneic transplantation from alternative donors (haplo-identical donors, or cord blood) are considered to have experienced a competing event at the date of transplantation.

10.6.3 Overall survival

Overall survival for all patients is defined as time from randomization until death.

10.6.4 Incidence of CR

Incidence of CR is calculated from the day of randomization. Death before CR is considered as competing event. The first documented CR is counted as event. Patients who did not achieve a CR by the six month landmark are censored.

10.6.5 Leukemia-Free Survival

Leukemia-free survival is calculated from the day of complete remission to either death or relapse. Relapse and death before relapse are considered as competing events.

10.6.6 Time-dependent endpoints after HCT

10.6.6.1 Overall survival after HCT

Overall survival after HCT is defined by time from HCT until death.

10.6.6.2 Event-free survival after HCT

Event-free survival after HCT is defined as survival without events after HCT. Events are death before relapse, relapse, and failure to achieve a CR at final remission assessment. These events are considered as competing events.

10.6.6.3 Leukemia-free survival after HCT

Leukemia-free survival after HCT is defined only for patients who achieved a CR at final remission assessment. The date of CR assessment is set as starting point. Competing events for this leukemia-free survival are relapse and death before relapse.

11 Adverse Event Reporting

11.1 Adverse Event Definitions

The principal investigator is responsible for monitoring the safety of patients who enrol in the study.

An **Adverse Event (AE)** is defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

The descriptions and grading scales found in the revised NCI CTCAE version 3.0 will be used for adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

Adverse events are classified as either serious or non-serious:

A **Serious Adverse Event (SAE)** is defined as any experience that suggests a significant hazard or side-effect with respect to patients participating in a clinical study. This includes any experience which:

- Is fatal or life-threatening.
- Is permanently disabling, i.e. incapacitating or interfering with the ability to resume normal life patterns.
- Requires hospitalisation or prolongation of hospitalisation.

- Is a congenital anomaly or defect.
- Other medically important circumstances (require medical treatment to avoid one of the above mentioned conditions).

The term “Life-threatening” in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalization means overnight admission.

Hospitalization without an underlying adverse event (AE) is not an SAE. Examples are:

- Hospitalization for protocol procedures e.g. scheduled chemotherapy or transplantation.
- Elective hospitalization for a pre-existing condition (i.e. a condition other than the indication for the chemotherapy) that has not worsened.
- Hospitalization which was already planned at the beginning of the trial. The hospitalization should have been reported at the screening visit in the source data and should have been performed as planned.
- Admission to a rehabilitation center or hospice.
- Hospitalization for administrative or social reasons (e.g. due to anxiety but otherwise treatable on an outpatient basis).

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions which are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

Adverse Reaction (AR) is any harmful and unintended reaction on the study medication regardless of its dosage.

Unexpected Adverse Reaction (UAR) is an adverse reaction that does not meet any criteria for adverse reactions that are listed as known or possible side effects, either in type, severity or outcome. The reference document for the assessment of expectedness will be the Summary of Product Characteristics (Fachinformation) of cytarabine and mitoxantrone, respectively.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)**, see guidelines 2001/20/EG, is considered when a SAE, has a certain degree of probability that it is an adverse reaction on the administered drug and the adverse reaction is not listed in the summary of product characteristics or prescription information (see above).

11.2 Study specific considerations

Cytopenia does not constitute a (serious) adverse event in itself since it frequently reflects the underlying disease or desired treatment effect.

A pathological finding, improved or unchanged in comparison to baseline, does not constitute an adverse event.

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation boundaries. Worsening of the underlying disease or other pre-existing conditions will be recorded as an AE.

Abnormal laboratory values without therapeutic consequences do not have to be documented on the AE form. Instead, they will be documented on the laboratory values form in the CRF only.

11.3 Documentation of Adverse Events

All adverse events have to be documented in the patient's chart. The subsequent AEs have to be documented in the CRF:

- All adverse events CTCAE grade ≥3 from randomization until Day 28 after the end of study treatment (see 8.7). In patients who did not receive any study drug but were just observed (DISC-arm, watch & wait only), adverse events CTCAE grade ≥3 will be documented until the start of subsequent anti-leukemic treatment (start of bridging therapy) or start of the conditioning regimen.

- All adverse events CTCAE grade ≥4 from randomization until Final Remission Assessment defined as primary endpoint assessment (end of trial).

The following data have to be documented in the CRF for each AE:

- Type of adverse event (symptoms, diagnosis etc.) coded according to CTCAE version 3.0
- Date of onset
- Maximum grade according to CTCAE version 3.0

- Differentiation between serious or non-serious adverse event
- Assessment of causal relationship to the study treatment
- Measures taken if applicable
- Date of resolution and/or outcome at the end of study

Patients will be followed until remission of the symptoms or until the patient condition stabilizes.

- Any SAE has to be documented at the AE page in the CRF and on the SAE form
  Each SAE has to be reported immediately to the safety desk as completely as possible by use of a separate SAE form (in case of death an autopsy should be performed and the report should be handed out to the Coordinating Investigator if possible)
- Cases of overdoses, misuse, or deviations in the administration of the study medication have to be documented even when there is no adverse event

11.4 Reporting of Serious Adverse Events

SAEs occurring during the study or within 28 days after the end of study treatment must be reported to the Sponsor's safety desk by fax within 24 hours of occurrence. SAEs occurring in patients who did not receive any study drug (DISC-arm, watch & wait only), must be reported to the Sponsor's safety desk by fax within 24 hours of occurrence until start of subsequent anti-leukemic treatment (start of bridging therapy) or the start of the conditioning regimen. The principal investigator is responsible for submitting follow-up reports to the safety desk for all SAEs regarding the patient's subsequent course until the SAE has been resolved, or until the patient's condition stabilizes (in the case of persistent impairment), or the patient dies.

Each SAE has to be documented as completely as possible but must include a minimum of criteria as follows:

- Patient characteristics (randomization number)
- Description of SAE (including onset date and outcome)
- Drug information (e.g. last application)
- Assessment of relatedness (possible or unlikely)
- Information about the reporting investigator

Via the safety desk, the Coordinating Investigator will on behalf of the sponsor review all reported SAEs for a reasonable suspected causal relationship to the investigational treatment, and for expectedness in terms of nature, severity and outcome of an SAR in relation to the investigational procedure.

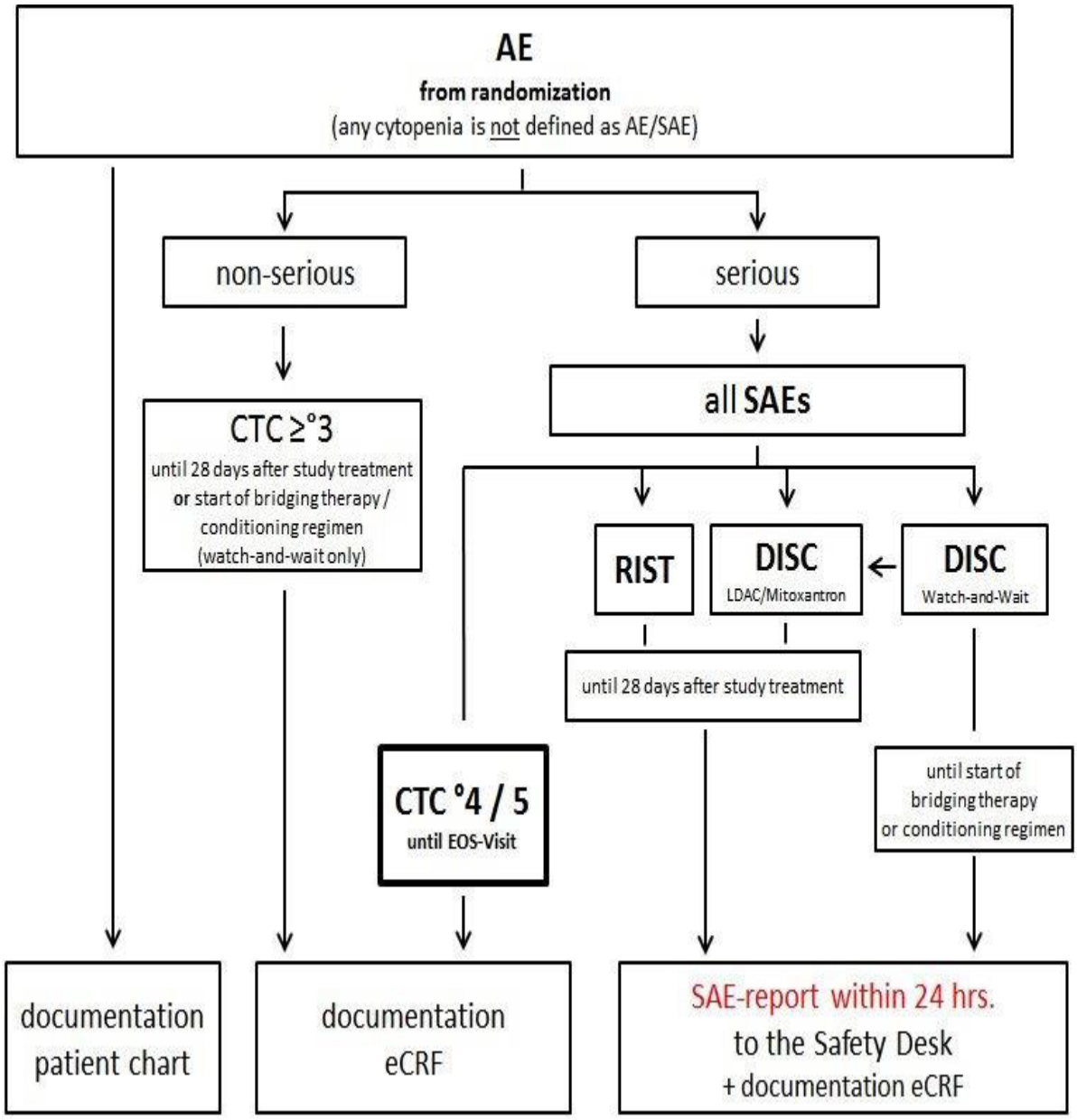

Figure 2. Adverse Event Documentation and Reporting.

11.4.1 Reporting responsibilities of the sponsor

SAEs

The sponsor (or its representative) has to document all reported serious adverse events completely and has to send this information to the national competent authorities if required.

SUSARs

The sponsor (or its representative) has to report any reported SUSAR immediately, the latest within **15 days** after notification, to the relevant ethics committee, the national competent authorities and to the investigators.

The sponsor (or its representative) has to send any important information that is relevant for assessment immediately, the latest within **7 days** after notification, to the relevant ethics committee, the national competent authorities and to the investigators when the SUSAR was followed by **death** or is **life threatening** for the patient. Other relevant information has to be sent no later than within the following **8 days**.

11.5 Re-examination of the risk benefit profile

The sponsor (or its representative) has to report immediately but the latest within **15 days** after s/he became aware of the occurrence of an event that requires a re-examination of the risk benefit profile of the study treatment to the relevant ethics committee and the national competent authorities. Included are:

- Case reports of expected serious adverse reactions with an unexpected outcome.
- Increase of the frequency of unexpected adverse reactions that are judged as clinically relevant.
- Suspected cases of serious adverse reactions that occurred after the patient had finished the clinical study.
- Events that are related to the clinical trial or the development of the study medication that can possibly affect the safety of the patient.

List of all SARs and Safety Report (Development Safety Update Report)

The sponsor (or its representative) has to submit a list of SAR and a safety report (acc. to ICH E2F guideline) to the relevant ethics committee and the national competent

authorities annually during the course of the clinical study until last patient last visit,, or on request. The time frame for this report starts as soon as approval by the federal authority (BfArM) is available.

Measures to protect against imminent danger

In cases where the safety of the patients is compromised and the sponsor (or its representative) as well as the investigator can take action to protect the patient from harm, the sponsor has to inform the relevant ethic committee and the national competent authorities about these measures and causal circumstances.

11.6 Pregnancies

Information on pregnancies in female partners of male trial participants, or information on pregnancies in female trial participants with a history of intensive chemo-immunotherapy, must be reported.

The investigator must report the pregnancy using the Clinical Trial Pregnancy Form. The pregnancy must be reported to the Safety Desk within 24h after receiving such notification.

Pregnancy complications, elective terminations for medical reasons, or spontaneous abortions must be reported as an AE or SAE. Any SAE in association with a pregnancy which occurred after completion of the study treatment, and which is considered possibly related to the study treatment, must be also reported.

The pregnancy must be followed up to determine the outcome (including premature termination), and the status of mother and child.

12 Documentation

It is the responsibility of the investigator to perform the clinical trial in accordance with the ICH-GCP guidelines, applicable national regulations, and the clinical trial protocol. All data have to be recorded correctly in the eCRF by authorized persons only.

The investigator records the participation of a person at the Patient Identification Log (PIL). This list is meant to identify participating persons at a later point of time. It includes the complete name, the date of birth, and the date of inclusion into the clinical trial. The PIL remains in the study center after the trial is finished. In addition, participation in the

clinical trial has to be recorded in the patient's chart (including study treatment, patient number/randomization number, start and end of the clinical trial).

It has to be ensured that the person responsible for documentation in the CRF can be identified. Therefore, a list with signatures and abbreviations (site signature log) is kept in the Investigator Site File (ISF) and in the Trial Master File (TMF).

If a patient is treated at more than one trial site (for example, induction chemotherapy at one site and transplantation at another), shared responsibilities must be defined and documented in advance by both sites. As a minimum the following information must be included:

- AEs documentation.
- SAE and SUSAR documentation and reporting.
- That source data verification must take place where source data is generated.
- Patient contact site for questions.
- Patient withdrawal.

In addition, the Sponsor must be kept informed on which site is responsible for each task, and from which time-point the responsibility takes effect.

12.1 Case report form (CRF)

All data of the patients have to be recorded in the electronic Case Report Forms (eCRF) exclusively designed for the study using Macro version 4.0. Data, that are not available or have not been collected, have to be clearly identified as such (NA or ND). If necessary the reasons should be documented.

The Investigator is responsible for ensuring that all data for the patient is documented in the case report form immediately, legibly, correctly and according to the patient's chart.

Corrections in the eCRF are to be conducted only by authorized personnel and must be justified. The previous database entry must stay retrievable. All data and corrections are recorded automatically concerning date, time point and person. Plausibility and completeness of the eCRF will be verified by a monitor.

12.2 Investigator Site File

Each study center keeps an Investigator Site File (ISF) provided by the sponsor. During monitoring, the ISF will be checked regularly for completeness and up-to-date. After the clinical trial is finished or stopped, the ISF has to be stored for 10 years.

12.3 Data Storage

12.3.1 Responsibilities of the Sponsor

As required by law, all important study documents have to be stored by the sponsor for at least 10 years after the clinical trial was finished or stopped.

12.3.2 Responsibilities of the Investigator

All documents that are related to the clinical trial and to the distribution of the study medication (e.g. CRFs, written informed consent forms, study medication lists and other relevant material) have to be stored for at least 10 years. Source data including patients' charts, laboratory analyses, and other original data have to be stored for the longest possible time that is usual practice at the investigator's site.

13 Monitoring and Audit

Monitoring and audits will be performed during the clinical trial to ensure that the trial meets specified quality criteria.

13.1 Monitoring

The investigator agrees that the monitor will visit the trial center at appropriate intervals. During these visits the monitor will check the quality of the data recording and ensure that the study center adheres to the timeframe set in the study protocol. The investigators agree to provide any relevant information and documentation whenever the monitor requires this information. This includes access to all original study documents and source data.

It is the responsibility of the investigator to keep the patient's chart as complete as possible (e.g. history, concomitant diseases, inclusion in the clinical study, visit dates, results of laboratory tests, distribution of the study medication, and adverse events). Source data are checked and compared with entries in the eCRFs. The patient will have

given consent to this procedure by signing the patient information and written informed consent form. Additional tasks of the monitor are:

- To check that the study center fulfils requirements of the clinical study (e.g. study population, technical equipment).
- Instruction of the investigators and personnel for the clinical trial.
- To check the ISF for completeness and up-to-date
- Documentation of the status of the patient.
- Matching of original data.
- To check SAE reports according to regulations.

The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the study patients.

13.2 Audit

To guarantee the conduct of the clinical trial according to GCP guidelines, internal (e.g. by the sponsor) and external (e.g. by the authorities) audits can be performed. The person who performs the audit is independent. During the audits the following points are checked:

- Conduct of the trial according to the protocol.
- Data validity;
- Quality of the study according to GCP guidelines.

Every external audit is followed by an audit confirmation for the investigators. This document has to be kept in the ISF and should be available at inspection by the authorities. It is also sent to the sponsor. At the end of the study an audit certificate is added to the final study report. In addition, according to national applicable regulations, inspections can be done by the authorities.

14 Data Entry and Data Management

14.1 Hardware and Software

Patient data will be remotely entered by treatment centers into a central database on a server located at Coordination Center for Clinical Studies (KKS) Dresden. The software used for this purpose will be MACRO version 4.0.

For analysis, data may be exported from the KKS Dresden database in CSV format.

14.2 Data Quality Control at Sponsor

Data arriving at the sponsor will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data should be re-checked for clinical plausibility and accuracy by visual / manual checks and verification during any input processes, in accordance with GCP guidelines.

Following data entry, software programmed range or limit checks, and validity checks will be performed to identify any data which are outside defined limits or values. This includes checks that patient-treatment and assessments are recorded in a logical sequence.

Where discrepancies are identified in either of the above steps, authorized personnel should take action to verify and correct the data, paying particular attention to the need to maintain patient confidentiality in any communications.

The number of patients in the per protocol population will be monitored once the number of recruited patients is larger than 246. The number of per protocol treated patients will be determined based on logged protocol deviations, study drug administration and information on subsequent bridging therapy by the Data Management Team. Once the target number of patients in the PP population has been reached the PIs will be informed and further patient recruitment will be stopped.

15 Statistics

15.1 Treatment allocation

In order to guarantee balanced risks, patients will be randomized between the two treatment strategies. Block randomization with variable block lengths will be utilised. The blocks will be generated by an R program. The random start seed, information on the block length and the random allocation sequence will be kept confidential by the external provider of the database, through which information on the randomization will be disclosed. After enrollment of the last patient the start seed, information on the block length and the random allocation sequence will be transferred to a separate part of the trial master file. The random allocation sequence will be used to generate the randomization list. The randomization process will be web-based via the trial database.

15.2 Populations for analysis

15.2.1 Intention-to treat population

The population for the primary efficacy analysis by intention-to-treat consists of all randomized patients. This population is defined as full analysis set (FAS). Only patients who withdraw their informed consent will be excluded from the FAS.

15.2.2 Per protocol population

The population for the Per-Protocol primary efficacy analysis (PP population) consists of patients in the FAS who are treated in line with the protocol. For example, patients who switch from the disease-control to the remission-induction strategy, or vice versa, will be excluded from the PP population. In addition, patients who died prior to the first day of study intervention (including watch and wait) will be also excluded. It is assumed that 80% of patients will belong to the PP population.

15.2.3 Populations for the analysis of secondary endpoints

In addition to the primary efficacy analysis, a number of exploratory and confirmatory analyses will be performed in subgroups of patients. The following analysis populations will be defined:

- Patients who received allogeneic HCT define the population for transplant specific outcome analysis.
- Patients who achieved a CR constitute the population in order to calculate Leukemia-free survival probability.
- Patients who are randomized to the remission-induction strategy will be subject to detailed description of the sequence of events, primarily remission-induction versus induction failure, relapse, and death prior to transplantation.

All patients will be followed up for annual updates until 2 years after the last patient's randomization.

15.3 Statistical hypothesis and sample size estimation

15.3.1 General concept

In order to estimate the success rates of the two treatment strategies, the anticipated treatment path was broken down to different stages within each strategy. These stages are: remission-induction chemotherapy and first response assessment (applicable only for the remission-induction strategy), the bridging strategy prior to transplantation, referral for transplantation depending on patient's physical performance, allogeneic transplantation, and final remission assessment. A literature review was performed in order to empirically substantiate assumptions for defined stages of this treatment path. Finally, average assumptions for patients with relapsed AML and poor response AML were consented to within the protocol committee.

15.3.1.1 Literature review

The literature review focused on the efficacy and safety of aggressive salvage chemotherapy based on HDAC plus anthracycline. The complete remission rate of subgroups of patients with relapsed AML or poor response AML was extracted whenever this information was available. The early death rate after aggressive salvage chemotherapy was analysed, and the early death rate after allogeneic transplantation was reviewed. Data were extracted from published manuscripts. Linear interpolation or visual readout was used when point-estimates were not available directly from the manuscript. The results are summarized in the tables below.

Table 15. Salvage therapy in relapsed and/or refractory AML.

Study	**Age (years)**	**Number of Patients**	**Disease status**	**Therapy**	**Day 30 mortality from start of therapy**	**Day 60 mortality from start of therapy**	**CR-Rate**
Becker, 2011[96]	Median 53	50	r/r	Clo/HDArac/GCSF	-	10%	61% CR(p)
Chun Yew Fong, 2012[97]	18-70	58	First relapse	FLAG-Amsa	3%	≈ 16%	59% (CR/CR(i))
Wierzbowska, 2008 [98]	Median 45	118	r/r	CLAG-M	8%	≈ 13%	58% CR
Thiel, subm.[99]	Median 59	252	relapsed or refractory	Mito-Flag (as bolus)	≈ 10%	≈ 16%	54% first CR
				Mito-Flag (continuous infusion)	≈ 10%	≈ 16%	43% first CR
Steinmetz,1999[46]	Median 52	75	r/r/sAML	IDA FLAG	14%	23% d42	52% CR
Lee, 2009[100]	Median 33	61	r/r	FLAG	-	≈ 11%	47% CR
Faderl, 2012[101]	> 55	320	r/r	AraC +/- Clo	16% / 5%	≈ 15%	
Liu Yin, 2001[16]	Median 48	235	r/r	ADE +/-CSA	20%	-	43% CR

Karanes, 1999[47]	Median 50	162	r/r	HiDAC+/- Mito	10%/13%	≈ 25%	32%/44% CR
Price, 2011[102]	Median 55	162	r/r	CLAG/ MEC	10%	≈ 20%	38%/24% CR
Chevallier, 2008[103]	Median 55	62	r/r	GO/AraC/Mito	7%	≈ 27%	63% CR(i)
Larson, 2012[22]	Median 63	78	HR	Mito-HiDAC	-	9% during IT	55% CR(i)
Kohrt, 2010[48]	Median 54	77	r/r	Mito/Eto/AraC	10%	20%	26% CR(i)
Armistead,2009[4]	Median 44	266	Relapse	Any Salvage chemo	≈ 20%	≈ 30%	2,3/5,6 noCR/CR
Fiegl, 2014[14]	Median 57	161	relapsed or refractory	SHAI (=Cytarabine+Idarubicin)	≈ 10%	20%	25% first CR 30% ORR 27% non-responder
	Median 52	165	relapsed or refractory	F-SHAI (Fludarabine+Cytarabine+Idarubicin)	≈ 10%	20%	31% first CR 38% ORR 18% non-responder
Braess, 2009[49]	Median 54	172	first diagnosis of de novo AML	S-HAM	≈ 7%	≈ 12%	61% CR, 22% CR with incomplete peripheral recovery 7% persistent leukemia

Abbreviations: AML, acute myeloid leukemia; OS, overall survival; NRM, non-relapse mortality; CR, complete remission; CR(i), complete remission with incomplete recovery of thrombocytes and/or neutrophils; HR, high risk; BM, bone marrow; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; m, month; y, years; ≈ indicates data extracted from Kaplan-Meier curves; for detailed information on dosage and schedule of the administered chemotherapies please see the original publication.

Table 16. Allogeneic Transplantation in patients with relapsed and/or refractory AML.

Study	**Age**	**Number**	**Disease status**	**Conditioning**	**Day +30 mortality after HCT**	**Day +60 mortality after HCT**	**CR rate**	**Comments**
Stelljes[9]	Median 55	162	De novo AML /secondary AML	MelFlu/TBI (only 60% of the patients)	≈ 5%	≈ 10%	100% refractory	
Schmid, 2008[104]	Median 48	23	HR	FLAMSA-RIC	≈ 1%	≈ 3%	100% first CR	
Schmid, 2006[8]	Median 52	103	relapse	FLAMSA	≈ 7%	≈ 14%	91% CR	
Schmid, 2012[105]	Median 53	18	complex karyotype AML	FLAMSA-RIC	≈ 4%	≈ 6%	89% CR	
Schmid, 2005[7]	Median 52	75	HR	FLAMSA-RIC	7%	-	42% 2y	
Lee, 2013[73]	Median 41	32	standard/high-risk AML	BuFlu	≈ 3%	≈ 6%	75% first CR 9% second /third CR 16% refractory disease	mortality rate only for all patients (56% AML, others: ALL, CML, MDS)
		38		BuCy	≈ 3%	≈ 6%	76% first CR 11% second/third CR 13% refractory CR	mortality rate only for all patients (56% AML, others: ALL, CML, MDS)

Buchholz, 2012[106]	Median 58	27	r/r/HR	CLARA + RIC	≈ 12%	≈ 15%	56% 2y	
Armistead, 2009[4]	Median 44	130	relapse	RIC/MAC	≈ 10%	≈14%	5/11 noCR/CR	
Bornhäuser, 2012[45]	Range 18-60	99	AML in first complete remission	FluTBI8	≈ 2%	≈ 4%	CR	
					≈ 6%	≈ 12%	Non-CR	
Bredeson, 2013[79]	Median 45	697	AML	IV-BU 41% FluBu 59% BuCy	≈ 2%	≈ 4%	60% first CR	mortality rate only for all patients (68% AML, others: CML, MDS)
					≈ 3%	≈ 6%	20% second CR	mortality rate only for all patients (68% AML, others: CML, MDS)
					≈ 5%	≈10%	20% relapsed	mortality rate only for all patients (68% AML, others: CML, MDS)

Abbreviations: AML, acute myeloid leukemia; OS, overall survival; NRM, non-relapse mortality; CR, complete remission; CR(i), complete remission with incomplete recovery of thrombocytes and/or neutrophils; HR, high risk; BM, bone marrow; PBSC, peripheral blood stem cells; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total body irradiation; m, month; y, years; ≈ indicates data extracted from survival graphic.

15.3.1.2 Assumptions for success rates

The success rates for the two treatment strategies were estimated independently by combining probabilities for the different treatment stages.

The main difference between the two strategies is that a higher mortality prior to transplantation must be assumed for the remission-induction strategy compared to the disease-control strategy (10% versus 5%). Since less time will be available for donor search with the disease-control strategy - aiming at transplantation as soon as possible - the probability of donor-related drop-out was set to 7.5% compared to only 5% for patients in the remission-induction strategy. Despite this, the rate of transplantation is assumed to be higher in the disease-control strategy (83.5%) compared to the remission-induction strategy (70.5%). This difference is explained by more severe complications expected after remission-induction chemotherapy compared to no or less toxic anti-proliferative medication with the disease-control strategy. Further, it is assumed that 50% of patients achieve a complete remission with remission-induction chemotherapy. The Day +56-mortality and complete remission rate after transplantation are assumed to be mainly related to the remission status and the treatment history. It is assumed that patients with residual disease but no aggressive pre-treatment have a Day +56-mortality of 10% but 90% of survivors will be in complete remission by that time. Patients who received remission-induction chemotherapy, but failed to achieve a complete remission, are assumed to have the highest mortality after transplantation (20%) and only 77.5% are expected to achieve a complete remission by Day +56. In contrast, patients who achieved a complete remission prior to transplantation, and had time to recover from aggressive remission-induction chemotherapy, are assumed to have a 5% probability of death up to Day +56, and a 95% probability to remain in complete remission.

By combining these probabilities, the success rate in the disease-control strategy is assumed to be 67.6% compared to 55.2% with the remission-induction strategy.
These average success rates are assumed to apply to all strata, including the stratum “poor response AML, intermediate disease risk and age ≤60 years” which is enrolled only from protocol version 5.0 onwards. There is neither sufficient medical justification nor clear evidence from literature that the treatment effect will differ significantly between the 8 strata.

15.3.2 Sample size estimation

The study is planned as single stage randomized trial, comparing remission-induction to disease-control as strategy in patients with high-risk AML scheduled for allogeneic HCT. The primary endpoint is disease-free survival at +56 days after HSCT. The outcome is binary (success versus failure). All patients for whom no treatment success can be determined, or who did not reach the landmark, will be considered as failures. Treatment success is defined as documented complete remission after allogeneic HCT.

For sample size calculation, a difference between the success rate in the disease-control strategy and the remission-induction strategy of 12.4% (67.6% to 55.2%) in favour of the disease-control arm is assumed. Further, the non-inferiority bounding has been set at 5%, the Type I error at 2.5% and the power at 80%. A balanced allocation ratio (1:1) is planned for the remission-induction and disease-control strategy. With these assumptions, the total number of patients for the primary efficacy analysis has to be 246 (123 per arm). Since the non-inferiority of the disease-control versus the remission-induction strategy has to be demonstrated both in the FAS and the PP population, and since the PP population is assumed to comprise only 80% of the FAS population, the number of patients to be enrolled into the study is determined as 246 x 10/8. The final patient number thus is 308 patients (154 in each arm). The trial is powered to demonstrate non-inferiority in the PP population in order to demonstrate that per protocol treated patients have a non-inferior outcome compared to control treatment after having demonstrated this in the FAS population.

15.4 Termination of Recruitment

Recruitment will be terminated once the PP population comprises at least 246 patients.

15.5 Statistical methods

15.5.1 Demographic and baseline characteristics

The FAS and per-protocol treated populations will be characterized separately. The baseline characteristics will be presented using summary statistics for continuous variables and frequency tables for categorical variables. Listings and summary tables of standard demographic and baseline disease characteristics will be produced for each population. Covariate imbalance between the two treatment arms will be tested in the FAS

and PP population by appropriate statistics. The chi-square test will be used for categorical variables and the Wilcoxon test for continous variables.

15.5.2 CONSORT statement

The clinical course of the FAS will be provided in a flow chart summarizing the clinical trial in accordance with the CONSORT statement[107]. The applied treatment strategies, the rates of transplantation, the success rate, and causes of failure will be described for the FAS population.

15.5.3 Primary efficacy analysis

The primary endpoint is disease-free survival on Day 56 after HCT. The primary endpoint is a success rate which is defined in a dichotomous way. Either the patient has a confirmed remission by Day 56 after HCT (defined as a treatment success) or the patient is considered as a treatment failure. The observation time and the subsequent definitions allow that all patients can be evaluated for the primary endpoint. The following events will be considered as failures:

- Complete remission has not been confirmed by Day 56 after HCT.
- Early relapse occurred before Day 56 after HCT.
- HCT has not been performed within 16 weeks from randomization.
- Patient was lost to follow-up before Day 56 after HCT.

The primary efficacy analysis will be completed once the target number of patients in the PP population has been achieved.

The null hypothesis is H_0: pi2 - pi1 ≤ -0.05, where pi2 is the success rate in the DISC arm and pi1 is the success rate in the RIST arm. The non-inferiority margin is 5%. Success rates in the DISC and RIST arm will be presented together with two-sided 95% confidence intervals. The null hypothesis will be tested by means of the test for non-inferiority of binomial trials described by Farrington and Manning (Statistics in Medicine, 1990, 1447-1454).

No interim analyses are projected. The non-inferiority margin is 5% and the one-side significance level is set at 2.5%. A hierarchical test-strategy will be applied. First, non-inferiority of disease-control versus remission-induction will be tested in the FAS population. If non-inferiority can be demonstrated in the FAS population, non-inferiority will also be tested in the PP population with the same test at the same significance level.

15.5.4 Secondary endpoints

Secondary endpoints will be analysed in the FAS population, the per-protocol population and further subgroups of patients. No formal adjustment for the significance level will be performed for analyses of secondary endpoints. Most importantly, the primary efficacy analysis will be supplemented by the multivariate analysis of overall survival in the FAS population. A Cox regression model will be fitted for this purpose. The treatment allocation and the stratification factors will be entered as covariates.

A follow-up analysis focusing on long-term disease-control and overall survival will be conducted after a minimum follow-up of two years from randomization has been reached. If non-inferiority for DISC versus RIST can be shown for the primary endpoint in the PP population and FAS, then – adopting the concept of hierarchical testing - non-inferiority for overall survival from randomization will also be tested in a multivariable Cox regression model in the PP population at the 5% significance level with a non-inferiority margin of 1.15 for the hazard ratio, i.e. at most 5% difference for the survival rates. One series of analyses will be performed in order to test for gender-specific effects of the treatment strategy.

Probabilities of time-dependent events will be estimated according to Kaplan-Meier. The log-rank test and Cox regression modeling may be applied for further analyses of time-dependent endpoints. The incidence of competing events will be compared with the Gray test. Multivariate regression models will be fitted using the Fine & Gray and the Cox regression model. Further, extensions of the Cox model will be used to assess time-dependent effects.

15.5.5 Safety analysis

Safety information will be summarized by descriptive statistics. AEs will be reported for the remission-induction and the disease-control strategy and for different stages of treatment. Mortality by Day 30, Day 60 and Week 24 will be compared between the two arms and analysed for different causes of death. The rates of AEs during the study period will be reported and compared to each other by chi-square tests.

In order to better describe the safety of allogeneic transplantation and post-remission chemotherapy, additional safety analyses will be performed in the as treated populations. The cumulative incidence of non-relapse-mortality at one and two years will be calculated for these populations and compared to each other. Acute and chronic GVHD will be described for the transplanted cohort. The incidence of maximum grades II-IV and III-IV acute GVHD,

and of overall and extensive chronic GVHD, will be described as time-dependent events with death as competing event.

15.6 Methods against bias

Contracts between the Sponsor and each site's principal investigators will be signed in order to formally agree upon the intention to conduct the trial according to the study protocol and applicable regulations, to comply with GCP, and to provide the support as needed. During the initiation process, the clinical monitor will introduce study procedures and documentation to the sites in detail, in advance of any recruitment. Independent clinical on-site monitoring will be undertaken to ensure integrity of the clinical data and adherence to the study protocol. The monitoring visits will focus on source data documentation, correctness of data, and adherence to the protocol.

Reasons for withdrawals will be evaluated and discussed in case of systematic differences. Sensitivity analyses will be performed in order to check for bias introduced by violation of eligibility criteria or lack of central confirmationP of the diagnosis.

Blinded central review of slides from the final remission assessment will be performed in order to rule out biased final remission assessment.

16 Reporting

All information concerning the clinical trial has to be treated confidentially. In all publications the confidentiality of patients' data has to be ensured. The trial has been registered at www.clinicaltrials.gov. By their agreement to participate in this trial, the investigators accept that the results of this clinical trial can be presented to national and international authorities. They also accept that in this context their name, address, qualification and grade of involvement in this trial will be published.

16.1 Confirmatory analysis

The confirmatory primary-efficacy analysis is to be performed within 6 months after final response assessment for the last patient in the study. The confirmatory statistical analysis and a statistical report will be carried out by the trial statistician. This study report will be written and published by the coordinating investigator together with the co-investigators on behalf of the Sponsor.

16.2 Follow-up analysis

A follow-up analysis focusing on long-term disease-control and overall survival will be published with a minimum follow-up of two years for the last patient enrolled. The analysis will be conducted by the trial statistician, and published by the coordinating investigator together with the co-investigators on behalf of the Sponsor.

17 Ethical, legal and administrative aspects

17.1 Responsibilities of the investigator and the sponsor

The **Sponsor** (DKMS gemeinnützige GmbH) has the overall responsibility for the clinical trial including initiation, organization, and financing. The sponsor and the Coordinating Investigator assure that the clinical trial is performed in accordance with:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996,
- Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh, 2000, Fortaleza 2013),

This trial must be carried out in compliance with the protocol and in accordance with the sponsor's standard operating procedures. The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice. The responsibilities of the investigator include:

- Understanding of the trial intervention, as described in the protocol and the prescription information.
- To treat patients according to the study treatment plan.
- Allocate sufficient time to perform the clinical trial.
- Correct documentation of study related data and reporting.
- Provide access to data for the sponsor, for the monitor, and for audits/inspections.
- Assure strict confidentiality and request similar confidentiality from her/his staff concerning information about patients and information provided by the sponsor.
- Study documents provided by the sponsor (protocols, prescription information, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

- Provide financial information and disclosures.

The investigator has full responsibility for the conduct of the clinical trial in the study center.

17.2 Vote of Ethics Committee, Notification of Authorities

Before implementing this trial, the protocol, the proposed informed consent form, and other information to patients must be reviewed by an independent Ethics Committee (EC). A signed and dated statement that the protocol and informed consent has been approved by the EC must be given to the sponsor before trial initiation. The name and occupation of the chairman and the members of the EC must be supplied to the sponsor. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Before implementing this trial, the approval of the federal authorities (Bundesinstitut für Arzneimittel und Medizinprodukte –Bfarm– or other national equivalents) has to be obtained (according to § 7 GCP, § 42 AMG). Furthermore, the study has to be notified to the local authorities (according to § 12 GCP, § 67 AMG).

17.3 Patient information and informed consent

Before inclusion in the clinical trial, the investigator must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail.

Each patient must be informed that participation in the clinical trial is voluntary and that she/he may withdraw from the trial at any time, and that withdrawal of consent will not affect her/his subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient should read and consider the statement before signing and dating it. (If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the trial, mentioning why the patient was unable to sign the form. No patient can enter the trial before his/her informed consent has been obtained).

The informed consent form is signed and dated by the patient and by the investigator. One original copy is kept in the ISF and another original copy is given to the patient.

Any changes to the proposed consent form suggested by the investigator must be agreed by the sponsor before submission to the EC, and a copy of the approved version must be provided to all participating study centers and the monitor after EC approval.

17.4 Patient insurance

On behalf of the sponsor, a patient insurance policy was enacted by the following company:

[redacted]

Number of policy: [redacted]

Cover extends to health impairments resulting from drugs and/or substances/investigational products administered in the course of the clinical trial for which the patient has given his/her written informed consent to participate. Cover also extends to health impairments through measures carried out on the body of the person in connection with the clinical trial of a drug and/or substance/investigational product carried out in accordance with the study protocol procedures. Cover extends to maximum [redacted] for the whole study and [redacted] for individual patients.

In order to ensure the cover, the study patients must strictly follow the instructions of the study team. They are not allowed to undergo any other medical treatment without consent of the investigators (except for emergencies). In case of an emergency treatment the patient must inform the investigator as soon as possible.

A health impairment that could possibly result from the study treatment has to be announced immediately to the investigator and to the insurance company. Furthermore the patients are forced to take all appropriate measures to clarify cause and extensiveness of the damage occurred. The conditions of the insurance are to be handed out to the patients together with his copy of the Informed Consent.

17.5 Privacy and confidentiality

Recording, storage, disclosure, and analysis of personal data of the patients within this clinical trial are in accordance with legal requirements. The patient has to agree on the handling of his/her data within the informed consent form. The patient has to be informed that:

- Data recorded on CRFs, will be handled confidentially, and disclosed to others (sponsor, local and national competent authorities, independent ethical committee, and European databases) only in pseudonymized form.
- Persons who are authorized by the sponsor and the authorities to monitor and inspect the clinical trial can have insight into patient related data. These persons have to handle the data confidentially. The clinical investigator is discharged from his/her medical confidentiality obligations toward the patient in respect of such persons.
- The written consent for data recording and documentation during this clinical trial is irreversible. When a patient withdraws the written consent, all data that are documented thus far can be used in pseudonymized form to analyse the effect of the study treatment if needed.

18 Publication Policy

The study will be registered in a clinical trials database (www.clinicaltrials.gov) which is accessible to the public. All information concerning the clinical trial has to be treated confidentially. In all publications, the confidentiality of patients' data has to be ensured.

By signing this study protocol, the investigators accept that the results of this clinical trial can be presented to national and international authorities. They also accept that in this context their name, address, qualification and grade of involvement in this trial will be published.

The findings from this clinical study, including the biometrics report, should be published in a reputable peer-reviewed medical journal in accordance with basic ethical principles, including preservation of the accuracy of the results and making both positive and negative results publicly available. Authorship will be credited in accordance with ICMJE guidelines (www.icmje.org): An author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1. Substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, and 2. Drafting the article or revising it critically for important intellectual content, and 3. Final approval of the version to be published, and 4. Agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. All four conditions should be met. Conversely, individuals who do not contribute in this manner do not warrant named authorship. Individuals who do not

meet criteria for authorship but who contributed materially to the manuscript will be recognized in acknowledgments when the manuscript is published.

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