Randomized Allogeneic Hematopoietic Study Stem cell transplantation compared to standard chemotherapy in patients in their first complete remission at the age of 60 years with AML intermediate Risk (standard risk) and HLA-compatible sibling or third-party donor

ETAL-1

A collaborative study by SAL, AMLCG and OSHO

Prospective, randomized, controlled, multicenter clinical study

Version 3.0, 06/22/2012

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sponsor
Technical University Dresden

Sponsor's study plan code: TUD-ETAL-1-045
EudraCT number 2010-019377-15

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List of abbreviations

a	acute
AE	Adverse Event
ALAT	Alanine aminotransferase
AMG	Medicinal Products Act
ASAT	aspartic aminotransferase
AR	Adverse Reaction (side effect)
ATG	Antithymocyte globulin
CR	Complete remission
CRA	Clinical Research Associate
CRF	Case Report Form (questionnaire)
CRi	Complete remission with no platelet recovery
CR1	Achievement of the 1st complete remission at the end of induction therapy
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board (data security committee)
eCRF	Electronic Case Report Form (electronic questionnaire)
FLT3	Fms-like tyrosine kinase 3
FPFV	First patient first visit
GCP	Good Clinical Practice
gGT	gamma-glutamyl transpeptidase
GvHD	graft-versus-host disease
HCT-CI	Hematopoietic Cell Transplantation-Comorbidity Index (Sorror-Score)
HSCT	blood stem cell transplant
iv	intravenous
I	International Conference on Harmonization
IMPD	Investigational medicinal product dossier
ISF	Investigator Site File
KKS	Coordination Center for Clinical Studies
KM	Bone marrow
KMP	Bone marrow puncture
LKP	Head of the clinical trial
LPLV	Last patient last visit
BILLION	Minimal residual disease
MUD	Matched unrelated donor (external donor with adequate HLA matching) not
N / A	applicable
ND	not done
NPM1	Nucleophosmin-1 (gene locus with predictive influence on important target parameters)
PBSZ	Peripheral blood stem cells

PEI	Paul Ehrlich Institute
po	per os
SAE	Serious Adverse Event
sAML	secondary AML
SAR	Serious Adverse Reaction
SAS	Statistical Analysis System
SCT	Blood stem cell transplant
SDV	Source Data Verification (original data comparison)
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction (Suspected Unexpected Serious Side Effect)
tAML	therapy-induced AML
TMF	Trial Master File (central exam folder)
UAR	Unexpected Adverse Reaction
ZKRD	Central Bone Marrow Donor Register Germany

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Synopsis

sponsor	Technical University Dresden
title	**Randomized study on allogeneic haematopoietic stem cell transplantation compared to standard chemotherapy in patients in first complete remission at the age of 60 years with AML intermediate risk (standard risk) and HLA compatible Sibling or third-party donors**
Short name	ETAL-1
Target population (or indication)	Patients with acute myeloid leukemia between the ages of 18-60 Years
Study design	Prospective, randomized, controlled, multicenter clinical study
Objectives of clinical test	- Study of the role of allogeneic hematopoietic Stem cell transplantation (HSCT) in primary post-remission therapy for acute myeloid leukemia (AML) contributes to intermediate risk Patients between the ages of 18 and 60 with an HLA-compatible sibling or unrelated donor - Improvement in overall survival after 4 years by 15% im Test arm (HSCT) compared to standard chemotherapy
Outcomes of the clinical trial	Primary target variable Overall survival 4 years after randomization Secondary outcomes - event-free survival - Incidence of recurrence - the cumulative incidence of non-recurrence-related lethality - Survey of the quality of life
Number of patients	356
Time schedule	• Planned duration of the recruitment phase: September 1, 2010 to August 31, 2013 • Expected time of 'last patient last visit': December 31, 2017
Inclusion criteria	• Acute myeloid leukemia • normal karyotype or none of the aberrations excluded below • Age 18 to ÿ60 • "fit for transplant" (suitable for an allogeneic transplant) • HLA-identical related donor (HLA-A / B / C / DRB1 high resolution 10/10 match) or HLA-compatible unrelated donor (A / B / C / DRB1 / DQB1 high resolution at least 9/10 match) identified. In patients with NPM1 positive / FLT3 negative AML, the donor should be identical in HLA-A / B / C / DRB1 / DQB1. • CR / CRi after induction chemotherapy • Written consent of the participant after the enlightenment
Exclusion-	• Cytogenetic changes: t (8; 21), inv. 16, complex karyotype, -7, -5, 5q-, abnormal 3, abnormal 11, t (6; 9), t (9; 11), 8+ with at least one

criteria	additional cytogenetic changes • Acute promyelocytic leukemia with evidence of t (15; 17) • Anamnestically known hypersensitivity to one of the drugs used or their ingredients or to Drugs with a similar chemical structure • Addiction or other illnesses that affect the person who do not allow to assess the nature and scope as well as possible consequences of the clinical trial • Pregnant or breastfeeding women o Women of childbearing age, except women who have the following Fulfill criteria: o Post-menopausal (12 months natural amenorrhea or 6 months amenorrhea with serum FSH> 40 U / l) o Postoperatively (hysterectomy or 6 weeks after bilateral oophorectomy) o Regular and correct use of a contraceptive method with an error rate of <1% per year (e.g. implants, depot syringes, oral contraceptives, intrauterine device IUD). It should be noted that combined oral contraception - in contrast to pure progesterone preparations - has a failure rate of <1%. With a Pearl Index <1%, IUDs are safer than copper IUDs. o Sexual abstinence o Partner vasectomy • Signs that the patient is unlikely to adhere to the protocol (e.g. unwillingness to cooperate) • Taking other study drugs or using others Study therapies within the last 28 days prior to study inclusion or simultaneous participation in other clinical studies
Course of the clinical test	***1. Study inclusion / randomization:*** Confirmation of the intermediate risk, donor availability and CR1 documentation (<5% blisters in the contrast medium) after the end of the final induction therapy for contrast medium puncture within 8 days after regeneration of the granulocytes> 500 / µl in the peripheral blood, maximum d56 from the start of therapy. G-CSF is optional; in the case of “regeneration blasts”, repunction within 10 days. **Patient information + study inclusion with randomization for CR / CRi and existing donor (related or unrelated with HLA A / B / C / DRB1 / DQB1 high resolution at least 9/10 match; with NPM1 pos. / FLT3 neg. AML 10/10 match).** Transplantation or consolidation therapy should be initiated within 4-Take place 6 weeks after randomization. ***2. Re-evaluation:*** KMP, if possible up to 28 days after CR1-Documentation, but at the latest immediately before consolidation or conditioning (a priori defined subgroups).
Exam related Procedures and laboratory tests	Remission controls Year 1 + 2: every 3 months Year 3 + 4: every 6 months

Treatment plan	**Test arm A:** Allogeneic stem cell transplantation as primary post-remission therapy **Conditioning therapy:** ÿ40 years: 12Gy / Cy 120 or Bu16 / Cy120 > 40-60 years (or Sorror Score ÿ 3): 8Gy / Flu or Flu / Bu8 or Mel 140 + / Flu **GvHD prophylaxis:** - CsA / MTX d1,3,6, (11) - External donors: also ATG **Transplant:** Preferably G-CSF-stimulated PBSZ (at least 4x 106 CD34 + cells / kg body weight), KM also possible. **Control arm B:** Consolidation therapy is optional (depending on the study group). Allogene stem cell transplantation in case of relapse or optionally in case of MRD increase / molecular relapse. The allogeneic stem cell transplantation in the control arm is not part of the clinical trial.

Visit plan

HSCT / Consolidation

phase	**recommended Standard diagnosis** up to	**Study inclusion / Randomization**	**Re-evaluation (HSCT preparation)** up to	**Rounds**
time	4 weeks after Initial diagnosis	4-6 weeks before HSCT / Consolidation	7 days before HSCT or Consolidation Therapy	Year 1: 3/6/9/12 months Year 2: 15/18/21/24 m. Year 3: 30/36 months Year 4: 42/48 months after starting conditioning / chemotherapy 4
Visits		**Study inclusion**	**Visit 1**	**Visit 2-13**
Inclusion / exclusion criteria		x		
Information and consent of the patient Report to the		x		
study center Randomization Demographic data		x		
Anamnesis Physical. Examination of vital signs		x		
		x	x (donor)	
		x		x
			x	
			x	
Karnofsky Index			x	x
HCT-CI			x	
KMP	x	x2	x3	x
laboratory [1]		x	x	x
pregnancy test		x	x	
HLA typing patient	x			
HLA typing siblings	x			
Initiation of donor search, contact with transplant center	x			
Donor availability		x		
AEs and SAEs			x	x
GvHD (at HSCT)				x
life quality		x		x

[1] Blood count with differential blood count, clin. Chemistry (creatinine, bilirubin, GOT / AST, CRP) and infection serology (CMV IgG)

[2] KMP to T15 / 16 + KMP according to IT2 (remission control)

[3] optimally up to 28d according to CR1 documentation, at the latest immediately before consolidation or conditioning)

[a] +/- 14 days in year 1 + 2 and +/- 4 weeks in year 3 + 4

1 initiation

1.1 Clinical Trial Background

Acute myeloid leukemia (AML) comprises a group of genetically heterogeneous clonal diseases of hematopoietic progenitor cells. It is the most common myeloid leukemia with a prevalence of 3.8 cases per 100,000 adults, rising to 17.9 per 100,000 over the age of 65. The most important prognostic indicators with regard to the therapy response are cyto- and molecular-genetic aberrations in the leukemic cells. On the basis of recurrent cytogenetic changes, a favorable, an intermediate and an unfavorable prognosis group can be distinguished. The approx. 45% of AML patients whose leukemia cells show no cytogenetic changes are assigned to the intermediate risk group, but differ considerably in their prognosis due to molecular genetic mutations / aberrations1 .

The cytogenetic classification is as follows1 :

- **low risk (LR):** t (8; 21) (q22; q22); inv (16) (p13q22) / t (16; 16) (p13; q22)
- **Intermediate risk (IR):** normal karyotype, t (9; 11) (p22; q23), all other characteristics that are neither high nor low risk
- **High risk / HR:** complex aberrant karyotype, del (5q), del (17p), -5, -7, -17, inv (3) (q21q26), t (3; 3) (q21; q26), t (6; 9) (p23; q34), t (9; 22) (q34; q11.2), t (v; 11) (v; q23) with Aus took t (9; 11) (p22; q23) (see intermediate risk)), 8+ with at least one additional zy togenetic change

In the case of largely standardized remission-inducing therapy after the initial diagnosis, post-remission therapy is of great importance for maintaining remission and the prospects of recovery from AML. After reaching an initial hematological complete remission (CR1), it is intended as a consolidating therapeutic measure to eliminate any residual tumor cells that may be present. Consolidation / maintenance chemotherapy, one-time dose-intensified chemo- or chemoradiotherapy with autologous haematopoetic stem cell transplantation (AHSCT) and allogeneic HSCT from a histocompatible family or third-party donor2 compete as essential modalities of post-remission therapy. Despite meaningful registry analyzes, oligocentric cohort studies, prospective studies based on the “donor versus no donor” principle and meta-analyzes, there is a lack of evidence from randomized controlled studies, especially with regard to the importance of allogeneic HSCT in patients in remission with AML at intermediate risk3.

Indeed, there is little doubt that allogeneic HSCT is the post-remission therapy with the highest antileukemic potential. This statement confirms the significantly lower recurrence rates compared to competing modalities in AML patients of all risk profiles4 .
The benefit, however, is partly due to the higher therapy-associated morbidity and mortality

[1] According to Döhner et. al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet, BLOOD, 21 January 2010, Vol. 115, No. 3

neutralized. Thus, allogeneic HSCT can only be considered if there is a risk of recurrence that has not yet been definitively determined, which is offset by a justifiable risk of transplantation, which is essentially determined by age and comorbidities4 .

Prospective data in a controlled comparison with alternative post-remission therapies were collected almost exclusively in the so-called “donor versus no donor” comparison, ie the allocation of a patient to allogeneic HSCT or post-remission therapy of the control arms depends on the availability of an HLA-identical sibling donor. On the one hand, this procedure harbors the risk of social or genetic bias. On the other hand, the availability of a donor in a variable high percentage is by no means a guarantee that the allogeneic HSCT can be carried out. The “intention-to-treat” analyzes therefore only allow conclusions to be drawn about the value of allogeneic HSCT in CR1 to a very limited extent, while the “on treatment” analyzes hardly allow or even allow definitive conclusions to be drawn in several prospective studies due to the small number of cases contrary trends and statements come up3,5. In addition, insufficient consideration is given to how the control groups are influenced by allogeneic HSCT in relapse.

Two published meta-analyzes evaluated the prospectively collected data on allogeneic HSCT as post-remission therapy for AML in CR16,7. The meta-analysis by Yanada et al. takes into account five prospective comparative studies with 3100 evaluable patients, of which 1151 patients were assigned to post-remission therapy in the form of allogeneic HSCT due to the availability of an HLA-identical sibling donor. For the entire study cohort, there was an overall survival advantage of approx. 15% ($p = 0.037$) in favor of allogeneic HSCT.
In further meta-regression analyzes, a very clear survival advantage for AML patients with unfavorable cytogenetics could be statistically confirmed, while no survival advantage could be demonstrated with a favorable cytogenetic risk. In the intermediate risk group, there was a survival benefit from allogeneic HSCT of approx. 9%, which, however, was not statistically significant6 .

The meta-analysis by Cornelissen et al. considers six prospective studies with more than 4000 patients. The authors come to the conclusion that the availability of a suitable sibling donor for AML patients in CR1 is associated with an average survival advantage of 12% after 4 years, provided that the cytogenetically favorable risk group is disregarded. For the intermediate risk group, the survival benefit from allogeneic HSCT in CR1 was particularly robust and significant due to the group size7 .

In the prospective study of the AML 96 of the SHG under the direction of Prof. G. Ehninger, a 15% higher probability of survival after four years was registered in patients with an intermediate risk for an allogeneic blood stem cell transplant compared with conventional post-remission therapy (60 vs. . 45%, Fig. 1). A comparison was made of patients who had achieved a complete remission after two cycles of induction and were then timely administered an allogeneic HSCT from a related donor or conventional chemotherapy according to the protocol. 70% of patients with an available family donor were transplanted in this study.

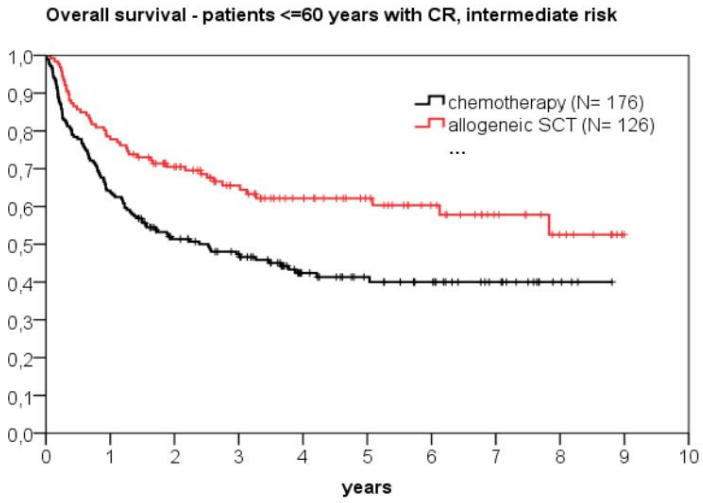

Fig. 1: Overall survival of patients <60 years with standard cytogenetic risk (intermediate risk) after achieving a complete remission as part of the AML 96 study of the DSIL. Patients after allogeneic blood stem cell transplantation from a related donor were compared with patients who received conventional post-mission therapy.

1.2 Necessity to conduct the clinical trial

These meta-analyzes have led to a consensus that the cytogenetically favorable risk group in CR1 does not require an allogeneic HSCT, whereas it is usually recommended in the case of a high-risk cytogenetic constellation. The question that is to be answered by the present study remains open as to whether allogeneic HSCT should already be carried out as post-remission therapy in CR1 in the large group of AML patients with intermediate cytogenetic risk or only if necessary when the disease recurs.

In a matched pairs analysis of data from the AMLCG 1999 study, we identified 746 from the group of patients allogenically transplanted in CR1 and the control arms with alternative post-remission therapy of 2547 evaluable patients who had achieved a first CR and were younger than 60 Years were. With the match criteria AML type (de novo, secondary, therapy-induced), cytogenetic risk group, age, time in CR1 (90 days) and optional gender and induction therapy, 97 patient pairs with a cytogenetically intermediate risk profile were found who either transplanted allogenically in CR1 or were treated conventionally in a control arm. With a significant advantage in favor of transplantation in recurrence-free survival of almost 25% (Fig. 2), an advantage in overall survival could not be statistically confirmed with a previously limited number of cases (Fig. 3), although here too a trend in the order of 15-
20% in favor of the transplant 8 .

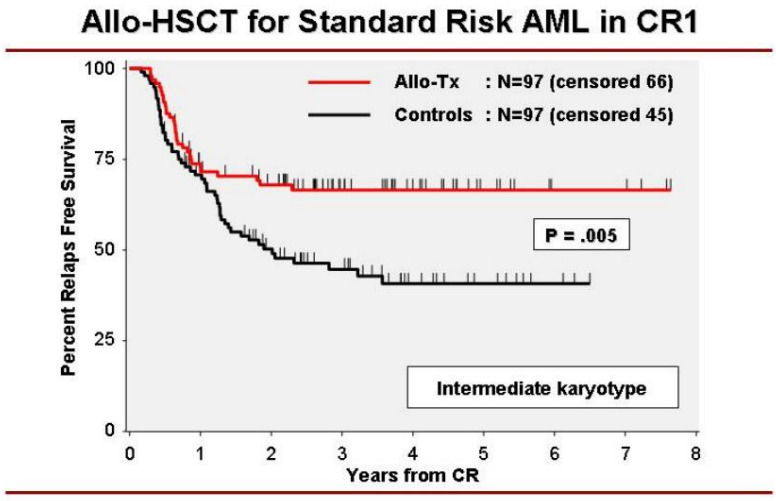

Fig. 2: Relapse-free survival in AML patients with standard cytogenetic risk. Results of a “matched pairs” analysis of data from the AMLCG 1999 study. Allo-Tx allogeneic HSCT in CR1; Controls, conventional post-remission therapy.

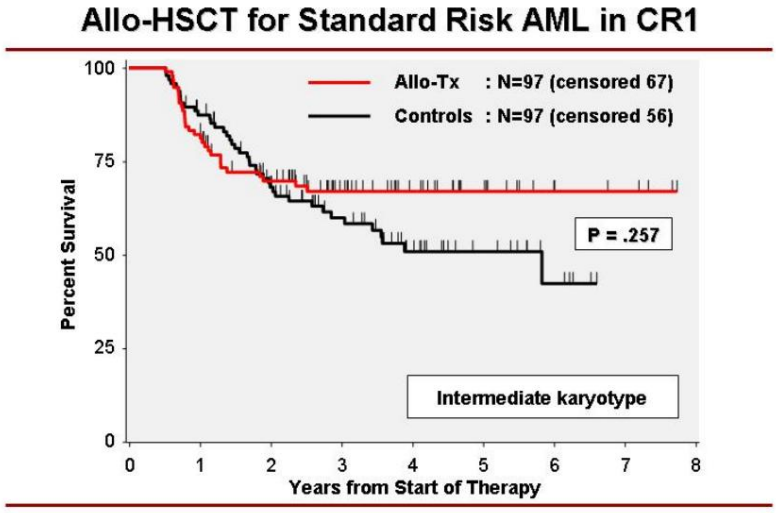

Fig. 3: Overall survival in AML patients with standard cytogenetic risk. Results of a "matched pairs" -
Analysis of data from the AMLCG 1999 study. Allo-Tx, allogeneic HSCT in CR1; Controls, conventional post-remission therapy.

Of particular interest is the observation that 1/3 of the patients with conventional post-remission therapy had to undergo allogeneic transplantation in relapse and that their overall survival was significantly less than 35% less than the control patients who were matched by the risk profile and who were transplanted in CR1 (Fig. 4).

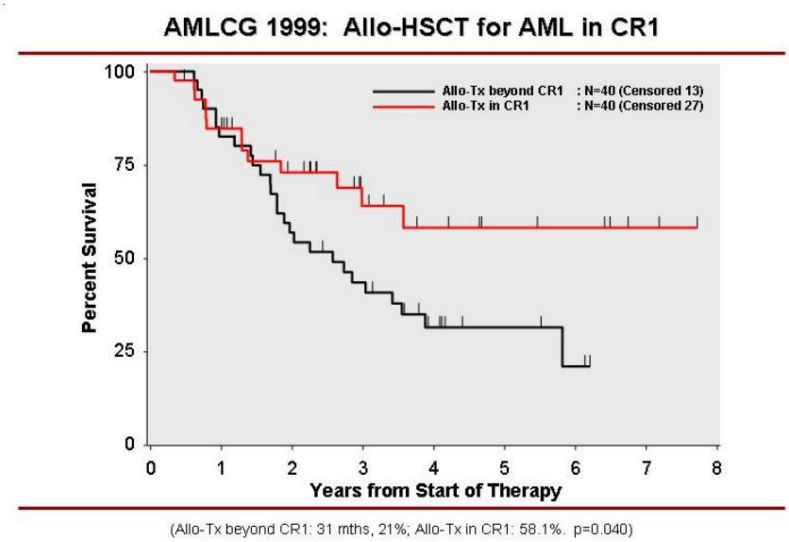

Fig. 4: Overall survival in AML patients with standard cytogenetic risk depending on the time of transplantation (CR1 versus relapse or CRÿ1). Results of a "matched pairs" analysis from the AMLCG 1999 study.
Allo-Tx beyond CR1, allogeneic HSCT in relapse or in CRÿ1.

1.3 Benefit-risk assessment

Literature data and the cited results of the “matched pairs” analysis allow the hypothesis that allogeneic transplantation in CR1 in AML patients with a cytogenetic intermediate risk can lead to an improvement in long-term overall survival in the range of 9-20%.
In order to achieve the 15% improvement in overall survival after 4 years, which was formulated as the primary study objective, around 40% of CR1 patients with a corresponding risk of morbidity and mortality would have to be transplanted, even though their leukemia has already been cured medically. Since, in the opinion of the study group, it is still not foreseeable today (molecular prognostic markers see below) who will benefit from allogeneic HSCT, needs it even at the earliest possible and evidently low-risk point in time in CR1 and who can postpone it until a relapse is necessary can even be postponed due to transplantation-associated risks (see also age and comorbidity score below), a randomized examination of these alternative approaches is not only ethically justifiable, but also advisable in terms of evidence-based medicine. It seems to the study group essential to include quality of life indices among the secondary goals of the study.

As obviously the question needs to be answered by a prospective study, the impracticability of the study is obvious if one restricts oneself to patients with a suitable sibling donor. In this approach, it is only possible to achieve the required number of recruits if CR1 patients with a suitable third-party donor are also included in the randomization. This is justified by the increasingly prevalent view that the results of third-party donor transplants with high-resolution HLA typing and under today's conditions of greatly improved supportive therapy no longer differ significantly from those of sibling donor transplantation9-13.

The question remains whether, at the present time, molecular risk markers of AML are already being taken into account as a randomization stratum or whether they should even lead to the exclusion of patients. A retrospective study by Schlenk et al.14 suggests that AML patients in the termed risk group with normal cytogenetics only benefit from an allogeneic HSCT in CR1.

if the leukemia cells have an FLT3-ITD mutation or none of the prognostically favorable NPM1 or CEBPÿ mutations without an FLT3-ITD mutation14. In our own "matched pairs" analysis, the prognostically favorable molecular phenotype NPM1 / FLT3 turns out mutated Wild type but also as a particularly favorable predictive criterion for patients who are in CR1 allo genes are transplanted (Fig. 4 and Fig. 5).

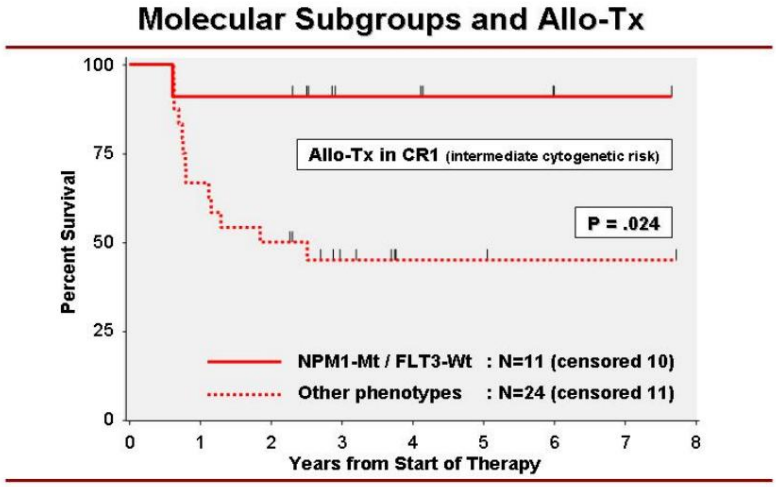

Fig. 5: Overall survival in AML patients with standard cytogenetic risk depending on the FLT3 / NPM1-Phenotype. Results of a “matched pairs” analysis of data from the AMLCG 1999 study. Mt, mutated; Wt, wild type.

So far, it has also been judged controversially whether molecular markers should or can already be taken into account as a randomization stratum or even used as a criterion for the definition of specifically treated sub-entities15. The participating centers are free to include patients with the NPM1 mutation in FLT3 wild type in the study. If possible, the NPM1 and FLT3 mutation status should be determined prior to inclusion in this clinical trial, as these parameters are used as a randomization stratum.

Since the aim of the study is to review a management algorithm, a definition of the conditioning therapy is not provided, especially since a clear superiority of a regime could not be shown so far. If a therapeutic benefit can be derived from the randomized previous study (comparison of standard conditioning with TBI 12 GY and cyclophosphamide with dose-reduced conditioning from TBI 8 Gy and fludarabine), a corresponding recommendation will be included in the present study protocol. The age- and comorbidity -dependent transplant risk4 is taken into account by recommending dose-reduced conditioning for patients aged ÿ40 years or with a transplantation-specific comorbidity score according to Sorror of ÿ3.

2 Objectives of the clinical trial

2.1 Primary objective of the exam

Investigation of the role of allogeneic hematopoietic stem cell transplantation in primary post-remission therapy of acute myeloid leukemia (AML) in patients at termed risk aged 18-60 years with HLA-compatible sibling or unrelated donors

Overall survival improved by 15% in the trial arm 4 years after randomization.

2.2 Secondary objectives of the exam

Event-free survival improved by 20% in the trial arm 4 years after randomization.
Events in the study sense are hematological relapse or death.

Reduction of the recurrence incidence after 4 years by 20% in the test arm.

Investigation of the cumulative incidence of non-relapse-related lethality in the test arm. The null hypothesis is that the cumulative incidence of non-relapse-related mortality in patients after allogeneic HSCT in first complete remission from both family and third-party donors does not exceed 15% over a period of 12 months.

Descriptive study of quality of life with the help of standardized questionnaires in both study groups.

3 Description of the clinical trial

3.1 Study design

It is a randomized, multicenter, controlled phase III study to investigate the importance of allogeneic blood stem cell transplantation in patients with AML at an intermediate risk (standard risk). The treatment takes place in 2 parallel groups.

3.2 Primary objective of the test

Overall survival 4 years after randomization

3.3 Secondary test objectives

- disease-free survival

- incidence of recurrence

- cumulative incidence of non-relapse-related lethality

- Quality of life over time

3.4 Examinations accompanying the examination

No accompanying research is planned. Should any questions arise in the course of the clinical trial, these will be submitted separately to the ethics committee.

Integrated examinations accompanying the examination result from the secondary questions and from the analysis of the a priori defined subgroups. These include routine examinations at initial diagnosis to confirm intermediate risk AML (cytogenetics). Molecular genetic examinations are also provided for the initial diagnosis, which can then be assigned

to enable the strata. These are also standard examinations in AML and are therefore not part of the clinical trial.

During the course of the study, regular examinations of the remission status with bone marrow and blood count tests are planned. These examinations are routine examinations in the treatment of AML and do not represent any deviations from normal medical practice. Central diagnostics are not provided.

3.5 Number of patients

For a possible inclusion in the study, approx. 600 patients with an initial diagnosis of AML and at termed risk after reaching a complete remission will be examined with regard to the further inclusion and exclusion criteria. In order to reach a number of 346 evaluable patients, 356 patients would have to be included and randomized. Allocation to the two study arms takes place in a ratio of 1: 1, taking into account the given randomization strata (molecular risk factors [NPM1 / CEBPÿ mutation without FLT3 mutation vs. other muations vs. not determined], age [ÿ40 vs.> 40 yrs.]. and donors [related vs. unrelated]).

3.6 Time schedule

- Planned duration of the recruitment phase: 01.09.2010 to 31.08.2013
- first patient first visit (FPFV): 09/01/2010
- Last patient first visit (LPFV): 08/31/2013
- Last patient last visit (LPLV): December 31, 2017
- Estimated time of the end of the examination: 30.06.2018

Definition of the end of the test: The study is ended when all randomized living patients have had a follow-up of at least 48 months and all data have been collected, quality checked, evaluated and prepared for publication.

3.7 Requirements for test centers and examiners

All centers and doctors with sufficient experience in the treatment of acute leukemia can take part in the study. Participation in a study center is voluntary. The necessary equipment of the centers and the qualification of the investigators must meet the requirements of modern hematological / oncological patient care. The study centers must be able to carry out the standard diagnosis of acute myeloid leukemia themselves using cytomorphology, cytochemistry, immunophenotyping and cytogenetics in accordance with the quality criteria of the “Acute and Chronic Leukemia” competence network, or to arrange for it to be validly carried out as quickly as possible. Since molecular risk factors are included in the randomization stratification (NPM1 / CEBPÿ mutation without FLT3 mutation vs. other mutations), the corresponding molecular genetic diagnosis should be initiated as part of the primary diagnosis (external or in-house laboratory). Furthermore, with the initial diagnosis, prompt HLA typing of the patient and possible family donors must be ensured and, if necessary, a quick search for an external donor must be initiated. In this regard, there should be close cooperation with appropriately experienced transplant centers. A protocol compliant

Each study center must be able to guarantee that the planned study therapy and follow-up care are carried out. The participation of a study center must be confirmed in writing by the study director and the doctor in charge of the respective study center before the first patient is reported.

The director of studies can decide to exclude a study center:

- if the documentation is of poor quality. This includes missing information, documentation errors or too long a delay between the reporting of a patient, the start of the study therapy and the arrival of the documentation at the study center

- if there are serious and repeated protocol violations

- in the event of inadequate or missing follow-up care or if there is no follow-up

- if external data monitoring to ensure data quality is rejected

4th Test population

Every patient with the initial diagnosis of acute myeloid leukemia is evaluated for possible inclusion in the study. During induction therapy, confirmation of the intermediate risk type with regard to AML and an immediate donor search (family and third-party donor search) are provided. If CR / CRi (blasts <5% in the bone marrow) are documented after the end of induction therapy and a donor is present (related or unrelated), the study is included with randomization.

The test population therefore consists of patients aged 18-60 years with AML with intermediate risk in first complete / incomplete remission who have an existing HLA-identical family or HLA-compatible donor.

Subgroups are defined a priori for later evaluation (see Chapter 11.4.3.)

4.1 Inclusion criteria

- Acute myeloid leukemia
- normal karyotype or none of the aberrations excluded below
- Age 18-60
- "fit for transplant" (suitable for an allogeneic transplant)
- HLA-identical related donor (HLA-A / B / C / DRB1 high-resolution 10/10 match) or HLA-compatible unrelated donor (A / B / C / DRB1 / DQB1 high-resolution at least 9/10 match) identified. In patients with NPM1 positive / FLT3 negative AML, the donor should be identical in HLA-A / B / C / DRB1 / DQB1.
- CR / CRi after induction chemotherapy
- Written consent of the person taking part after the information has been given

4.2 Exclusion criteria

- Cytogenetic changes: t (8; 21), inv. 16, complex karyotype, -7, -5, 5q-, abnormal 3, abnormal 11, t (6; 9), t (9; 11), 8+ with at least one additional cytogenetic change tion
- Acute promyelocytic leukemia with evidence t (15; 17)
- History of known hypersensitivity to one of the drugs used or their ingredients or to drugs with a similar chemical structure
- Addiction or other illnesses that do not allow the person concerned to Assess the nature and scope as well as possible consequences of the clinical trial
- Pregnant or breastfeeding women
- Women of childbearing age, excluding women who meet the following criteria:
  - Post-menopausal (12 months natural amenorrhea or 6 months amenorrhea with serum FSH> 40 U / l)
  - Postoperative (hysterectomy or 6 weeks after bilateral oophorectomy)
  - Regular and correct use of a method of contraception with an error rate of <1% per year (e.g. implants, depot syringes, oral contraceptives, intrauterine sar IUDs).

    It should be noted that combined oral contraception - in contrast to pure progesterone preparations - has a failure rate of <1%. With a pearl index <1%, hormone IUDs are safer than copper IUDs.
  - Sexual abstinence
  - Partner's vasectomy
- Signs that the patient is unlikely to adhere to the protocol (e.g. lack of willingness to cooperate)
- Taking other study drugs or using other study therapies in within the last 28 days prior to study inclusion or simultaneous participation in other clinical studies

4.3 Patient recruitment

At the end of the final induction therapy and after regeneration of granulocytes> 500 / µl in the peripheral blood (maximum d56 from the start of therapy), the inclusion and exclusion criteria are checked and the study is included with subsequent randomization. All patients between the ages of 18 and 60 who can be included and who have been diagnosed with AML will be reported by fax to the study center from the trial centers (exception: patients with a definite diagnosis of AML FAB M3).

The central element following the initial diagnosis is the donor search. Therefore, a high-resolution HLA typing (4 "digits" for HLA A / B / C / DRB1 and DQB1) including confirmation typing must be carried out for the initial diagnosis. Possible family donors should be typed within the first 1-2 weeks. If no family donor is available, after the patient has been informed (ZKRD forms), the

primary treating clinic. The search center must be informed immediately of the urgency of the search. The aim is to have identified a possible stem cell donor by the end of induction therapy (approx. 6 weeks after the initial diagnosis).

5 Trial intervention (allogeneic HSCT) / conventional consolidation and maintenance therapy

5.1 Description of the test intervention

Study inclusion with randomization occurs after documented complete remission (CR) or incomplete remission (CRi, i.e. CR bone marrow, granulocytes <1000 / µl in the peripheral blood, no blasts in the peripheral blood, no evidence of extramedullary AML manifestations, persistent anemia and / or thrombocytopenia) and identification of an existing donor. For the purpose of subgroup assignment as part of the planned confirmatory analysis, a new remission assessment with documentation of the clinical findings including a new bone marrow puncture is necessary (a maximum of 28 days after CR1 documentation, optionally immediately before conditioning therapy).

Donor selection / conditioning therapy

The corresponding randomization result will be communicated to the primary treatment center (trial center) as well as to the planned transplant center within 2 working days of the study inclusion by the study center (Dresden). If necessary, if a patient is assigned to the test arm (A), an order for the allogeneic stem cells with the note "high urgent" must be made immediately via the ZKRD. The transplant center is responsible for this.

Transplant conditioning therapy should occur within 4-6 weeks of randomization. Bridging consolidation therapy is possible in justified exceptional cases. If there are family donors, the request via the ZKRD is not applicable. For the start of the conditioning therapy, the same rules apply as for third-party donors.

The possible conditioning regimes are specified (see Section 5.5). The donor selection with regard to the necessary matches in the HLA characteristics is specified in the inclusion criteria (related or unrelated donors: HLA A / B / C / DR / DQ high resolution at least 9/10 match; for NPM1 pos. / FLT3 neg. AML 10 / 10 match). If several possible donors are available, the following criteria should be observed in descending order:

1. Male patients should receive stem cells from male donors whenever possible.
2. CMV-positive patients should preferably not transplan from CMV-negative donors be animalized.
3. CMV-negative patients should preferably be transplanted from CMV-negative donors will.
4. Blood group major incomatiblities should be avoided

Regarding the risk of virus and prion infections, the selection of donors is also based on Directive 2006/17 / EC and the "Guidelines for the collection of blood and blood components and for the use of blood products (haemotherapy)".

Stem cell preparation

The following guidelines are given for the transplant:

- Peripheral blood stem cells: at least 4x 106 CD34 + cells / kg body weight of the patient - Bone marrow: at least 1.5x 106 CD34 + cells / kg body weight of the patient

In vitro manipulations of the transplant such as T-cell depletion are not intended (exception: erythrocyte depletion from bone marrow transplants as specified by the transplant center).

Previous cryopreservation of allogeneic stem cell preparations should be avoided.

Growth factors

G-CSF stimulation of the patient after allogeneic HSCT is not intended.

GvHD prophylaxis

As a GvHD prophylaxis, the following regimen is uniformly provided regardless of the conditioning therapy:

Cyclosporin A (CSA), start on day -1 (target level 150-200 ng / ml), tapering of CSA, as far as possible, from day +100 with the goal of completely discontinuing CSA by day +180.

Methotrexate (MTX) 15 mg / m2 on day 1, 10 mg / m2 on days 3, 6 and optionally 11,

preferably ATG Fresenius (3 x 10-20 mg / kg day -3 to -1) 27, alternatively ATG Genzyme (3 x 2.5 mg / kg day -3 to -1) additionally only for third-party donors with and without allele / antigen mismatch.

Supportive therapy

Supportive therapy as well as the corresponding treatment of complications (severe organ toxicities, infections or GvHD) are provided according to the transplant unit. Transplant centers should have written procedures in place that are regularly updated for supportive therapy and the most common complications.

5.2 List of side effects and interactions

Only established and approved drugs and cytostatics are used. There are numerous side effects with all of the cytostatics used. Their intensity varies with the individual substances and depends on the dosages. The application requires extensive experience from the test center.

Potential side effects, which essentially result from the effect of these substances on proliferating tissue and from intolerance reactions, can be found in the specialist information for healthcare professionals.

Additional information can be found in the "Investigator's Brochure" or the "IMPD".

5.3 Control arm (conventional consolidation therapy)

Consolidation therapy should take place within 4-6 weeks of randomization.
For the purpose of subgroup assignment (a priori defined subgroups), a new remission assessment with documentation of the relevant clinical findings including a new conchinal puncture (maximum 28 days after CR1 documentation, optionally immediately before consolidation therapy) is necessary. Consolidation and, if necessary, maintenance therapies in the control arm ~~are optional~~ (depending on the study group). According to the ELN guidelines and the DGHO guideline, three cycles of high dose AraC on days 1-3-5 with 3000 mg / m2 / 12 hours each are recommended.

An allogeneic stem cell transplant should be performed in the event of relapse (relapse and conditioning therapies are also optional). If the recurrence is detected early (molecular / cytogenetic) and the donor is available, the allogeneic salvage HSCT can also be performed without prior induction therapy. The post-remission therapies and the indications for allogeneic HSCT in the control arm are documented and evaluated within the study.

5.4 Randomization

Patients who meet all inclusion criteria after completion of induction therapy, who have given their consent to participate in the study and for whom there is no exclusion criterion, will be included in the study and randomized into one of the two therapy arms.

The randomization was carried out in a ratio of 1: 1 in both study arms.

Stratification features are:

- Age ÿ40 vs.> 40 years,
- unrelated donor (at least 9/10 HLA match: HLA-A, B, C, DRB1, DQB1 high-resolution) vs. HLA-ident. Family donors,
- Isolated NPM1 or CEBPÿ mutation vs. other molecular markers

This results in the following strata:

ÿ 40 years				> 40 years			
unrelated donor	related donor	unrelated donor	related donor				
NPM1 ÿ u./o. CEBPÿ ÿ With FLT3 ÿ	FLT3 ÿ With CEBPÿ ÿ / ÿ and / or. NPM1 ÿ / ÿ *or* other mutation *or* none mutation or not definitely	NPM1 ÿ u./o. CEBPÿ ÿ With FLT3 ÿ	FLT3 ÿ With CEBPÿ ÿ / ÿ and / or. NPM1 ÿ / ÿ *or* other mutation *or* none mutation or not definitely	NPM1 ÿ u./o. CEBPÿ ÿ With FLT3 ÿ	FLT3 ÿ With CEBPÿ ÿ / ÿ and / or. NPM1 ÿ / ÿ *or* other mutation *or* none mutation or not definitely	NPM1 ÿ u./o. CEBPÿ ÿ With FLT3 ÿ	FLT3 ÿ With CEBPÿ ÿ / ÿ and / or. NPM1 ÿ / ÿ *or* other mutation *or* none mutation or not definitely
Stratum 1	*Stratum 2*	*Stratum 3*	*Stratum 4*	*Stratum 5*	*Stratum 6*	*Stratum 7*	*Stratum 8*
Arm A2							
Arm B							
Arm A							
...							

The randomization of the patient to the therapy group is carried out centrally by the study center in Dresden. The result will only be made known to the doctor and the patient after the patient has been included in the study. The randomization list cannot be viewed by the study participants and the assignment of the patient to the therapy group cannot be foreseen by either the doctor or the patient.

The study center must report back within 2 working days after receipt of the fax. The investigator is informed of the patient number and the respective treatment arm by fax.

The following therapy arms are provided:

A - test arm:

Allogeneic hematopoietic stem cell transplant in first complete remission.

B - standard arm:

Post remission with conventional chemotherapy according to center-specific standards

[2] The sequence of stratification shown is arbitrary and is shown here as an example.

5.5 Approved treatment regimens in the test arm (allogeneic HSCT)

In the present study, different conditioning therapies are not used against one another der, but the “early allogeneic HSCT” procedure with non-transplanation-based consolidation Therapy compared with the allogeneic HSCT option after relapse. For the intended scheme ta there is sufficient evidence regarding its applicability in the context of allogeneic HSCT. The individual elements of conditioning therapy are not the subject of clinical Check, but are used as standard in the treatment routine. The definition A largely uniform therapy for the patient should be based on the conditioning regimen shown ensure ducks in the test arm.

The time sequence of the individual chemotherapeutic agents and / or the radiation can correspond according to center-specific standards. The time sequence of ATG, MTX and CSA in Reference to the time of transplantation (day 0) is fixed. The MTX administration on day 11 is opti onal and can be omitted in the case of severe mucositis and / or higher-grade organ toxicity. The add The use of ATG is foreseen if the donor is not related. The recommended dose tion when using ATG-Fresenius is 3 x 10-20 mg / kg body weight.

Patient-specific dose modifications in the event of severe functional restrictions of Or gans are possible.

Conditioning protocols for patients aged 18-40 years

TBI (12 Gy) / cyclophosphamide

Day	-6	-5	-4	-3	-2	-1	0				+ 1 / + 3 / + 6 / + 11	+100	+180
Whole-body irradiation [a] (2 x 2 Gy / day)	X	X	X	X	X	X							
Cyclophosphamide [b] (60 mg / kg iv)							XX						
Pause									X				
SZ Infusion										X			
Methotrexate [c]											X		
Cyclosporine A									XX		X	Taper taper	
Unused Donor: ATG [d]							XX	X					

[a] Lung dose 8 Gy, supportive therapy with serotonin antagonists and hydration according to the protocol of the participating center

[b] Cystitis prophylaxis with

[c] MESNA 15 mg / m2 on day 1, 10 mg / m2 on days

[d] 3, 6 and 11 preferably ATG Fresenius 3 x 10-20 mg / kg27, alternatively ATG Genzyme 3 x 2.5 mg / kg, premedication with corticosteroids , H1 or H2 blockers.

Busulfan [a] / Cyclophosphamide

Day	-7	-6	-5	-4	-3	-2	-1	0				+ 1 / + 3 / + 6 / + 11	+100	+180
Busulfan away (4 mg / kg po)	X	X	X	X										
Cyclophosphamide [c] (60 mg / kg iv)								X	X					
Pause										X				
PBSZ Infusion											X			
Methotrexate [d]												X		
Cyclosporin										X	X		Taper taper	
A *Unverw. Donor:* [e]								X	X	X				

[a] *ATG* as an alternative to oral busulfan, Busulfex® iv can also be given in a dose of 4 x 0.8 mg / kg on 4 consecutive days (total dose: 12.8 mg / kg ideal body weight)

[b] Prophylaxis of cerebral seizures according to the center's internal standards, cystitis

[c] prophylaxis with MESNA 15 mg / m2 on day 1, 10 mg / m2 on days 3, 6 and 11,

[d] preferably ATG Fresenius 3 x 10-20 mg / kg27, alternatively ATG Genzyme 3 x 2.5

[e] mg / kg, premedication with corticosteroids, H1 or H2 blockers.

Conditioning protocols for patients> 40 years of age and for patients with multiple comorbidities (HCT-CI ÿ3, see Appendix II)

TBI (8 Gy) / fludarabine

Day	-6	-5	-4	-3	-2	-1	0				+ 1 / + 3 / + 6 / + 11	+100	+180
Whole body irradiation [a] (2 x 2 Gy / day)						X	X	X	X				
Fludarabine (30 mg / m2 iv)	X	X	X	X									
Pause										X			
PBSZ Infusion											X		
Methotrexate [b]											X		
Cyclosporin A										XX	X	Taper taper	
Unverw. Donor: ATG [c]							X	X	X				

[a] Supportive therapy with serotonin antagonists and hydration according to the participant's protocol Center

[b] 15 mg / m2 on day 1, 10 mg / m2 on day 3, 6 and

[c] 11 preferably ATG Fresenius 3 x 10-20 mg / kg27, alternatively ATG Genzyme 3 x 2.5 mg / kg, premedication with corticosteroids, H1 or H2 blockers.

Busulfan [a] / Fludarabine

Day -6 -5 -4 -3 -2 -1 0								+ 1 / + 3 / + 6 / + 11	+100 +180	
Busulfan [away] (4 mg / kg po)			**XX**							
Fludarabine (30 mg / kg iv)	**XXXXX**									
Pause						**X**				
PBSZ Infusion							**X**			
Methotrexate [c]								**X**		
Cyclosporin						**XXX**			**Taper taper**	
A *Unverw. Dispenser* [d]		**XXXX**								

[a] *ATG* as an alternative to oral busulfan, Busulfex® iv can also be given in a dosage of 2 x 0.8 mg / kg on 4 consecutive days (total dose: 6.4 mg / kg ideal body weight)

[b] Prophylaxis of cerebral seizures according to the center's internal standard 15 mg /

[c] m2 on day 1, 10 mg / m2 on days 3, 6 and 11, preferably ATG Fresenius 4 x 10 mg /

[d] kg27, alternatively ATG Genzyme 3 x 2.5 mg / kg, premedication with corticosteroids, H1 or H2 blockers.

Treosulfan / Fludarabine

Day -6 -5 -4 -3 -2 -1 0								+ 1 / + 3 / + 6 / + 11	+100 +180	
Treosulfan (14 g / m2 iv)	**XXX**									
Fludarabine (30 mg / kg iv)	**XXXXX**									
Pause						**X**				
PBSZ Infusion							**X**			
Methotrexate [a]								**X**		
Cyclosporin A						**XX**		**X**	**Taper taper**	
Unverw. Donor: ATG [b]				**XXX**						

[a] 15 mg / m2 on day 1, 10 mg / m2 on day 3, 6 and

[b] 11 preferably ATG Fresenius 3 x 10-20 mg / kg27, alternatively ATG Genzyme 3 x 2.5 mg / kg, premedication with corticosteroids, H1 or H2 blockers. .

Melphalan / fludarabine

Day -6 -5 -4 -3 -2 -1 0								+ 1 / + 3 / + 6 / + 11	+100 +180	
Melphalan (140 mg / m2 iv)					**X**					
Fludarabine (30 mg / kg iv)	**XXXXX**									
Pause						**X**				
PBSZ Infusion							**X**			
Methotrexate [a]								**X**		
Cyclosporin A						**XXX taper taper**				
Unverw. Donor: ATG 15 [b]				**XXX**						

[a] mg / m2 on day 1, 10 mg / m2 on days 3, 6 and

[b] 11, preferably ATG Fresenius 3 x 10-20 mg / kg27, alternatively ATG Genzyme 3 x 2.5 mg / kg, premedication with corticosteroids , H1 or H2 blockers.

6th Examination process

The examination process consists of study inclusion, re-evaluation, the study / intervention phase (HSCT / consolidation) and the planned therapies, both in the test and in the control arm, are established standard procedures. Both possible post-remission therapies (conventional chemotherapy and allogeneic HSCT) are being examined as procedures. Individual therapy elements are not the subject of the clinical trial. In the study / intervention phase, regular remission controls are recommended, the results of which are documented for the purpose of assessing the progress.

6.1 Standard diagnostics before the start of the study

AML initial diagnosis: The initial diagnosis should be accompanied by an appropriate biological classification of AML using cytology, immunophenotyping, cytogenetics and molecular genetics. The individual examinations are part of the general routine diagnostics for patients with the initial diagnosis of AML and are not part of the ETAL-1 study. For the purpose of later assignment to the subgroups defined *a priori ,* molecular genetic diagnostics should take into account at least NPM1, FLT 3 and CEBPÿ muations. The cytogenetic classification of AML is specified in the inclusion and exclusion criteria (see Chapter 4) and must therefore be available for each study patient. Once the AML diagnosis has been confirmed, blood or a cheek swab should be obtained from the patient for HLA typing.

HLA typing: Fig. 6 gives an overview of the typing algorithm that should ideally be attempted after the patient has reported. For HLA typing, 10 ml of EDTA blood should be drawn. Alternatively, a swab of the cheek mucous membrane can be performed as instructed.

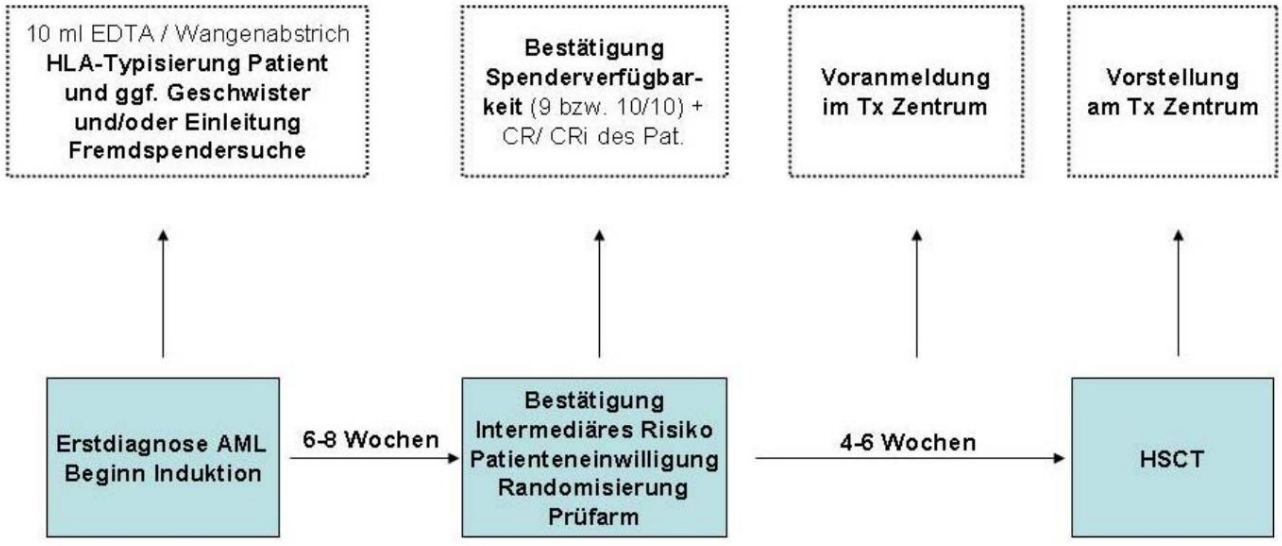

Fig. 6: HLA typing / donor search

After the initial diagnosis , sample material from the patient and possible sibling donors should be sent to the cooperating HLA laboratory for HLA typing. In general, use of the reference immunogenetics laboratory DKMS-Life Science Lab (Fiedlerstrasse 34, 01307 Dresden

den) open. At this point in time, once the initial typing has been made, a query is made in the Bone Marrow Donors Worldwide register (www.bmdw.org) in order to clarify the likelihood of donor availability.

If the diagnosis of AML with intermediate risk is confirmed, another 10 ml EDTA blood is drawn for HLA confirmation typing. This should preferably be done in the same HLA laboratory as the primary typing.

If no family donor has been identified, both the patient and the attending study doctor should fill out the ZKRD form (www.zkrd.de) to initiate the search for a third-party donor while the confirmation typing is being taken. The relevant forms (medical reports and the patient's consent) can be found in the annex to the study protocol, and an exemplary completed copy can also be viewed. Ideally, the search for an external donor should be carried out via the search center that works with the relevant transplant clinic. Appendix IX lists the search units for the respective study transplant centers with contact addresses.

Immediately after a family donor has been identified or when the search for an external donor has been initiated, the cooperating transplant center should be contacted so that, in the event of randomization in the test arm, the patient can be presented to the center approx. 3-4 weeks after contact has been made.

During the search for external donors, the centers will query the status of the sample receipt and the typing results in the search unit every 7-14 days.

Patient information: The information is provided personally by the treating doctor and in writing by the patient information department. Only after clarifying all of the patient's questions will he be asked to sign the consent to participate in the study and to date it himself. The participant is then given a copy of the patient information / declaration of consent; the original is kept in the investigator's folder. A message is sent to the study center.

6.2 Study inclusion / randomization

The study inclusion takes place with documentation of the first complete remission or incomplete remission (<5% blasts in the contrast medium without complete peripheral regeneration) and the signing of the consent to the study by the patient and the investigator. After the end of the induction therapy, the contrast puncture takes place within 8 days after regeneration of the granulocytes> 500 / µl in the peripheral blood, maximum d56 from the start of therapy (G-CSF is optional; in case of regeneration blasts, repunction within 10 days). In addition, the successful identification of an existing donor (related or unrelated to HLA A / B / C / DRB1 / DQB1 high resolution at least 9/10 match; with NPM1 pos. / FLT3 neg. AML 10/10 match) is a prerequisite for inclusion .

Examination program: -

Checking the inclusion / exclusion criteria / checking the donor availability

- Informing the patient + signing the declaration of consent

- Report the patient to the study center for randomization
- Demographic data
- Anamnese
- Bone marrow puncture (determination of CR / CRi) including determination of the level of the minimum Residual disease
- Blood count with differential blood count, infection serology (CMV IgG)
- Pregnancy test
- Questions about quality of life

Transplantation or consolidation therapy should take place within 4-6 weeks of randomization!

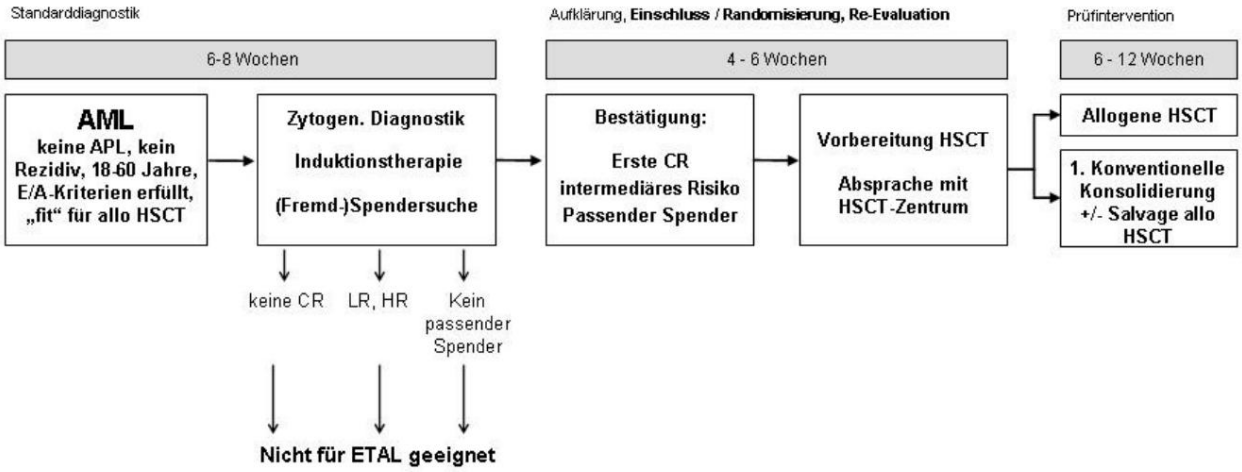

Fig. 7: Overview of the course of the study up to the test intervention

6.3 Re-evaluation (visit 1)

The following examinations are necessary as part of the re-evaluation:

- Physical examination
- vital signs
- Karnofsky index
- HCT-CI
- Bone marrow puncture (maximum 28 days according to CR1 documentation; optionally immediately before consolidation or conditioning) including MRD determination
- Blood count with differential blood count, clinical chemistry (creatinine, bilirubin, GOT / AST, CRP) and infecti onsserology (CMV IgG)
- Pregnancy test
- Documentation of infections / organ-specific toxicities (AE / SAE)

The time should be at least 7 days before the stem cell transplant (if possible up to 28 days after documentation of the first CR; but at the latest immediately before consolidation or conditioning).

6.4 Visit 2-13

3, 6, 9 and 12 months (year 1) after the start of conditioning / consolidation chemotherapy (+/- 14 days each), remission is assessed by means of bone marrow puncture and blood count / differential blood count determination. If initially available, a determination of the minimal residual disease by means of cytogenetics or molecular genetics by the respective laboratories of the study groups is also planned. In year 2 the visits take place at the same time intervals.
In years 3 and 4 after the start of conditioning / consolidation chemotherapy (+/- 4 weeks each), the visits should be carried out every 6 months.

The following examinations are necessary for all visits:

- Anamnese
- Bone marrow puncture + if necessary with MRD determination + if necessary chimerism analysis
- blood count with differential blood count, clinical chemistry (creatinine, bilirubin, GOT / AST, CRP)
- Karnofsky index
- Questions about quality of life
- Documentation of infections / organ-specific toxicities (AE / SAE)
- Documentation from GvHD

6.5 Central diagnostics

Central diagnostics are not planned within the scope of the study.

6.6 Dealing with pregnancies

Pregnant and breastfeeding women are generally excluded from participating in the clinical trial. For the first 2 years after transplantation or chemotherapy, participants in the clinical trial are required to use efficient contraceptive methods. This also applies as long as immunosuppressants are taken. Pregnancies occurring during the follow-up period are documented in the CRF.

6.7 Departure of patients (drop-out)

Participating persons can withdraw from the clinical trial at any time at their own request and without giving reasons and without any consequences for their future treatment. In addition, they can be excluded from the examination by the examiner for reasons of health risk.

The reason for the person concerned leaving the examination is documented in the CRF.

6.8 Early termination of the clinical trial

The director of studies is entitled to terminate the examination prematurely due to relevant medical / administrative reasons. The reasons for discontinuing the examination are documented in detail. Patients who were still in treatment at the time the exam was discontinued

have to undergo a final examination, which is documented in the CRF. If an examiner has ethical concerns regarding the continuation of the examination, this must be reported to the LKP immediately.

The sponsor is entitled to terminate the clinical trial early if

- the patient recruitment rate is inadequate
- Serious problems that cannot be resolved arise with the quality of the data collected
- unforeseeable circumstances have occurred in the respective trial center that do not allow the clinical trial to be continued
- in the first or second interim analysis after 20 or 26 months, the lower limit of the 90% confidence interval around the estimate for the cumulative incidence of therapy-related mortality up to 12 months in the transplant arm exceeds the value of 15%
- the continuation of new scientific knowledge during the duration of the examination not allow the same

LKPs can decide to abort the test in coordination with the sponsor and the protocol committee.

7th Adverse events, side effects

7.1 Definitions

An **Adverse Event (AE)** is any disadvantageous occurrence that happens to an affected person (exam participant) and that is not necessarily causally related to the treatment of the study. These could be illnesses, symptoms, clinically significant laboratory values, or symptoms that occur or worsen after the patient is included in the study.

Grade 1-3 complications according to CTCAE Version 3-0 that usually occur during treatment are **not defined as AEs in the context of the study and are not documented in the Case Report Form (CRF).**

A **Serious Adverse Event (SAE)** or Serious Adverse Reaction (SAR) is any adverse event or side effect that occurs

- leads to death or
- is life-threatening or
- leads to permanent or serious disability or disability, or
- makes inpatient treatment or its extension necessary, or
- leads to congenital malformations or birth defects or
- Is medically significant for other reasons (event in which medical intervention was required to prevent an outcome as serious).

A **suspected case of an unexpected serious side effect** is referred to as a **Suspected Unexpected Serious Adverse Reaction (SUSAR)** according to Directive 2001/20 / EG .
A serious side effect is unexpected if it is not listed in the relevant basic document (Fachinfo, IB, IMPD).

Study-specific exceptions

Serious adverse events associated with leukemia or chemotherapy are part of the disease or properly performed therapy and are therefore expected events. Cohort studies on large AML patient collectives show grade 3/4 toxicities in up to 100% of all patients receiving induction chemotherapy. Grade 4 toxicities (CTC-AE grading) are therefore also expected events. They should be documented and evaluated as serious undesirable events in the CRF, but are not subject to the immediate reporting obligation of other SAEs. SAEs exempted from the immediate reporting obligation are the following grade 4 toxicities (CTCAE classification):

- o Grade 4 mucositis
- o Grade 4 haematological toxicity
  (Leuco-granulocytopenia, anemia and thrombocytopenia)
- o Grade 4 infections
  (Aspergillosis, pneumonia)
- o Nausea and vomiting

7.2 Documentation of AEs

After signing the declaration of consent and randomization, all adverse events must be regularly documented in the patient file. The following flow chart applies to the documentation in the CRF. AEs with grade 1-3 according to CTCAE (version 3.0) are **not** documented:

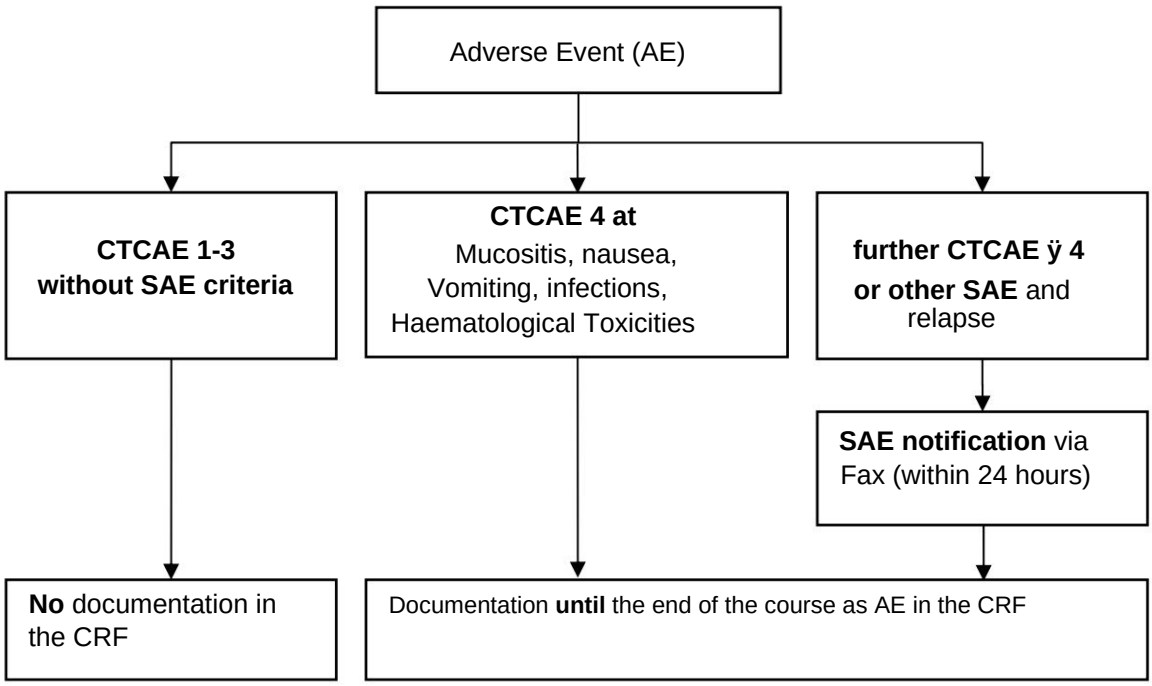

Fig. 8: Flow chart for the documentation of AE / SAE

If an adverse event occurs, regardless of the causal relationship between the event and the investigational product, the person concerned must be observed in any case until the symptoms have subsided or pathological laboratory values have returned to the initial values, or until, in the opinion of the investigator, no further ones More knowledge can be expected. If the undesired event results in a persistent secondary illness, this must be classified as SAE and documented accordingly at the end of the test. All findings and results must be documented on the appropriate Adverse Events page in the CRF and in the patient record.

The following information is required:

- Type of adverse event (signs, symptoms, if possible diagnoses)
- Assessment of the (worsening of existing) comorbidities as undesirable t event
- Differentiation (severe / not severe)
- Beginning and end of occurrence
- Intensity according to CTCAE (version 3.0)
- Causality to therapy possible?
- Measures or actions to restore or improve well-being the data subject
- the outcome of the event

7.3 Documentation of SAEs

The following points must be strictly observed when documenting the SAEs:

ÿ the SAE must be documented on the corresponding AE page in the CRF and on the SAE form be mentored

ÿ Each SAE must be reported as completely as possible (the person responsible for monitoring must check the data in the test center for completeness and ensure that the information in the SAE report matches the information in the database and other data sources

Cases of overdose, abuse, application errors, etc. should be documented, even without an AE occurring.

7.4 Reporting of Adverse Events and Side Effects

7.4.1 Notification obligations of the examiner (§ 12 (4) - (6) GCP-V)

SAEs

The investigator must inform the Safety Management, which works for the sponsor, of the occurrence of a Serious Adverse Event within 24 hours of becoming aware of it. The report is made by the examiner by fax (0351 458 4367)
of the "Serious Adverse Event" form.

The following grade 4 toxicities are excluded from the immediate reporting requirement:

- o mucositis
- o Haematological toxicity
  (Leuco-granulocytopenia, anemia and thrombocytopenia)
- o infections
  (Aspergillosis, pneumonia)
- o Nausea and vomiting

Death of a candidate

In the event of the death of a participating person, the examiner shall provide the responsible ethics committee, the responsible higher federal authority (PEI) and the safety management with all additional information required for the fulfillment of their tasks (on request).

7.4.2 Notification obligations of the sponsor (§ 13 (1) - (6) GCP-V according to § 42 AMG)

AEs

On behalf of the sponsor (or his representative), Safety Management has to document in detail all undesirable events communicated to it and forwards these to the competent higher federal authority (PEI) on request.

SUSARs

Safety Management must inform the responsible ethics committee, the competent higher federal authority (PEI) and the examiners involved in the clinical trial immediately of any suspected case of an unexpected serious side effect (SUSAR) that it becomes aware of, but no later than 15 days after it becomes known teach.

If it becomes aware of any suspected unexpected serious side effect that has led to a **death** or is **life-threatening ,** Safety Management **shall** notify the competent ethics committee, the competent higher federal authority (PEI) and the to the examiners involved in the clinical trial to provide all information important for the assessment and, **within a maximum of eight additional days ,** the other relevant information.

Re-examination of the benefit-risk assessment

Safety Management informs the responsible ethics committee and the competent higher federal authority (PEI) immediately, but no later than **15 days** after becoming aware, of any matter that requires a re-examination of the risk-benefit assessment of the test intervention. These include in particular:

- ÿ Individual reports of expected Serious Side Effects with an Unexpected
  th exit
- ÿ Increase in the frequency of expected Serious Adverse Events that are considered clinically rele
  vant is valued

ÿ Suspected Serious Unexpected Side Effects That Occurred After the participating person has already completed the clinical trial

ÿ Events in connection with the conduct of the trial or the development of the investigational product that could potentially affect the safety of the persons taking part

List of all SARs and safety report

Safety Management must submit a list of all suspected serious side effects that occurred during the trial and a report on the safety of the people involved to the responsible ethics committee and the responsible higher federal authority (PEI) for the duration of the clinical trial , **once a year or upon** request.

Measures to protect against immediate danger

If the safety of the participating persons is impaired and the sponsor and the investigator take measures to protect them from immediate danger, the sponsor shall immediately inform the responsible ethics committee and the responsible higher federal authority (PEI) about these measures and the circumstances that triggered them.

7.5 Data Safety Monitoring Board (DSMB)

For the regular assessment of the safety aspects of this clinical trial with regard to the occurrence of SAEs, an independent committee - the Data Safety Monitoring Board - is set up, which meets once a year to assess the SAEs prepared by the safety management and any interim analyzes and make recommendations to the sponsor will give.

Interim analyzes are only carried out if required by the DSMB, with the exception of the analysis mentioned under 6.8.

8th documentation

It is the responsibility of the examiner to ensure that the test is carried out in accordance with the GCP guidelines, the AMG and the test plan and that the data is correctly entered in the CRF. All data collected in this test must be entered in the CRF by appropriately authorized persons. This also applies to data from persons who were excluded from the examination.

The examiner notes the participation on a special patient identification list (enrollment log). It is used to later identify the participating persons and contains the patient number, full name, date of birth and the date of admission to the clinical trial. The patient identification list will remain in the trial center after the test is completed. In addition, the participation of the person concerned in this clinical trial must be noted in the patient file (trial intervention, patient number / randomization number, start and end of the trial).

It must also be ensured that the person responsible for documentation in the CRF can be identified. A list with the signature and abbreviations of the persons who

tests in the CRF are stored in the trial center folder (ISF) and in the central test folder (Trial Master File).

8.1 Questionnaire (CRF)

All patient data and test results should be entered in the CRFs (Case Report Forms) specially created for this test. The questionnaires used in the course of the study (see Annex IV to Annex VI) are considered source data and do not have to be transferred to the CRF.

The questionnaire may only be filled out with a ballpoint pen. Corrections must be made in such a way that the old entry remains legible (the use of correction media is not permitted). Corrections must be signed and dated by the authorized person making them. Data that are not available or that have not been collected must be clearly identifiable as such (NA or ND). The reasons for this should be documented if necessary.

The examiner ensures that all data of the participants are entered into the CRFs immediately, legibly, completely, correctly and in accordance with the patient files.

8.2 Trial center folder

A trial center folder will be made available to the trial center. This is where those documents are stored that are required for the clinical trial. As part of the monitoring, the test center folder is checked for up-to-dateness and completeness in accordance with the regulations. It must be kept for at least 10 years after the examination has been completed or broken off.

8.3 Retention of the data

8.3.1 Storage obligations of the sponsor

All essential documents of the clinical trial must be kept by the sponsor for a period of at least 10 years after the end or termination of the clinical trial. The sponsor must archive the test-relevant documents and documents in accordance with the statutory provisions.

8.3.2 Obligations to retain the examiner

The examiners must keep records and documents in connection with the testing or the allocation of investigational drugs (e.g. questionnaires, declarations of consent, lists of medication distribution and other relevant documents) for at least 10 years.

The medical records and other original data must be retained for the longest possible period permitted by the hospital, institution, or private practice.

9 Monitoring and Audit

Monitoring and audits are carried out as part of the clinical trial for quality assurance.

9.1 Monitoring

The examiner declares that he / she agrees that the person responsible for monitoring should regularly check the data in order to ensure that the data is collected satisfactorily and that the test plan is adhered to.

He or she also agrees to work with this person and to provide them with all necessary information whenever necessary. This includes access to all documents related to the examination, including the original patient files relevant to the examination. One of the tasks of the examiner is to keep the patient file as complete as possible, ie to record information on the medical history, concomitant illnesses, admission to the examination, visit dates, results of examinations, dispensing of medication and undesirable events. The monitor is also enabled to check the data and make a comparison with the relevant patient files in accordance with the SOPs and the ICH-GCP guidelines at the time intervals specified in advance in order to ensure compliance with the study plan and the continuous recording of the data guarantee. The original medical findings, which are necessary as a source for the information in the CRF or in the database, are checked. The participant has agreed to such a review by signing the declaration of consent.

Other monitoring tasks are:

- ÿ Check whether the trial center meets the requirements of the clinical trial (patient population, devices, storage of the investigational medicinal products, etc., see Chapter 3.7)
- ÿ Briefing of the examiners and the staff involved in the clinical trial
- ÿ Checking the test center folder for completeness and topicality
- ÿ Documentation of the patient status
- ÿ Original data comparison
- ÿ Review of the correct reporting of SAEs and documentation of the AEs

The person responsible for monitoring is obliged to treat all information confidentially and to uphold the fundamental right of the participants to the integrity and protection of their privacy. Monitoring takes place according to a central monitoring plan.

9.2 Audit

In order to guarantee that the test is carried out in accordance with GCP guidelines, internal (e.g. by the sponsor) and external (e.g. by authorities) audits can be carried out. The auditor is independent of the persons involved in the examination.

The following points, among others, are checked during the audit:

- ÿ Carrying out the test in accordance with the test plan
- ÿ Data validity
- ÿ Quality of the test according to GCP guidelines

After each external audit, the auditor receives an audit confirmation from the person responsible for the audit. This confirmation must be kept in the trial center folder in order to have it available in the event of an inspection by the authorities. The audit report is sent to the sponsor of the test. At the end of the test, an audit certificate is attached to the final report. In addition, audits and inspections can be carried out by authorities in accordance with the German Medicines Act.

10 Data entry and data management

10.1 Examination with paper-based documentation

For the documentation of the study, the KKS Dresden will use a GCP-compliant database for ver

provided. The data is managed and processed by the data management of the study center Dresden with the help of the study software MACRO 3.0.

The data are checked using the programmed range, validity and consistency checks. In addition, a manual / visual check for medical plausibility is carried out in accordance with the requirements of the GCP. If necessary, queries can arise that are forwarded to the relevant test center. The examiner must check and answer any discrepancies that have arisen. The answered queries are then sent back to data management.

At the end of the examination, the database will be closed after all entries have been entered and any queries have been clarified. This process is documented.

11th statistics

11.1 Sample size planning

In a prospective multicenter previous study (AML SHG96), which was carried out in one of the participating study groups from 1996 to 2003, biological randomization took place in the intermediate risk group: Patients with an HLA-compatible family donor should undergo an allogeneic HSCT. In an intention-to-treat analysis of the group with family donors (73% were actually transplanted), the overall survival 4 years after the 1st CR was 60%, while the survival probability of patients with chemoconsolidation at the same time was 45% (unpublished data).

Based on these survival probabilities and a significance level ÿ of 5% (two-sided) with a 1: 1 randomization, 346 patients would be sufficient to make up the above-mentioned difference of 15% four years after randomization with a power of 80% with sufficient compliance within the framework an intention-to-treat analysis using the uncorrected chi-square test.

~~to actually recognize the rigorous chi-square tests.~~ Comparable experience has shown that, thanks to the randomization technique (see below under randomization), despite the eight strata and the center-specific lists, a balanced number of cases between the two treatment groups can be expected. Assuming ten patients for whom the survival status after four years cannot be ascertained, 356 patients should be randomized in order to be able to evaluate 346 patients for an intention-to-treat analysis.

The sample size calculations were carried out with the program PS Power and Sample Size Calculation, Version 2.1.31 (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize).

11.2 Recruitment

The study groups are currently jointly recruiting around 500 patients between the ages of 18 and 60 per year. Of these, around 60% fall into the group with intermediate risk and 200 of these 300 patients will achieve a complete remission after induction therapy. With a donor availability of 70%, 140 patients annually would be eligible for the present study. 420 patients could be recruited within the planned three years. The recruitment figures are checked every 6 months in order to enable an early termination reason or the need for a study extension if the recruitment goal is not achieved.

11.3 Randomization

After the induction therapy has been completed, the inclusion and exclusion criteria (see Section 4.3) are checked. If all requirements are met, the randomization takes place in a ratio of 1: 1 between the test and control arm.

A - test arm: allogeneic hematopoietic stem cell transplant in first complete remission.

B - control arm: conventional consolidation with cytarabine-based chemotherapy according to center-specific standards

The following strata are taken into account for randomization:

- Age 18-40 years vs.> 40-60 years
- Unrelated donor (at least 9/10 HLA match: HLA-A, B, C, DRB1 / DQB1 high-resolution) vs. HLA-identical family donor
- FLT3 wild type with NPM1 mutated and / or CEBPÿ mutated vs. FLT3 mutated with NPM1 / CEBPÿ wild type or $^{\text{mutated}}$ or other mutations or no mutations at all or not determined

The randomization is carried out centrally by the study center in Dresden as a stratified randomization. In addition to a stratification for the eight possible groups that result from the three stratification criteria, stratification is also carried out for each participating center. Eight lists are thus created for each center, with a random arrangement of the therapy arms for each list.

In two earlier studies on chronic myeloid leukemia, using a comparable randomization technique for more than 60 centers, the number of cases between the treatment groups was roughly balanced.

After the patient has been included in the study, the patient is randomized in the study center and the therapy group is announced to the doctor and the patient.
The randomization lists cannot be viewed by the doctors in the trial centers or the study participants, and the assignment of the patient to the therapy group cannot be foreseen for either the doctor or the patient.

After receiving the randomization request from a study center, the study center must respond within 2 working days. The respective treatment arm is communicated to the investigator by fax.

If the molecular diagnostics were carried out incompletely, the following assignment rule to the strata applies:

FLT3	**NPM1**	**CEBPA**	**Stratum**
wt	wt	wt	no single NPM / CEBPA mutation mut single NPM / CEBPA mutation
wt	wt		no single NPM / CEBPA mutation mut single NPM / CEBPA mutation
wt	wt	courage	no single NPM / CEBPA mutation mut single NPM / CEBPA mutation
wt	courage	courage	no single NPM / CEBPA mutation no single NPM / CEBPA mutation
wt	courage	nd	no single NPM / CEBPA mutation
wt	nd		
wt	nd		
courage	-	-	
nd	-	-	

Wt = wild type / mut = mutation / nd = not done

11.4 Statistical Methods

11.4.1 Target quantities

Primary outcome measure (primary endpoint of the test)

The primary endpoint for assessing whether one of the two treatment arms can be regarded as superior for the patient population defined by the protocol is the probability of survival 4 years after randomization. The date of the randomization is available as the start time for all patients. The survival status, which is clearly to be ascertained, can be determined for all four years after randomization, with the exception of a few patients who forgave unknown or withdraw their consent to participate in the study.

Secondary outcomes (secondary endpoints of the test)

Disease-free survival 4 years after randomization Disease

-free survival 4 years after randomization describes the probability of neither having suffered a hematological relapse (see Appendix I) nor having died at this point in time.

Recurrence incidence 4 years after randomization

Here, the probability of having observed a hematological recurrence 4 years after randomization is to be reported for the two treatment arms. "Death" does not count as an event.

Cumulative incidence of treatment-related, non-relapse-related mortality one year after Randomization in the test arm

With a view to patient safety in the test arm, the one-year probability of dying due to the stem cell transplantation procedure is examined.

Quality of life during follow-up

Before the transplant or the start of chemotherapeutic consolidation and at the follow-up appointments, patients in both study arms were asked to fill out a validated questionnaire to record their quality of life. In addition, the respective medication is registered at the specified times in order to record the duration of the intake of immunosuppressants.

11.4.2 Definition of the evaluation populations

Intention-to-treat population

The intention-to-treat population to be evaluated includes all randomized persons. In the intention-to-treat analysis, the patients are evaluated strictly according to their original group assignment, regardless of whether they received the assigned therapy or not. The statistical analysis of this collective decides on the statement “statistically significant” or “not statistically significant”. For all patients for whom intention-to-treat analysis is not possible, e.g. B. because of a withdrawal from the study and no result available at the four-year time point, the reasons for leaving the intention-to-treat population are recorded.

Per protocol population

The result of the intention-to-treat analysis is compared with the result in the per protocol population in the final evaluation. This is made up of those people who were actually treated according to their randomized therapy. The reasons for not receiving randomized therapy are documented. Patients who started conditioning for stem cell transplantation or chemotherapy and then experienced an event belong to the per-protocol population.

11.4.3 Data analysis

Confirmatory data analysis

The two-sided null hypothesis is:

H0: The probabilities of survival four years after randomization *do not* differ between the two treatment arms A and B.

Accordingly, the alternative hypothesis reads:

H1: The probabilities of survival four years after randomization differ between the two treatment arms A and B.

With the almost completely ascertainable survival status, the problem of censored survival times for the primary target variable no longer applies. The relationship between the study arm and survival status is tested for the null hypothesis using the likelihood ratio test. This is a

multiple logistic regression model without the variable “therapy arm” compared with a multiple logistic model plus therapy arm.17 The significance level of the likelihood ratio test is 0.05. The probabilities of survival and the odds ratio of the two groups are given together with their 95% confidence interval.

The determination of the multiple logistic model as the basis of the therapy comparison

The choice of stratified randomization supports the preservation of two patient groups that are comparable with regard to predictive influencing factors on survival for the two treatment arms. Since one has to limit oneself with the number of strata in order not to give away the advantage of stratified randomization again, not all possibly predictive influencing factors on the survival probabilities can be taken into account.

Statistically disregarded inequalities of these influencing factors between the two therapy groups could lead to an incorrect assessment of the therapeutic effect. The following parameters showed a predictive (prognostic) influence on the probability of survival in previous studies:

- ÿ sAML / tAML versus “primary” AML [21-22]
- ÿ on day 16 after induction therapy detection versus no detection of blasts (</> 10% Myeloblasts) [23]
- ÿ Sorror score (HCT-CI ÿ 3 vs.> 3, see Appendix II) [24]
- ÿ CRi versus complete CR [25th]
- ÿ Level of minimal residual disease at the time of inclusion [26th]
- ÿ Normal vs. aberrant karyotype

According to the stratified randomization, the logistic base model will consist of the three stratification variables and the factors listed above. The test described above for the influence of the therapy arm is now carried out: The likelihood ratio test is used to check whether the basic model has a statistically significant difference (alpha = 0.05) from the basic model + therapy arm. If so, the significant therapeutic effect has been proven.

The sample size estimation was carried out on the basis of the uncorrected chi-square test. A stratified randomization of influencing factors on the target variable reduces the variance between the therapy arms and increases the power to test for a significant survival effect of the therapy arm. The addition of further influencing factors from the list above will further strengthen the power if they are significant. How strong the effect of the stratification variables and the other listed influencing factors will be in the present study cannot be foreseen in advance. Overall, no power reduction is to be expected compared to the uncorrected chi-square test.

With the stratified randomization, also with regard to the participating study centers, a distortion of results due to center effects can be counteracted. Because of the many strata, it is not possible to consider the center in the confirmatory testing of the therapeutic effect. However, center effects are examined as part of a sensitivity analysis.

The reason for not using a stratified Cox regression model, which can also take individual censored survival times into

The main reason is that its application requirement of a time-independent constant difference in the parameter of the exponential distribution of the two therapy arms will not be met. Rather, because of the initial transplant-related mortality and the subsequent plateau in the patients presumably cured after HSCT, the two survival curves - with and without adjustment according to the Cox model - should cross after about two years.

For all randomized patients, the survival status must be obtained before the decisive test. In the case of patients for whom this is not possible, the reason must be recorded.

According to the principle of a priori ordered hypotheses, if the main target parameter is significant at the second level, the following two secondary target values at the level alpha = 0.05 can be confirmed confirmatory. If no significant result is achieved for the main outcome measure, the results on the two secondary outcome measures are to be understood as exploratory. The two secondary target values are considered to be equal on their second level after the main target value and, in the event of a possible confirmatory procedure, are tested using the Bonferroni-Holm adjustment.

Secondary outcome measure disease-free survival 4 years after randomization.

It is assumed that 4 years after randomization, disease-free survival in the test arm is 20% higher than that of the control arm.

Disease-free survival 4 years after randomization describes the probability of neither having suffered a hematological relapse nor having died at this point in time. The diagnosis of the recurrence is usually delayed (when visiting a doctor); in contrast to the date of death, the exact date is not available. The aim is, however, to subject all patients living four years after their randomization who have not yet relapsed to an examination of their remission status immediately after the four years have elapsed. The test of the null hypothesis that there is no difference in the disease-free survival probability 4 years after randomization between the two treatment arms is then carried out in the same way as the comparison for the main target parameter (see above).

Secondary outcome measure, incidence of recurrence 4 years after randomization

For the test arm, compared to the treatment arm, a reduction in the incidence of recurrence of 20% 4 years after randomization is assumed.

Since only “relapse” is to be regarded as an event, “death without previous relapse” must be viewed as a competing event. This is reflected both in the calculation of the likelihood of recurrence, in which those who have died up to four years of age are included in the denominator, and in the discussion of the results. The test of the null hypothesis that there is no difference between the two treatment arms for the incidence of recurrence 4 years after randomization is carried out in the same way as the comparison for the main outcome measure. During the discussion of the results, the result of the recurrence incidence 4 years after randomization is compared with a comparison of the probabilities of dying in the four years without a recurrence.

Exploratory data analysis

Secondary outcome measure cumulative incidence of therapy-related (non-relapse-related) Mortality one year after randomization in the test arm (safety analysis)

The cumulative incidence of non-relapse-related mortality in patients after allogeneic HSCT in the first complete remission, both in the case of family and third-party donors, should not exceed the limit of 15% one year after HSCT. First results on this can reasonably be considered a little more than one and a half years after the start of recruitment, between months 19 and 20 after the start of the study, if data at the one-year time are available for up to one sixth (n = 30) of the 173 patients randomized for the test arm. The death of a patient is reported to Safety Management Dresden as an SAE and recorded immediately so that all events are available. At least for all living patients who were observed for at least six months, the previous observation time is included in the estimate of the cumulative mortality rate (procedure see Kalbfleisch and Prentice18 and Gooley19), which is estimated for the first time after 19 to 20 months one. With the help of Choudhury20 , the confidence interval is formed around the calculated cumulative incidence. If the study is not terminated prematurely, the procedure to maintain patient safety is repeated 25 to 26 months, 31 to 32 months, 37 to 38 months, 43 to 44 months and 49 to 50 months after the start of recruitment. At 37 to 38 months, all patients will be randomized, but not all have been transplanted, so stopping therapy would still benefit some. In the case of the last two points in time, it is too late to drop out, but not to publicize any problems that may have been encountered. This safety analysis is only performed in the per-protocol population of the trial arm.

If you are above 15% after 12 months, the procedure in the test arm must be discussed in the Data Safety Monitoring Board or the protocol committee.

If at any point in time the 15% are even below the lower limit of the 90% -
Confidence interval around the estimate of the cumulative therapy-related mortality at the time of the year, the LKP must decide whether to terminate the study in consultation with the sponsor or the Data Safety Monitoring Board or the protocol committee.

Secondary outcome measure quality of life

The quality of life is analyzed descriptively.

Sensitivity and subgroup analyzes

In order to analyze the influence of new possible predictive parameters on the difference between the two treatment groups, multiple regression analyzes are carried out ..

With regard to the main target parameter, subgroup analyzes are prospectively planned for the following variables:

ÿ gender

ÿ Age (18-40 years vs.> 40 years)

ÿ sAML / tAML versus “primary” AML

ÿ on day 16 after induction therapy detection versus no detection of blasts (</> 10% Myeloblasts)

ÿ Sorror score (HCT-CI ÿ 3 vs.> 3, see Appendix II)

ÿ CRi versus complete CR

ÿ FLT3 wild type mutated with NPM1 and / or CEBPÿ vs. FLT3 mutated with NPM1 / CEBPÿ wild type or must animals or other mutations or no mutations at all

ÿ Performing additional consolidation therapy prior to transplantation

ÿ Normal vs. aberrant karyotype

ÿ Transplantation in hematological vs. molecular cytogenetic relapse in the control arm

ÿ Transplantation with an unrelated donor vs. transplantation with a relative donor

ÿ Transplantation> 90 days versus <90 days after initial diagnosis

ÿ MRD detection at the start of conditioning versus molecular / cytogenetically negative BILLION findings

An interaction test is carried out before each subgroup analysis. The interaction test examines whether the true therapeutic effect differs between the subgroups. A significant interaction test indicates different therapeutic effects in the subgroups. Only if the interaction test is significant (alpha = 0.1) is the therapeutic effect analyzed within the subgroups. It is also examined whether an uneven distribution of predictive variables between the subgroups could be responsible for the observation of different therapeutic effects.

All exploratory analyzes are viewed as generating hypotheses. For all tests in this section, unless otherwise stated, a significance level of 0.05 is retained and no adjustment is made for multiple testing.

software

SAS and / or the R program package are used for data analysis

12th reporting

To document the progress and development of the test, minutes of the meetings of the various bodies are drawn up.

12.1 report

The statistical evaluation and the creation of an integrated final report are carried out by the study centers in Münster and Dresden and are responsible for the LKP and all others

12.2 Publications

The results of this clinical trial are published in accordance with the recommendations of the CONSORT statement (www.consort-statement.org). At the beginning of the course, the examination is registered in the publicly accessible database www.clinicaltrials.gov.

The publication or presentation of the results requires prior comment and approval by the LKP. It applies to all publications that data protection must be maintained for all patient data.

By signing the test plan, the examiners give their consent to the results of this clinical test being presented to national and international licensing and monitoring authorities, the German Medical Association, the National Association of Statutory Health Insurance Physicians and the health insurance companies. At the same time, they agree that their names, addresses, qualifications and the extent of their participation in the clinical trial will be disclosed in this context.

In the case of publication, the first and / or last authorship is assigned to the initiators of the study, with both first and last authorship being shared. Both first and last authorship can be stated as shared between the study initiators from the three main centers (Münster, Munich, Dresden). Further authorship will be assigned to the participating test centers according to the recruited / randomized number of patients:

> 10	1 co-author
> 20	2 co-authors

Trial centers that bring in fewer than 20 patients are listed in the appendix with the names of the investigators and the name of the center if they are published accordingly.

In addition, authorship is provided for people who are significantly involved in the evaluation and creation of the publication.

13th Ethical, legal and administrative aspects

13.1 Sponsor and investigator responsibilities

The sponsor of the clinical trial (Technische Universität Dresden) assumes responsibility for initiating, organizing and financing the clinical trial to be carried out in accordance with Section 4 AMG. The sponsor and investigator ensure that the clinical trial is carried out in accordance with the existing laws and regulations, in accordance with the ICH-GCP guidelines (1996), the Declaration of Helsinki (1996) as well as the provisions of the AMG and the GCP regulation (2004) is carried out. The examiner accepts the requirements of the signed study plan.

Your or his responsibilities include:

- ÿ Understand the properties of the investigational drug described in the Investigator's Brochure rates
- ÿ Understanding and implementing the treatment plan

- ÿ Ensure that there is sufficient time and capacity to carry out the test to be available
- ÿ Correct collection and documentation of data, reporting
- ÿ Provision of all data for sponsor, monitoring or corresponding authorities for Audits and / or inspections
- ÿ

- ÿ Declaration on the involvement of persons who may be dependent on the sponsor or the investigator

- ÿ Information on possible economic and other interests of the examiners in the Connection with the investigational drugs

The respective examiner assumes responsibility for the implementation of the clinical trial in the trial center in accordance with Section 4 AMG.

13.2 Voting of the ethics committee and notification to the authorities

The application for approval of the clinical trial is submitted to the ethics committee of Medical Faculty Carl Gustav Carus Dresden and the Paul Ehrlich Institute (PEI) on behalf of the sponsor (Technische Universität Dresden) according to § 7 GCP-V according to § 42 AMG by the Clinical Studies Division of the Medical Clinic and Polyclinic I of the University Clinic Drs the.

Furthermore, a notification of the clinical test according to § 12 GCP-V according to § 67 AMG is made by the Clinical Studies department of the Medical Clinic and Polyclinic I of the University Hospital Dresden at the Dresden Regional Council. Notification to the competent local authorities of the trial centers is also taken over by the Clinical Studies department.

13.3 Patient information and declaration of consent

Before the start of the examination, every person taking part in the examination must give the examiner their consent in writing, after having been fully informed about the nature, meaning and scope of the clinical examination in an oral and written form. The content of this information is documented on the declaration of consent. The participant will be informed if material new information about the investigational product emerges during the trial.

The declaration of consent for participation in the clinical trial is made with the date and signature of the person taking part and the doctor. One copy of the signed patient information / declaration of consent is given to the participant, the second copy is stored in the trial center folder.

It is expressly pointed out that until a legally valid declaration of consent is available, no examinations in connection with the test may be carried out.

13.4 Patient Insurance

On behalf of the sponsor, the mandatory patient insurance in accordance with Section 40 Paragraph 1 No. 8 and Paragraph 3 AMG was taken out for all persons taking part in the test with the following insurer:

Company name: Allianz Versicherungs AG

Insurance number:	30/0406/3726605/490
Address:	10900 Berlin
Fax:	01802/400 102

This means that health damage caused by the exam is insured with a maximum coverage of 500,000 euros per participant. This insurance covers all possible damage that the patient suffers directly or indirectly through participation in the special clinical trial.

In order not to endanger the insurance cover, the persons taking part in the test must strictly adhere to the instructions of the test staff. Furthermore, they may not undergo any other medical treatment during the clinical trial without the consent of the examiner (with the exception of emergencies). You must inform the examiner immediately about emergency treatment. Any damage to health that could have occurred as a result of the clinical trial must be reported to the examiner and the insurance company immediately by the participating persons. In addition, the participants must take all appropriate measures to clarify the cause and extent of the damage that has occurred.

The participating person receives the insurance conditions together with their copy of the declaration of consent.

13.5 Data protection

The collection, transfer, storage and evaluation of personal data within this clinical examination is carried out in accordance with the statutory provisions (data protection legislation). The prerequisite for this is the voluntary consent of the persons taking part in the declaration of consent prior to participation in the clinical trial. For this purpose, they will be informed about the following as part of the explanation of this clinical trial:

1. Data collected in the course of this clinical trial are recorded on paper questionnaires or electronic data carriers

   ÿ the client of the test for the scientific evaluation and assessment of undesirable events,

   ÿ the responsible supervisory authorities (the regional councils or the higher federal authorities PEI), the ethics committee of the Technical University of Dresden and the European database for checking that the test is being carried out correctly and for evaluating test results and adverse events.

2. As far as this is necessary for the review of the clinical trial, authorized agents of the client who are bound to secrecy (monitoring, auditing)

and / or the responsible supervisory authority can inspect the personal data available in the trial center.

3. The consent to the collection and processing of personal data in the context of this clinical trial is irrevocable. The participant is informed that he or she can terminate participation in the clinical trial at any time - without giving reasons and without any of the following disadvantages. If the declaration of consent is withdrawn, the data stored up to this point will continue to be used without naming a name, insofar as this is necessary to determine the effects of the investigational product and to ensure that the interests of the person concerned are not impaired.

13.6 Financing

The study is financed by the Technical University (sponsor) and the German Research Association (DFG).

14 Changes to the study plan (amendments)

In order to ensure largely comparable conditions in all test centers and in the interests of a flawless data evaluation, a change to the agreed test conditions laid down in the test plan is not intended.

In exceptional cases, however, changes to the examination conditions are possible. These only take place after mutual agreement between the examiner and the sponsor. Any change to the procedure provided for in the test plan must be made in writing, stating the respective reasons, and signed by all persons responsible for the test. The changes are then considered part of the test plan. If necessary (e.g. when changing the dose of the investigational medicinal product and / or other significant changes that have a direct impact on the safety of the test subjects), the approval of the responsible ethics committees and / or authorities as well as the person taking part must be given to the Obtain protocol changes and submit the amendment to the federal agency (PEI).

15 Signatures The following

persons agree to the content of the clinical trial and confirm this with their signature. Changes that affect the responsibility of each and every one of the undersigned must be reported immediately.

Representative of the sponsor and
director of the clinical trial

Prof. Dr. med. Martin Bornhauser

06/28/12 C.

Date, signature

biometrics

Michael Kramer, M.Sc. Medical biometry

02.09.2012 lindult

Date, signature

Examiner

I hereby confirm that I have read and understood the present test plan and that I accept it in all parts. I undertake to ensure that the persons brought into the test by my center are treated, observed and documented in accordance with the specifications of this test plan.

Surname, first name (in block letters)

Date, signature

Clinic stamp

The present test plan was created in accordance with the ICH-GCP criteria.

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Attachments

Appendix I DEFINITIONS

Morphologic Complete Response (CR):

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

Complete remission with incomplete regeneration of peripheral blood (CRi)

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

Cytogenetic Complete Response (CRc):

- Platelet count> 100,000 / µl
- Granulocyte count of> 1,000 / µl
- Bone marrow (aspirate with marrow spicules): <5% blasts, absence of Auer rods • No evidence of persisting leukemia by flow cytometry (sensitivity: 5%) • Absence of extramedullary leukemia • Transfusion independent stable hemoglobin value • Normal cytogenetics (based on conventional banded studies and FISH)

Molecular Complete Response (CRm):

- Platelet count> 100,000 / µl
- Granulocyte count of> 1,000 / µl
- Bone marrow (aspirate with marrow spicules): <5% blasts, absence of auer rods
- No evidence of persisting leukemia by flow cytometry (sensitivity: 5%)
- Absence of extramedullary leukemia
- Transfusion independent stable hemoglobin value
- Normal cytogenetics (based on conventional banded studies and FISH)

- Molecularly negative (no detection of pretreatment genetic markers with a methodology providing a sensitivity of at least 1: 103)

Partial Remission (PR):

- Platelet count> 100,000 / µl
- Granulocyte count of> 1,000 / µl
- Bone marrow (aspirate with marrow spicules): Decrease of at least 50% in the percentage of blasts to 5% - 25%

Relapse:

- Bone marrow blasts ÿ5%; or reappearance of blasts in the blood; or development of ex tramedullary disease

Resistant disease:

- patient survives ÿ 7 days post chemotherapy (CT); persistent AML in blood or bone marrow

Death in Aplasia:

- patient survives ÿ 7 days post chemotherapy (CT); death while cytopenic, with aplastic bone marrow

Indeterminate cause:

- Patients who die <7 days post CT; Patients who die> 7 days post CT with no PB blasts, but no bone marrow examination; Patients who do not complete the first course of therapy

Morphologic relapse:

- Reappearance of blasts post CT in PB or bone marrow

Event free survival (EFS):

Time interval from day 1 of study treatment until

- Treatment failure (no CR / CRi 5 weeks after the beginning of the second induction therapy course),
- relapse from CR •

relapse from morphologic leukemia-free state (CRi) •

death from any cause

whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR or Morphologic leukemia-free state will be noted. For a patient with none of these

events before the end of study follow-up, observation of EFS will be censored at the date of his or her last follow-up examination.

Overall survival (OS):

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

Appendix II HCT-SPECIFIC COMORBIDITY INDEX

Comorbidities	definition	Score
Migraine / headache		**0**
Osteoporosis		**0**
Osteoarthritis		**0**
Hypertension		**0**
Gastrointestinal	Including inflammatory bowel disease	**0**
Mild pulmonary	DLco and / or FEV1 > 80% or Dyspnea on moderate activity	**0**
Mild renal	Serum creatinine 1.2-2 mg / dl	**0**
Endocrine		**0**
Bleeding		**0**
Coagulopathy	Deep venous thrombosis or pulmonary embolism	**0**
asthma		**0**
Arrythmia		**1**
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EFÿ50%	**1**
Mild hepatic	Chronic hepatitis, bilirubin> ULN- 1.5x ULN, or AST / ALT> ULN-2.5x ULN	**1**
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular acci dent	**1**
Morbid obesity		**1**
diabetes	Requiring treatment	**1**
Depression / anxiety		**1**
Infection	Requiring continuation of treatment after day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	**2**
Moderate pulmonary	DLco and / or FEV1 > 65% -80% or Dyspnea on slight activity	**2**
Peptic ulcer	Patients who have required treatment	**2**
Moderate severe renal	Serum creatinine> 2 mg / dl, on dialysis, or prior renal transplantation	**2**
Valvular heart disease	Except mitral valve prolapse	**3**
Prior solid tumor	Requiring treatment with chemotherapy	**3**
Moderate-severe hepatic	Liver cirrhosis, bilirubin> 1.5x ULN, or AST / ALT> 2.5x ULN	**3**
Severe pulmonary	DLco and / or FEV1 ÿ65% or Dyspnea at rest or requiring oxygen	**3**

Appendix III KARNOFSKY PERFORMANCE STATUS SCALE

general	index	Specific criteria
Able to carry on normal activity; no special care needed.	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease.
	80	Normal activity with effort, some signs or symptoms of disease.
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.	70	Care for self, unable to carry on normal activity or to do work.
	60	Requires occasional assistance from others but able to care for most needs.
	50	Requires considerable assistance from others and frequent medical care.
Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.	40	Disabled, requires special care and assistance.
	30th	Severely disabled, hospitalization indicated, death not imminent.
	20th	Very sick, hospitalization necessary, active supportive treatment necessary.
	10	Moribund
	0	dead

Annex IV QUALITY OF LIFE QUALITY QUESTIONNAIRE: QLQ-C30

GERMAN

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Ihr Geburtstag (Tag, Monat, Jahr): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Das heutige Datum (Tag, Monat, Jahr): 31⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

	Überhaupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Appendix V QUALITY OF LIFE QUALITY QUESTIONNAIRE: SF-36

Monika Bullinger und Inge Kirchberger

Fragebogen zum Allgemeinen Gesundheitszustand SF 36

Selbstbeurteilungsbogen — Zeitfenster 4 Wochen

In diesem Fragebogen geht es um die Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede der (grau unterlegten) Fragen, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

	Ausge-zeichnet	Sehr gut	Gut	Weniger gut	Schlecht
1. Wie würden Sie Ihren Gesundheitszustand im allgemeinen beschreiben?	1	2	3	4	5

	Derzeit viel besser	Derzeit etwas besser	Etwa wie vor einem Jahr	Derzeit etwas schlechter	Derzeit viel schlechter
2. *Im Vergleich zum vergangenen Jahr,* wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben?	1	2	3	4	5

	Im folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben.		
3. *Sind Sie durch Ihren derzeitigen Gesundheits-zustand* bei diesen Tätigkeiten *eingeschränkt*? Wenn ja, wie stark?	Ja, stark eingeschränkt	Ja, etwas eingeschränkt	Nein, überhaupt nicht eingeschränkt
3.a **anstrengende Tätigkeiten,** z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben	1	2	3
3.b **mittelschwere Tätigkeiten,** z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf spielen	1	2	3
3.c Einkaufstaschen heben und tragen	1	2	3
3.d **mehrere** Treppenabsätze steigen	1	2	3
3.e **einen** Treppenabsatz steigen	1	2	3
3.f sich beugen, knien, bücken	1	2	3
3.g **mehr als 1 Kilometer** zu Fuß gehen	1	2	3
3.h **mehrere** Straßenkreuzungen weit zu Fuß gehen	1	2	3
3.i **eine** Straßenkreuzung weit zu Fuß gehen	1	2	3
3.j sich baden oder anziehen	1	2	3

Hatten Sie *in den vergangenen 4 Wochen aufgrund Ihrer* ***körperlichen*** *Gesundheit* irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?	Ja	Nein
4.a Ich konnte nicht **so lange** wie üblich tätig sein	1	2
4.b Ich habe **weniger geschafft** als ich wollte	1	2
4.c Ich konnte **nur bestimmte Dinge** tun	1	2
4.d Ich hatte **Schwierigkeiten** bei der Ausführung	1	2

Hatten Sie *in den vergangenen 4 Wochen aufgrund* ***seelischer*** *Probleme* irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?	Ja	Nein
5.a Ich konnte nicht **so lange** wie üblich tätig sein	1	2
5.b Ich habe **weniger geschafft** als ich wollte	1	2
5.c Ich konnte nicht so **sorgfältig** wie üblich arbeiten	1	2

	Überhaupt nicht	Etwas	Mäßig	Ziemlich	Sehr
6. Wie sehr haben Ihre körperliche Gesundheit oder seelische Probleme in den *vergangenen 4 Wochen* Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder zum Bekanntenkreis beeinträchtigt?	1	2	3	4	5

	Keine Schmerzen	Sehr leicht	Leicht	Mäßig	Stark	Sehr stark
7. Wie stark waren Ihre Schmerzen in den *vergangenen 4 Wochen?*	1	2	3	4	5	6

	Überhaupt nicht	Etwas	Mäßig	Ziemlich	Sehr
8. Inwieweit haben die Schmerzen Sie in den *vergangenen 4 Wochen* bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?	1	2	3	4	5

	In diesen Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen *in den vergangenen 4 Wochen* gegangen ist. (Bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht.) Wie oft waren Sie *in den vergangenen 4 Wochen*	Immer	Meistens	Ziemlich oft	Manch-mal	Selten	Nie
9.a	... voller Schwung?	1	2	3	4	5	6
9.b	... sehr nervös?	1	2	3	4	5	6
9.c	... so niedergeschlagen, daß Sie nichts aufheitern konnte?	1	2	3	4	5	6
9.d	... ruhig und gelassen?	1	2	3	4	5	6
9.e	... voller Energie?	1	2	3	4	5	6
9.f	... entmutigt und traurig?	1	2	3	4	5	6
9.g	... erschöpft?	1	2	3	4	5	6
9.h	... glücklich?	1	2	3	4	5	6
9.i	... müde?	1	2	3	4	5	6

		Immer	Meistens	Manchmal	Selten	Nie
10.	Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den *vergangenen 4 Wochen* Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt?	1	2	3	4	5

	Inwieweit trifft *jede* der folgenden Aussagen auf Sie zu?	trifft ganz zu	trifft weit-gehend zu	weiß nicht	trifft weit-gehend nicht zu	trifft überhaupt nicht zu
11.a	Ich scheine etwas leichter als andere krank zu werden	1	2	3	4	5
11.b	Ich bin genauso gesund wie alle anderen, die ich kenne	1	2	3	4	5
11.c	Ich erwarte, daß meine Gesundheit nachläßt	1	2	3	4	5
11.d	Ich erfreue mich ausgezeichneter Gesundheit	1	2	3	4	5

Vielen Dank.

Appendix VI QUESTIONNAIRE PERSONALITY CHARACTERISTICS (24-AM)

Identifikation:_____

Hier sind einige Persönlichkeitseigenschaften aufgezählt, die auf Sie zutreffen können oder nicht. Schreiben Sie in jede Zeile eine Zahl von 1 bis 7, die angibt, wie sehr sie jeder Aussage zustimmen oder nicht zustimmen. Bitte beantworten Sie alle Aussagen.

Starke Ablehnung	Mittlere Ablehnung	Leichte Ablehnung	Neutral (weder Ablehnung noch Zustimmung)	Leichte Zustimmung	Mittlere Zustimmung	Starke Zustimmung
1	2	3	4	5	6	7

1.	——	zuverlässig	2.	——	selbstdiszipliniert
3.	——	offen für neue Erfahrungen	4.	——	leicht aus der Fassung zu bringen
5.	——	ängstlich	6.	——	vielschichtig
7.	——	zurückhaltend	8.	——	emotional stabil
9.	——	verständnisvoll	10.	——	warmherzig
11.	——	unordentlich	12.	——	kontaktfreudig
13.	——	gelassen	14.	——	unkreativ
15.	——	gewissenhaft	16.	——	introvertiert
17.	——	still	18.	——	unorganisiert
19.	——	tolerant	20.	——	misstrauisch
21.	——	gesellig	22.	——	gesprächig
23.	——	unnachgiebig	24.	——	traditionell

Appendix VII GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

Severity of Individual Organ Involvement		
skin	+1	a maculopapular eruption involving less than 25% of the body surface
	+2	a maculopapular eruption involving 25-50% of the body surface
	+3	generalized erythroderma
	+4	generalized erythroderma with bullous formation and often with desqua mation
Liver	+1	bilirubin (2.0-3.0 mg / 100 ml)
	+2	bilirubin (3-5.9 mg / 100 ml)
	+3	bilirubin (6-14.9 mg / 100 ml)
	+4	bilirubin> 15 mg / 100 ml
Good	Diarrhea is graded +1 to +4 in severity. Nausea and vomiting and / or anorexia caused by GVHD is assigned as +1 in severity. The severity of good involvement is assigned to the most severe involvement noted. Patients with visible bloody diarrhea are at least stage +2 gut and grade +3 overall ÿ 1000 ml	
Diarrhea	+1	of liquid stool / day * (ÿ 15ml of stool / kg / day) †
	+2	> 1,000 ml of stool / day * (> 15ml of stool / kg / day) †
	+3	> 1,500 ml of stool / day * (> 20ml of stool / kg / day) †
	+4	2,000 ml of stool / day * (ÿ 25ml of stool / kg / day) †

*

In the absence of infectious / medical cause †

For pediatric patients

Severity of GVHD	
Grade I.	+1 to +2 skin rash
	No gut or liver involvement
Grade II	+1 to +3 skin rash
	+1 gastrointestinal involvement and / or +1 liver involvement
Grade III	+2 to +4 gastrointestinal involvement and / or
	+2 to +4 liver involvement with or without a rash
Grade IV	Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms or death

For more information, see www.gvhd.de

Annex VIII CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

Chronic GVHD in allogeneic transplant recipients resembles autoimmune disorders such as scle roderma, Sjogren syndrome, primary biliary cirrhosis, lichen planus, wasting syndrome, bronchiolit is obliterans among others manifestations (see below). Approximately 50% of patients will develop this complication within 6 months after the transplant despite continued treatment with immuno suppressive medications. Close monitoring is recommended during the first 2 years after allogeneic ic stem cell transplantation so that appropriate treatment can be instituted promptly in patients who develop chronic GVHD. Debilitation, joint contractures and profound immunosuppression resulting in recurrent bacterial infections are prominent characteristics of untreated chronic GVHD.

A. Classification of Chronic GVHD

The purpose of this classification is to identify patients with cGVHD who need long-term systemic immunosuppression according to clinical and laboratory findings and risk factors at the time of initial diagnosis. In addition, a morbidity scale has been developed to help grade the severity of mani festation of chronic GVHD at the time of diagnosis, when changes in treatment are made and when assessing treatment response.

1. Chronic GVHD not requiring systemic treatment: mild abnormalities involving a single site, with platelet count> 100,000 / ÿL and no steroid treatment at the onset of chronic GVHD

a) Oral abnormalities consistent with cGVHD, a positive skin or lip biopsy, and no other man ifestations of cGVHD

b) Mild liver test abnormalities (alkaline phosphatase ÿ2x upper limit of normal, AST or ALT ÿ3 x upper limit of normal and total bilirubin ÿ1.6) with positive skin or lip biopsy, and no other manifestations of cGVHD

c) Less than 6 papulosquamous plaques, macular-papular or lichenoid rash involving <20% of body surface area (BSA), dyspigmentation involving <20% BSA, or erythema involving <50% BSA, positive skin biopsy, and no other manifestations of cGVHD

d) Ocular sicca (Schirmer's test ÿ5mm with no more than minimal ocular symptoms), positive skin or lip biopsy, and no other manifestations of cGVHD

e) Vaginal or vulvar abnormalities with positive biopsy, and no other manifestations of cGVHD

2. Chronic GVHD requiring systemic treatment: more severe abnormalities or involve ment of multiple sites, or platelet count <100,000 / ÿL, or steroid treatment at the onset of chronic GVHD

a) Involvement of two or more organs with symptoms or signs of cGVHD, with biopsy documentation of cGVHD in any organ

b) ÿ15% base line body weight loss not due to other causes, with biopsy documentation of cGVHD in any organ

c) Skin involvement more extensive than defined for clinical limited cGVHD, confirmed by biopsy

d) Scleroderma or morphea

e) Onycholysis or onychodystrophy thought to represent cGVHD, with documentation of cGVHD in any organ

f) Decreased range of motion in wrist or ankle extension due to fascitis caused by cGVHD

g) Contractures thought to represent cGVHD

h) Oral involvement with functional impairment, refractory to topical treatment

i) Vaginal involvement with functional impairment, refractory to topical treatment

j) Bronchiolitis obliterans not due to other causes

k) Positive liver biopsy; or abnormal liver function tests not due to other causes with alkaline phosphatase> 2 upper limit of normal, AST or ALT> 3 x upper limit of normal, or total bili rubin> 1.6, and documentation of cGVHD in any organ Positive upper or lower GI biopsy

l)

m) Fasciitis or serositis thought to represent cGVHD and not due to other causes

B. Physical manifestations of Chronic GVHD

Manifestations that are distinctive for chronic GVHD can begin before day 100 after the transplant, and manifestations that are typical of acute GVHD can persist long after day 100. For this reason, the differential diagnosis between acute and chronic GVHD cannot be made solely according to the time interval from transplant. The diagnosis of chronic GVHD requires at least one manifesta tion that is distinctive for chronic GVHD *(identified by italic print below)* as opposed to acute GVHD.
In all cases, infection and other causes must be ruled out in the differential diagnosis of chronic GVHD.

Karnofsky or Lansky Clinical Performance scores <60%, ÿ15% weight loss, and recurrent infections are usually signs of clinical extensive chronic GVHD. Abnormalities that could indicate chron ic GVHD are categorized by organ system are listed below *(italic print identifies manifestation more distinct of chronic GVHD):*

skin	Erythema, dryness, pruritis, macular-papular or urticarial rash, *pigmentary changes (ie, hyperpigmentation, vitiligo), mottling, papulosquamous or lichenoid plaques, hyperkera tosis, exfoliation (ichtyosis), nodules, scleroderma, morphea (one or several circum scribed, indurated and shiny lesions).* The extent of skin involvement and the skin thick ness score for patients with scleroderma needs to be recorded at the time of diagnosis, when changes in treatment are made and when assessing treatment response. Medical photos are also useful for assessing the extent of skin involvement and response to treatment.
Nails	*Ridging, onychodystrophy, onycholysis*
Hair	*Premature graying (scalp hair, eyelashes, eyebrows), thinning scalp hair, alopecia, de creased body hair*
Mouth	Dryness, burning, gingivitis, mucositis, striae, *dryness, atrophy, erythema, lichenoid changes, ulcers, labial atrophy or pigmentary changes, tightness around the mouth, sen sitivity to acidic, strong flavors, heat or cold, tooth decay*
Eyes	*Dryness, burning, blurring, gritty eyes, photophobia, pain*
Vagina / vulva	*Dryness, dyspareunia, stricture or stenosis, erythema, atrophy or lichenoid changes not induced by ovarian failure or other causes*
Liver	Jaundice and elevated liver function tests not due to other causes (see laboratory tests)

Lung	*Bronchiolitis obliterans (see diagnostic indicators), cough, wheezing, dyspnea on exer tion, history of recurrent bronchitis or sinusitis*
GI	Anorexia, nausea, vomiting, diarrhea, *malabsorption, dysphagia, odynophagia*
Myofascial	*Stiffness and tightness with restriction of movement, occasionally with swelling, pain, cramping, erythema and induration, most commonly affecting the forearms, wrists and hands, ankles, legs and feet, inability to extend the wrists without flexing the fingers or the elbows, contractures*
Muscle	*Proximal muscle weakness, cramping*
Skeletal	*Arthralgia of large proximal girdle joints and sometimes smaller joints*
Serosal	*Unexplained effusions involving the pleural, pericardial, or peritoneal cavities not due to venocclusive disease of the liver, cardiac insufficiency, malignancy, infection, GM-CSF toxicity or other causes*

C. Laboratory Testing and Diagnostic Indicators of Chronic GVHD

Eye	*Schirmer's test with a mean value ÿ 5 mm at 5 minutes, or values of 6-10 mm in patients who have sicca symptoms, or keratitis detected by slit lamp examination*
Liver	Elevated liver function tests not due to other causes (alkaline phosphatase ÿ2x upper limit, of normal, AST or ALT> 3x upper limit of normal or total serum bilirubin ÿ1.6)
Lung	*New obstructive lung defect defined as an FEV1 <80% of predicted with either an FEF 25-75 <65% of predicted or RV> 120% of predicted, or a decrease of FEV1 / FVC by> 12% within a period of less than 1 year, though not to be caused by an infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux. In the absence of GVHD in any other organ, the diagnosis of bronchiolitis obliterans re quires negative microbiological tests from bronchoalveolar lavage, evidence of air trap ping by high resolution end-expiratory and end-inspiratory CAT scan of the lungs, or confirmation by thoracoscopic biopsy .*
Esophagus	*Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry* Endoscopic findings of mucosal edema and erythema or
Intestine	focal erosions with histological changes of apoptotic epithelial cells and crypt cell drop out. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions including ulcers and mu cosal sloughing.
Muscle	*Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process* Thrombocytopenia (usually 20,000-100,000 / l), eosinophilia
Blood	(> 0.4 x 103 / ÿL), hypogamous maglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

D. Guidelines for Treatment of Chronic GVHD after allogeneic HSCT

We strongly recommend that you consult the LTFU office before beginning treatment for chronic GVHD and before making changes in immunosuppressive treatment. Clinical trials should always be considered because current standard therapies are associated with high morbidity and de creased survival for patients with high risk chronic GVHD.

Standard treatment of chronic GVHD usually begins with administration of glucocorticoids (1mg / kg / day) followed by taper to eventually reach an alternate-day regimen, with or without daily CSP or tacrolimus (FK506). Other medications used for treatment of corticosteroid-resistant chron ic GVHD are summarized on the next page. Telephone consultation with the LTFU medical team is available to you, seven days a week, to discuss appropriate treatment and provide other follow up recommendations. In addition to immunosuppressive treatment, antibiotic prophylaxis for encapsu-

Lated bacterial infections and PCP must be given to all patients being treated for chronic GVHD. (see Section IV).

The duration of systemic immunosuppressive treatment of chronic GVHD varies but requires at least one year of therapy. Approximately 80% of patients require systemic immunosuppressive for 2 years and 40% of them requires therapy for at least 4 years.

Adapted From: Long-Term Follow-up After Hematopoietic Stem Cell Transplant General Guide lines For Referring Physicians, Fred Hutchinson Cancer Research Center Standard Practice Manual, Section X, Chronic Graft Versus Host Disease (GVHD), Nov / 2003 Version

Appendix IX ADDRESS LIST OF SEARCH UNITS IN GERMANY

Source: http://www.zkrd.de/adressen_sc.html#html_0 as of February 2010

Institution:	**DKMS Life Science Lab GmbH**
Department:	Search unit Dresden, clinical HLA laboratory
Contact person: Ms. Dr. Füssel, Frau Platz Street: Fiedlerstr. 34 ZIP code and place:	**01307 Dresden**
Tel. And Fax No .: E-Mail: Website:	0351 / 450-4530 0351 / 450-4545 fuessel@dkms-lab.de www.dkms.de

Institution:	**Jena University Hospital**
Department:	Institute for Transfusion Medicine, external donor search unit
Contact person: Ms. Prof. Barz, Mr. Dr. Oberle Street: Stoystr. 3 ZIP code and city: **07743 Jena**	
Tel. And Fax No .:	03641-935461 03641/935462
E-mail:	dagmar.barz@med.uni-jena.de volker.oberle@med.uni-jena.de

Institution:	**International Center for Stem Cell Donor Search of the Stefan Morsch Foundation at the Charité Campus Benjamin Franklin** Hematology / Oncology Department: Contact: Dr. I.-W. Blue, Dr. O.

Berlin Tel. And fax no .: 030 / 8445-4430 Marienfelder Chaussee 31-69 030 / 8445-4438 E-Mail: ingeborg.blue@charite.de **12200**

Institution:	**Charité, Medical Faculty of the Humboldt University of Berlin, Campus Virchow-Klinikum** Blutbank
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Postal code and city:	**13353 Berlin**
Tel. And Fax No .:	030 / 450-55-3012 030 / 450-55-3955

Institution:	**Universitätsklinikum Hamburg-Eppendorf**
Department:	Diagnostikzentrum, Ost 38, 1st floor, room 117 Institute for Transfusion Medicine, HLA Laboratory Contact: Ms.

Dittmer, Ms. Kisselmann, H. Prof. Eiermann Street: Martinistr. 52 Post code and city: **20246 Hamburg** Tel. And fax no .: 040 / 7410-54844 040 / 7410-55829 E-Mail: hlalab@uke.uni-

Institution:	**Hannover Medical School**
Department:	Transfusion Medicine Department
Contact person: Ms. Krüger Street: Carl-Neuberg-Str. 1 ZIP code and place:	**30625 Hanover**

Tel. And Fax No .: 0511 / 532-6700 0511 / 532-4178
E-mail: registerspendersuche@mh-hannover.de www.mh-
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Institution: **Institute for Clinical Immunology and Transfusion Medicine**
Department: HLA laboratory
Contact person: Ms. Dr. Wienzek, Ms. Müller Street: Langhansstr. 7
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E-mail: HLA.Labor@immunologie.med.uni-giessen.de www.med.uni-
Website: giessen.de/immunologie/

Institution: **ME of the Heinrich-Heine University** Institute
Department: for Transplantation Diagnostics Moorenstrasse
Street: 5 **40225 Düsseldorf**
Postal code and city:

Institution: **University Hospital Essen** Institute
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Institution: **Clinic of the University of Cologne**
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Institution: **DRK-BSD Baden-Württemberg - Hessen gGmbH** Tissue Typing
Department: Laboratory (HLA)
Street: Sandhofstrasse 1
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Institution: **Search unit for unrelated stem cell donors Heidelberg** Department: Institute for
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Institution: **Medical University Clinic Tübingen** Department: Hematology, Oncology, Immunology and Hillenbrand Strasse: Otfried-Müller-Straße 10 Prof. Dr. CA

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Institution: **Medical University Clinic Freiburg** Department: Department and Hematology / Oncology, KMT Stroke: 55 Hugstetter Ms. Lenartz Street: **79106 Freiburg**

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Institution: **Bavarian Donor Search Center (BSZ)**

Contact person: Dr. Knabe Strasse: Robert-Koch-Allee 7

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Institution: **Institute for Clinical Transfusion Medicine and Immunogenetics** Contact: Martina Baumann, Marlene Fischer, Renate Hanold, Sabine Simon Department: Transplantation Immunology Street: Helmholtzstr. 10

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Statistical Analysis Plan

Sponsor	Technische Universität Dresden 01062 Dresden
Study title	Randomisierte Studie zur allogenen hämatopoetischen Stammzelltransplantation im Vergleich zur Standard-chemotherapie bei Patienten in erster kompletter Remission im Alter von <=60 Jahren mit AML intermediären Risikos (Standardrisiko) und HLA-kompatiblem Geschwister- oder Fremdspender ETAL-1
EudraCT	2010-019377-15
IMP	Allogeneic HSCT
Responsible Persons	
Name	Prof. Dr. med. Martin Bornhäuser
Position	Coordinating Investigator
Date	
Signature	
Name	
Position	Clinical Coordinator
Date	
Signature	
Name	Michael Kramer
Position	Biostatistician
Date	
Signature	

1 Purpose of this document

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical analyses outlined in the Study Protocol of the TUD-ETAL-1-045 study (V3-0; 22/06/2019) more detailed and technical. The SAP will be finalized before the final data review meeting (DRM) and database lock.

The following SOPs and guidelines are applicable:

- K-FOR-KS-BI03_Statistischer_Analyseplan_V1-0
- ICH E3 – Structure and Content of Clinical Study Reports
- ICH E9 - Statistical Principles for Clinical Trials

2 Scope

The SAP applies to all personnel of the MK1 Clinical Trials Unit who are involved in the statistical analysis during the course of the TUD-ETAL-1-045 study.

3 Abbreviations and Definitions

3.1 List of Abbreviations

Abbreviation	Description
AE	Adverse event
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutical Chemical Classification
CIR	Cumulative incidence of relapse
CR	Complete remission
CRi	Complete response with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
DRM	Data Review Meeting
EFS	Event free survival
FAB	French American British classification of AML
FAS	Full Analysis Set
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
LLT	Lowest level term
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
MK1	Medizinische Klinik 1
MLFS	Morphological Leukemia-Free State
MRD	Measurable Residual Disease
nval	Number of valid (non-missing) observations
nmiss	Number of missing observations
NRM	Non-relapse mortality
OS	Overall survival
PPS	Per Protocol Set
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SCT	Stem cell transplantation
SD	Standard Deviation
SES	Safety Evaluation Set
SOC	System Organ Class
SOP	Standard Operating Procedure
TU	Technische Universität
WT	wildtype

3.2 Definitions

Not applicable

4 Statistical Analysis Plan Updates

Changes of the SAP have to be documented in the table of section 13. All changes lead to a version change. Each updated version has to be distributed to all involved persons.

5 Study Design and Objectives

5.1 Synopsis

Sponsor	Technische Universität Dresden
Titel	**Randomisierte Studie zur allogenen hämatopoetischen Stammzelltransplantation im Vergleich zur Standardchemotherapie bei Patienten in erster kompletter Remission im Alter von <=60 Jahren mit AML intermediären Risikos (Standardrisiko) und HLA-kompatiblem Geschwister- oder Fremdspender**
Kurzbezeichnung	ETAL-1
Zielpopulation (oder Indikation)	Patienten mit akuter myeloischer Leukämie im Alter zwischen 18-60 Jahren
Studiendesign	Prospektive, randomisierte, kontrollierte, multizentrische klinische Studie
Ziele der klinischen Prüfung	• Untersuchung des Stellenwerts der allogenen hämatopoetischen Stammzelltransplantation (HSCT) in der primären Postremissionstherapie der akuten myeloischen Leukämie (AML) intermediären Risikos bei Patienten im Alter von 18 - 60 Jahren mit HLA-kompatiblem Geschwister- oder Fremdspender • Verbesserung des Gesamtüberlebens nach 4 Jahren um 15% im Prüfarm (HSCT) im Vergleich zur Standardchemotherapie
Zielgrößen der klinischen Prüfung	<u>Primäre Zielgröße</u> - Gesamtüberleben 4 Jahre nach Randomisierung <u>Sekundäre Zielgrößen</u> - ereignisfreies Überleben - Rezidivinzidenz - kumulative Inzidenz der nicht-rezidivbedingten Letalität - Erhebung der Lebensqualität
Patientenzahl	356
Zeitplan	- geplante Dauer der Rekrutierungsphase: 01.09.2010 bis

	31.08.2013 - voraussichtlicher Zeitpunkt 'last patient last visit': 31.12.2017
Einschlusskriterien	- Akute myeloische Leukämie - normaler Karyotyp bzw. keine der nachfolgend ausgeschlossenen Aberrationen - Alter 18 bis <=60 - „fit for transplant“ (für eine allogene Transplantation geeignet) - HLA-identer verwandter Spender (HLA-A/B/C/DRB1 hochauflösend 10/10 Match) oder HLA-kompatibler unverwandter Spender (A/B/C/DRB1/DQB1 hochauflösend mind. 9/10 Match) identifiziert. Bei Patienten mit NPM1 positiver / FLT3 negativer AML sollte der Spender hochauflösend in HLA-A/B/C/DRB1/DQB1 ident sein. - CR / CRi nach Induktionschemotherapie - Schriftliche Einwilligung der teilnehmenden Person nach erfolgter Aufklärung
Ausschlusskriterien	- Zytogenetische Veränderungen: t(8;21), inv.16, komplexer Karyotyp, -7, -5, 5q-, abnorm 3, abnorm 11, t(6;9), t(9;11), 8+ mit mind. einer zusätzlichen zytogenetischen Veränderung - Akute Promyelozytenleukämie mit Nachweis t(15;17) - Anamnestisch bekannte Überempfindlichkeit gegenüber einem der eingesetzten Medikamente oder deren Inhaltsstoffe oder gegenüber Medikamenten mit ähnlicher chemischer Struktur - Sucht- oder sonstige Erkrankungen, die es der oder dem Betreffenden nicht erlauben, Wesen und Tragweite sowie mögliche Folgen der klinischen Prüfung abzuschätzen - Schwangere oder stillende Frauen - Frauen im gebärfähigen Alter, außer Frauen, die die folgenden Kriterien erfüllen: - Post-menopausal (12 Monate natürliche Amenorrhoe oder 6 Monate Amenorrhoe mit Serum FSH > 40 U/l) - Postoperativ (Hysterektomie oder 6 Wochen nach beidseitiger Ovarektomie) - Regelmäßige und korrekte Anwendung einer Verhütungsmethode mit Fehlerquote <1 % pro Jahr (z. B. Implantate, Depotspritzen, orale Kontrazeptiva, Intrauterinpessar–IUP). Dabei ist zu berücksichtigen, dass die kombinierte orale Kontrazeption – im Gegensatz zu reinen Progesteronpräparaten – eine Versagerquote von <1 % hat. Hormonspiralen sind mit einem Pearl Index <1 % sicherer als Kupferspiralen. - Sexuelle Enthaltsamkeit - Vasektomie des Partners - Anzeichen darauf, dass die Patientin/Patient den Prüfplan voraussichtlich nicht einhalten wird (z. B. mangelnde Kooperationsbereitschaft) - Einnahme anderer Studienmedikamente oder Anwendung anderer Studientherapien innerhalb der letzten 28 Tage vor Studieneinschluss oder gleichzeitige Teilnahme an anderen klinischen Studien
Ablauf der klinischen Prüfung	1. Studieneinschluss/Randomisierung: Bestätigung des intermediären Risikos, Spenderverfügbarkeit und CR1-Dokumentation (<5% Blasten im KM) nach Ende der abschließenden Induktionstherapie bei KM-Punktion innerhalb von 8 Tagen nach Regeneration der Granulozyten >500 /µl im

	peripheren Blut, maximal d56 ab Therapiestart. G-CSF ist freigestellt; bei V.a. ‚Regenerationsblasten' Repunktion innerhalb von 10 Tagen. **Patientenaufklärung + Studieneinschluss mit Randomisierung bei CR/CRi und vorhandenem Spender (verwandt oder unverwandt mit HLA A/B/C/DRB1/DQB1 hochauflösend mind. 9/10 Match; bei NPM1 pos. / FLT3 neg. AML 10/10 Match).** Die Transplantation oder Konsolidierungstherapie sollte innerhalb von 4-6 Wochen nach Randomisierung stattfinden. **2. Re-Evaluation**: KMP, möglichst bis 28 Tage nach CR1-Dokumentation, aber spätestens unmittelbar vor Konsolidierung oder Konditionierung (a priori definierte Subgruppen).
Prüfungsbezogene Verfahren und Laboruntersuchungen	Remissionskontrollen Jahr 1+2: alle 3 Monate Jahr 3+4: alle 6 Monate
Behandlungsplan	Prüfarm A: Allogene Stammzelltransplantation als primäre Postremissions-therapie Konditionierungstherapie: <=40 Jahre: 12Gy/Cy 120 oder Bu16/Cy120 >40-60 Jahre (oder Sorror-Score >= 3): 8Gy/Flu oder Flu/Bu8 oder Mel 140+/Flu GvHD-Prophylaxe: - CsA / MTX d1,3,6, (11) - Fremdspender: zusätzlich ATG Transplantat: Vorzugsweise G-CSF stimulierte PBSZ (mind. 4x 106 CD34+ Zellen /kg KG), KM ebenfalls möglich. Kontrollarm B: Die Konsolidierungstherapie ist freigestellt (je nach Studiengruppe). Allogene Stammzelltransplantation bei Rezidiv oder optional bei MRD-Anstieg / molekularem Rezidiv. Die allogene Stammzell-transplantation im Kontrollarm ist nicht Gegenstand der klinischen Prüfung.

5.2 Study Design

Prospective, randomized, controlled, multicenter clinical trial

5.3 Treatments

5.3.1 Investigational Group

Experimental arm A: allogeneic stem cell transplantation as primary post-remission therapy

5.3.2 Control Group

Control arm B: Post-remission therapy is optional (depending on study group). Allogeneic stem cell transplantation in relapsed disease or optional in case of increasing MRD / molecular relapse is allowed. Allogeneic stem cell transplantation in the control arm is not subject of the trial.

5.4 Trial Schedule

TUD-ETAL-1-045

Visitenplan

HSCT/Konsolidierung

Phase	empfohlene Standarddiagnostik	Studieneinschluss / Randomisierung	Re-Evaluation (Vorbereitung HSCT)	Visiten
Zeitpunkt	bis 4 Wochen nach Erstdiagnose	4-6 Wochen vor HSCT / Konsolidierung	bis 7 Tage vor HSCT oder Konsolidierungstherapie	Jahr 1: 3/6/9/12 Monate Jahr 2: 15/18/21/24 M. Jahr 3: 30/36 Monate Jahr 4: 42/48 Monate nach Beginn der Konditio-nierung/ Chemotherapie[4]
Visite		**Studieneinschluss**	**Visite 1**	**Visite 2-13**
Ein-/Ausschlusskriterien		x		
Aufklärung und Einwilligung des Patienten		x		
Meldung an Studienzentrale		x		
Randomisierung		x		
Demographische Daten		x	x (Spender)	
Anamnese		x		x
körperl. Untersuchung			x	
Vitalzeichen			x	
Karnofsky-Index			x	x
HCT-CI			x	
KMP	x	x[2]	x[3]	x
Labor [1]		x	x	x
Schwangerschaftstest		x	x	
HLA-Typisierung Patient	x			
HLA-Typisierung Geschwister	x			
Einleitung Spendersuche, Kontaktaufnah-me mit Transplantationszentrum	x			
Spenderverfügbarkeit		x		
AEs und SAEs			x	x
GvHD (bei HSCT)				x
Lebensqualität		x		x

[1] Blutbild mit Differentialblutbild, klin. Chemie (Kreatinin, Bilirubin, GOT/AST, CRP)und Infektionsserologie (CMV IgG)
[2] KMP zu T15/16 + KMP nach IT2 (Remissionskontrolle)
[3] optimal bis 28d nach CR1-Dokumentation, spätestens unmittelbar vor Konsolidierung o. Konditionierung)
[4] jeweils +/- 14 Tage im Jahr 1+2 und +/- 4 Wochen im Jahr 3+4

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5.5 Study Objectives

5.5.1 Primary objectives

Primary objective of the trial is the investigation of the significance of allogeneic haematopoietic stem cell transplantation in the primary post-remission therapy of acute myeloid leukemia (AML) in patients with intermediate risk in the age of 18 to 60 years with HLA-compatible sibling or unrelated donor. Improvement of 4-year overall survival by 15% is expected.

5.5.2 Secondary objectives

Improvement of event-free survival 4 years after randomization by 20% in the experimental arm. Events considered are relapse and death from any cause.

Twenty percent reduction in relapse incidence after 4 years in the experimental arm.

Descriptive analysis of quality of life with standard questionnaires in both treatment arms.

5.5.3 Safety Objectives

Investigation of the cumulative incidence of non-relapse mortality (NRM) in the experimental arm.

5.5.4 Exploratory Objectives

Not applicable

5.6 Study Hypothesis

The primary endpoint of the trial is the overall survival rate at 4 years after randomization. The primary endpoint is a binary variable.

The null hypothesis is p0 = p1 with p0 and p1 being the 4 year survival rates of the control arm respective the treatment arm.

The alternative hypothesis is p0 ≠ p1.

5.7 Handling of Screening Failures and Drop-Outs

Patients registered for participation in the trial, who were not randomized, are defined as screening failures. Patients who were randomized are no screening failures and will be included in the primary analysis. Screened and not randomized patients were documented in a screening log.
Exclusion of patients after randomisation is to be avoided. If the circumstances described in the ICH E9 Guideline in section 5.2.1 are fulfilled a patient can be excluded after randomisation. The reasons will be documented and reported in the clinical study report.

5.8 Randomization and Stratification

Patients are randomized in a 1:1 ratio to the experimental and control arm.

Randomization is stratified by:

- Age <= 40 vs. > 40 years
- Unrelated donor (9/10 HLA-Match: HLA-A, B, C DRB1, DQB1 high resolution) vs. HLA-identical sibling donor
- Isolated NPM1 or CEBPa mutation vs. other molecular markers

Combination of these factors results in 8 strata:

1. <= 40 years and unrelated donor and isolated NPM1 or CEBPa mutation
2. <= 40 years and unrelated donor and other molecular markers
3. <= 40 years and identical sibling donor and isolated NPM1 or CEBPa mutation
4. <= 40 years and identical sibling donor and other molecular markers
5. > 40 years and unrelated donor and isolated NPM1 or CEBPa mutation
6. > 40 years and unrelated donor and other molecular markers
7. > 40 years and identical sibling donor and isolated NPM1 or CEBPa mutation
8. > 40 years and identical sibling donor and other molecular markers

5.9 Blinding

Blinding was not possible in this study.

5.10 Sample Size Calculation

In an earlier prospective multi center trial (AML SHG96), which was conducted in the study group between 1996 and 2003 the patient group with intermediate risk was randomized biologically: i.e. patients with an HLA-compatible sibling donor were planned to undergo allogeneic HSCT (73% were actually transplanted). In this study the 4-year overall survival after first CR was 60%, whereas the survival probability of patients who underwent chemo consolidation at 4 years was 45% (unpublished data).

Based on these survival probabilities and a significance level of 5% (two-sided), a total of 346 patients are necessary to detect a difference of 15% in 4-year survival probabilities with a power of 80% using the uncorrected Chi-squared test. To account for 10 patients for whom the 4-year survival status cannot be evaluated, 356 patients will be randomized.
Sample size calculations were conducted with the software PS Power and Sample Size Calculation, Version 2.1.31
(http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerAndSampleSize).

5.11 Planned Interim or Sequential Analysis

No interim or sequential analysis is planned.

5.12 Handling of Changes to Study Protocol

All deviations from the initially planned analyses and their reasons, as well as additional statistical analyses are described in amendments to the trial protocol and/or the SAP, if they were decided before database lock.
All statistical analyses not pre-specified in the SAP and run after database lock will be considered as additional, exploratory analyses.

6 Technical Aspects and Coding Conventions

6.1 Software

Analyses will be conducted using the R software environment for statistical computing version 3.5.3 or higher and RStudio version 1.2.1335 or higher.

6.2 Date Coding and Day Numbering

If dates needed for listings are only partially given, they will be presented as is. If dates needed for calculation are only partially given, they will be cross-checked with other relevant dates that are given in the database, and then completed, if meaningful, according to a worst-case imputation.
All imputed dates and values obtained from calculations with these imputed dates will be listed and discussed during the DRM. In case the DRM decides an imputation is not meaningful, the missing date should be imputed in another way or be excluded, if a meaningful imputation seems to be impossible.

6.3 Coding Systems and Conventions

6.3.1 Coding of Adverse Events, Medical History and Concomitant Diseases

Adverse event (AE), medical history and concomitant disease terms are assigned to a lowest level term (LLT) and a preferred term (PT) and are classified system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. In addition, severity of adverse events (AEs) is classified according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.0.

6.3.2 Separation of Medical History from Concomitant Diseases

Medical conditions stopping before date of randomization will be allocated to medical history. Medical conditions stopping at or after date of randomization will be allocated to Concomitant Diseases.

6.3.3 Coding of Medications

Frequencies of prior and concomitant medication terms will be given based on Anatomical Therapeutic Chemical Classification (ATC) code levels 2 and 3 according to the Anatomical Therapeutic Chemical classification system in effect at the time the database is closed. Non-drug treatments will not be coded.

6.3.4 Separation of Previous from Concomitant Medications

Medication stopped before date of randomization will be allocated to Previous Medications. Medication stopped at or after date of randomization will be allocated to Concomitant Medications.

7 Analysis Populations and Subgroups

7.1 Analysis Populations

Statistical analyses will be conducted in the following analysis sets:
Full analysis set (FAS): The FAS consists of all patients who were randomized and not excluded according to principles outlined in the ICH E9 guideline section 5.2.1.

Safety evaluation set (SES): The SES consists of all patients who started conditioning for transplantation in the transplant arm or who started consolidation chemotherapy in the control arm.

Per protocol set (PPS): The PPS consists of all patients of the FAS who were transplanted in first CR in the transplant arm or who completed at least one cycle of consolidation chemotherapy and were not transplanted in first CR in the control arm.

7.2 Subgroups

Analyses of the primary variable in subgroups based on the following variables are planned:

- Sex (female vs. male)
- Age (18-40 years vs. > 40 years)
- AML type (sAML/tAML vs. de novo AML)
- Response on day 16 of primary induction (< 10% bone marrow blasts vs. >= 10% bone marrow blasts)
- Sorror score (HCTCI <= 3 vs. > 3)
- Remission (CRi vs. CR)
- Molecular markers (FLT3 wildtype with NPM1 or CEBPA mutation vs. other combinations)
- Consolidation chemotherapy (no additional consolidation chemotherapy vs. additional consolidation therapy)

- Karyotype (normal vs. aberrant)
- Relapse status before HSCT in the control arm (molecular relapse vs. hematological relapse)
- Donor type (unrelated vs. sibling donor)
- Time form diagnosis to HSCT (>90 days vs. <= 90 days)
- MRD status at start of conditioning (MRD (molecular or cytogenetic) positive vs. MRD negative)

Before each subgroup analysis, an interaction test is carried out. The interaction test investigates, whether the treatment effect is different between the subgroups. A significant interaction test indicates a different treatment effect in the subgroups. Only in case of a significant interaction test (significance level alpha = 0.1), the treatment effect is analyzed in the subgroups. It is also investigated whether an uneven distribution of predictive variables between the subgroups could be responsible for the observation of different treatment effects.

All subgroup analyses are considered hypothesis generating. For all these tests a significance level of 0.05 is applied, if not stated otherwise. No adjustment for multiple testing will be applied.

7.3 Stratification

To account for the stratified randomization, the stratification factors are included in the analysis model for the primary hypothesis. Stratification factors are described in section 5.8.

8 Data Handling

8.1 Handling of Missing Data and Outliers

Missing values of the primary endpoint will be imputed according to a worst case approach for the primary analysis. Missing values in the transplant arm are imputed as event and missing values in the chemo arm are imputed as no events. This very conservative approach ensures preservation of the type-1-error probability. As sensitivity analyses an analysis is conducted excluding patients with missing data in the primary endpoint as well as an analysis imputing all missing values as no events.

Time to event endpoints will be censored at the time of the last known status of a patient. No missing values are expected. Sensitivity analyses will be conducted to investigate the influence of treatment arm on the censoring distribution.

The primary analysis is planned to be conducted with an adjusted logistic regression model. Missing values of adjusting variables will be imputed with a simple single imputation approach. For continuous variables the median of all observed values in the respective treatment arm will be imputed. For categorical variables the most frequent of all observed categories will be imputed. This single imputation approach leads to underestimation of standard errors of the variables that were imputed. It is also possible that some bias is introduced to the estimation of the effect of the imputed covariates. But, because the estimation of the adjusting variables is not of primary interest, these unwanted effects seem to be acceptable. It is also possible that bias is introduced to the estimation of the primary effect. But due to the fact, that all adjusting variables are variables that should be known prior to the randomization, we expect balance of missing values between both arms, which should lead to similar bias of the effect estimate not favouring one treatment. This seems to be acceptable, because it is unlikely to affect the type-1-error probability. Furthermore this approach enables analysis according to the intention-to-treat principle. A sensitivity analysis using only complete cases will be conducted.

Adjusting variables for which more than 15% of values are missing can be excluded from the primary analysis model.

8.2 Handling of Data from Drop-Outs

All available data of patients who prematurely terminate study treatment will be used in the respective analyses.

8.3 Handling of Multiple Comparisons and Multiple Primary Variables

No multiple comparisons are planned. Only one primary variable is defined for the study. Multiple subgroup analyses are preplanned, but no adjustment for multiple testing is planned, because all these analyses are considered hypothesis generating.

8.4 Data Review

A data review meeting (DRM) will be held before database lock at the end of the study in order to evaluate and accept the data management report, discuss remaining issues (outstanding queries, unresolved errors) and to confirm and approve relevant protocol violations on an individual base. The DRM is also responsible for the exclusion of outliers and exclusion of subjects from the analysis populations. After this final DRM has taken place and the database is considered cleaned, the database will be locked and the statistical analysis started.

9 Variables for Analysis

Variables that will be used as recorded in the database are listed only. Variables that need to be derived are listed and the derivation rule is given.

9.1 Disposition of Subjects

Disposition of subjects will be presented by means of:

- Number of patients who consented
- Number of patients who consented and were eligible with respect to inclusion and exclusion criteria
- Number of patients who consented and were not eligible with respect to inclusion and exclusion criteria
- Number of eligible patients who were randomized
- Number of non-eligible patients who were randomized
- Number of eligible patients who were not randomized
- Number of patients who prematurely discontinued study treatment (completion status and reason for discontinuation will be listed)

9.2 Demographic and Baseline Characteristics

- Age at date of informed consent (full years)
- Age categorized
    - Age <= 40 years
    - Age > 40 years
- Sex
- Disease status (de novo AML, AML with prior MDS, treatment related AML)
- Bone marrow blasts (%)
- FAB classification of AML (M0, M1, M2, M4, M4eo, M5, M5a, M5b, M6, M7)
- Karyotype (normal, aberrant)

- Aberrant karyotypes
- CEBPa mutation (WT, mutated, not analyzed)
- NPM1 mutation (WT, mutated, not analyzed)
- FLT3 mutation (WT, ITD, point mutation, not analyzed)
- FLT3-ITD ratio
- Other mutations
- CMV IgG (positive, negative, not analyzed)
- Blood group (A Rh pos, A Rh neg, B Rh pos, B Rh neg, AB Rh pos, AB Rh neg, 0 Rh pos, 0 Rh neg)
- Donor type (related, unrelated)
- HLA match of recipient and donor
- Stratum for randomization

9.2.1 Prior therapy of AML

- Medication
- Start date of therapy
- Duration of treatment (days)
- Cumulative dose of medication
- Days from start date of first induction treatment until randomization calculated as:
    - Date of randomization – start date of first induction therapy + 1
- Cumulative dose of cytarabine is calculated per patient as sum of cumulative cytarabine doses of a patient's induction cycles

9.2.2 Response to induction 1

- Bone marrow blasts (%)
- Response to induction 1 is calculated as follows:
    - Bone marrow blasts < 5% = good response
    - Bone marrow blasts >= 5% and < 10% = no good response

9.2.3 Response to induction 2

- Bone marrow blasts (%)
- Remission status (MLFS, CR)

9.2.4 Physical examination

- Body height
- Body weight
- Pulse rate
- Blood pressure systolic/diastolic
- Karnofsky index (100%, 90%, 80%, 70%, 60%, below 60%)

9.2.5 Concomitant diseases / comorbidities

Category unknown will be flagged as missing value (nmiss).

- Headache / migraine (no, yes, unknown)
- Osteoporosis (no, yes, unknown)
- Arthrosis (no, yes, unknown)
- Hypertension (no, yes, unknown)
- Gastrointestinal disease including inflammatory bowel disease (no, yes, unknown)
- Mild pulmonary disease (no, yes, unknown)
- Mild renal disease (no, yes, unknown)
- Metabolic disease (no, yes, unknown)
- Bleeding (no, yes, unknown)

- Coagulation disorder (no, yes, unknown)
- Asthma (no, yes, unknown)
- Arrhythmia (no, yes, unknown)
- Cardiac disease (no, yes, unknown)
- Mild hepatic disease (no, yes, unknown)
- Cerebrovascular disease (no, yes, unknown)
- Obesity (no, yes, unknown)
- Diabetes (no, yes, unknown)
- Psychiatric disturbance (no, yes, unknown)
- Infection (no, yes, unknown)
- Rheumatologic disease (no, yes, unknown)
- Moderate pulmonary disease (no, yes, unknown)
- Peptic ulcer (no, yes, unknown)
- Moderate / severe renal disease (no, yes, unknown)
- Heart valve disease (no, yes, unknown)
- Prior solid malignancy (no, yes, unknown)
- Moderate / severe hepatic disease (no, yes, unknown)
- Severe pulmonary disease (no, yes, unknown)
- HCT-CI comorbidity score
- HCT-CI comorbidity score categorized is calculated as:
    - HCT-CI = 0
    - HCT-CI = 1 or HCT-CI = 2
    - HCT-CI > 2

9.3 Extent of Exposure

- allogeneic SCT as post remission therapy:
    - documented date of SCT and no molecular relapse and no hematological relapse before SCT = yes; no documented date of SCT or molecular relapse or hematological relapse before SCT = no
- allogeneic SCT as salvage therapy:
    - documented date of SCT and molecular relapse or hematological relapse before SCT = yes; no documented date of SCT or no molecular relapse and no hematological relapse before SCT = no
- chemo consolidation therapy performed:
    - documented date of start of consolidation therapy = yes; no documented date of start of consolidation therapy = no
- number of cycles of consolidation therapy

9.4 Primary Variable

- Death within 2 years from randomization:
    - In case of death and OS time < 24 months: OS2Y = death
    - In case of death and OS time >= 24 months: OS2Y = alive
    - In case of no death and OS time >= 24 months: OS2Y = alive
    - In case of no death and censored OS time < 24 months: OS2Y = missing
    - Missing values will be imputed as described in section 8.1.

9.5 Secondary Variables

- Event free survival:
    - Events: relapse, death without relapse
    - In case of relapse: EFS time in months = (date of relapse – date of randomization + 1) / 30.43

  - In case of death without relapse: EFS time in months = (date of death – date of randomization + 1) / 30.43
  - In case of no relapse and no death: EFS time in months = (date of last follow up – date of randomization + 1) / 30.43; observation is censored
- Cumulative incidence of relapse (CIR):
  - Event: relapse; NRM is considered competing event
  - Time variable for estimation of CIR is EFS time.
- Cumulative incidence of non-relapse mortality (NRM):
  - Event: death without preceding relapse; relapse is considered competing event
  - Time variable for estimation of NRM is EFS time.
- Overall survival:
  - Event: death from any cause
  - In case of death: OS time in months = (date of death – date of randomization + 1) / 30.43
  - In case of no death: OS time in months = (date of last follow up – date of randomization + 1) / 30.43; observation is censored

9.6 Safety Variables

- Incidence, intensity, seriousness, relationship to SCT, and outcome of adverse events graded according to CTCAE 3.0
- GvHD grade:
  - Overall
  - Skin
  - Gastrointestinal tract
  - Liver
- Karnofsky index
- Duration of hospitalization

9.6.1 Blood count

- Hemoglobin (mmol/l)
- White blood count (G/L)
- Neutrophile count (%)
- Segmented neutrophile count (%)
- Band neutrophile count (%)
- Lymphocyte count (%)
- Monocyte count (%)
- Eosinophile count (%)
- Basophile count (%)
- Peripheral blasts (%)
- Other (%)
- Platelets (G/L)

9.6.2 Clinical chemistry

- Creatinine (µmol/l)
- Total bilirubin (µmol/l)
- ASAT (µmol/s*l)
- CRP (mg/dl)

9.6.3 Pregnancy test

- Pregnancy test (positive, negative, not applicable)

9.7 Exploratory Variables

Not applicable

9.8 Pharmacokinetic Variables

Not applicable

9.9 Other Variables

- Treatment of GvHD
  - Immunosuppression
  - Medication
  - DLI

10 Statistical Analysis Methods

10.1 General Design of Descriptive Statistics

In general the descriptive statistics are separated into total sample, treatment arms, and eventually subgroups (if appropriate).

For continuous variables in general, the number of non-missing observations (nval), number of missing observations (nmiss), arithmetic mean, standard deviation (SD), minimum (min), 1st quartile, median, 3rd quartile and maximum (max) is given.

For categorical variables in general, the number of non-missing observations (nval), number of missing observations (nmiss), and percentage of patients with non-missing data per category is given. For categorical variables measured at baseline and end of study (visit 13), shift tables for pre-post-differences are provided at end of study treatment (in case of premature termination during the treatment period the last available value is used).

For time-to-event variables, the number of non-missing observations (nval), number of missing observations (nmiss), number and percentage of censored observations, median survival with two-sided 95% confidence interval, Kaplan-Meier survival curves, survival rates at meaningful time points (with two-sided 95% confidence intervals), numbers at risk at meaningful time points and cumulative number of censored observations at meaningful time points are given. Additionally survival tables with survival rate, standard error, cumulative number of events and number at risk at all event- and censoring-times will be given.

10.2 Evaluation of Demographics and Baseline Characteristics

10.2.1 Disposition of Subjects

Tables with absolute numbers and percentage will be given. A CONSORT chart describing the patient flow from registration to the analysis sets will be presented.

10.2.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be analyzed as described in section 10.1. Aberrant karyotypes will be listed. Other molecular diagnostic detected mutations will be listed.

10.2.3 Prior therapy of AML

Therapies before randomization will be listed. Medication, start date of medication, duration of treatment in days and cumulative dose of each drug will be listed for each cycle of induction therapy.
Cumulative cytarabine dose and days from start date of first induction treatment until randomization are analyzed as continuous variable as described in section 10.1.

10.2.4 Response to induction 1

Variable bone marrow blasts (%) is analyzed as continuous variable as described in section 10.1.
Response to induction 1 is analyzed as categorical variable as described in section 10.1.

10.2.5 Response to induction 2

Variable bone marrow blasts (%) is analyzed as continuous variable as described in section 10.1.
Remission status is analyzed as categorical variable as described in section 10.1.

10.2.6 Physical examination

Body height, body weight, pulse rate and blood pressure are analyzed as continuous variables as described in section 10.1.
Karnofsky index is analyzed as categorical variable as described in section 10.1.

10.2.7 Concomitant diseases / comorbidities

The HCT-CI comorbidity score is analyzed as continuous variable as described in 10.1.
The categorized HCT-CI and all other variables (except the continuous HCT-CI comorbidity score) described in section 9.2.5 are analyzed as categorical variables as described in section 10.1.

10.3 Evaluation of Extent of Exposure

Allogeneic SCT as post remission therapy, allogeneic SCT as salvage therapy, and chemo therapy performed are analyzed as categorical variables as described in section 10.1.
Number of cycles of consolidation therapy is analyzed as continuous variable as described in section 10.1.

10.4 Evaluation of Primary Variable

The primary hypothesis is tested with the likelihood ratio test comparing two multiple logistic regression models with and without the factor ‘treatment arm’. The significance level is two-sided 0.05. Adjusting variables in the multiple logistic regression model are:

- Age dichotomized <= 40 vs. >40 years
- Donor type: unrelated vs. sibling
- Isolated NPM1 or CEBPa mutation (including simultaneous NPM1 and CEBPa mutations) vs. other molecular markers
- AML type with categories de novo AML vs. sAML vs. tAML
- Blast count on day 16 after start of first induction therapy dichotomized <10% vs. >=10%
- Sorror score (HCTCI) dichotomized <=3 vs. >3
- Remission status CRi vs. CR
- Normal vs. aberrant karyotype

Center effects are not considered in the primary analysis. A sensitivity analysis is conducted to investigate the effect of centers. Centers are modelled as random intercept in a generalized linear mixed model with logit link function. Fixed effects are the same as in the primary analysis model. Again the multiple models with and without the factor 'treatment arm' will be compared with the likelihood ratio test.

10.5 Evaluation of Secondary Variables

Event free survival

Event free survival is analyzed as time-to-event variable described in section 10.1. Event free survival rates will be presented for 6, 12, 24, 36, 48 months time points. Proportionality of the hazards of both groups is tested as described in Grambsch and Therneau (1994). In case of proportional hazards the survival time distributions between both arms are compared with a univariate and a multiple Cox model. The multiple Cox model includes the same adjusting variables as the logistic regression model described in section 10.4. In case of non-proportionality of the hazards a dichotomous variable for event free survival at 2 years after randomization is calculated. Descriptive analysis of this binary variable is conducted as described for categorical variables in section 10.1. A univariate and a multiple logistic regression are fitted to test for differences of the proportions in the two treatment arms. Adjusting variables for the multiple logistic regression model will be the same as described in section 10.4.

Cumulative incidence of relapse

Cumulative incidence of relapse is analyzed using competing risk methodology. Cumulative incidence curves will be plotted for both arms separately. Estimates for cumulative incidence of relapse are presented at 6, 12, 24, 26, 48 months together with two-sided 95% confidence intervals. Proportionality of the cause specific hazards for relapse is tested as described for event free survival. In case of proportionality of the hazards cumulative incidences of both treatment arms are compared with the Gray test. Univariate and multiple Cox regression models will be fitted to estimate the cause specific hazard for relapse. The multiple Cox model will contain the same adjusting variables like the logistic regression model for analysis of the primary endpoint. In case of non-proportional hazards no tests will be performed. Comparisons will be based on the estimates and its 95% confidence intervals only.

Cumulative incidence of non-relapse mortality

Cumulative incidence of non-relapse mortality is analyzed the same way as cumulative incidence of relapse.

Overall survival

As supporting analysis to the primary analysis overall survival is analyzed as time-to-event variable as described in section 10.1. Overall survival rates will be presented for 12, 24, 36, 48 months time points. Proportionality of hazards is tested as described for event free survival. In case of proportional hazards the survival time distributions between both arms are compared with a univariate and a multiple Cox model. The multiple Cox model includes the same adjusting variables as the logistic regression model described in section 10.4. In case of non-proportional hazards a univariate logistic regression model is fitted using the binary 2-year overall survival variable (primary variable) as dependent variable and treatment arm as independent variable. The corresponding multiple regression model is described in section 10.4.

10.6 Evaluation of Safety Variables

Adverse events and serious adverse events

All adverse events that occurred after randomization will be used for the safety analyses. Safety analyses will be conducted in the SES. The following descriptive analyses will be conducted as described in section 10.1.

- Number and percentage of patients with at least one adverse event per study arm
- Absolute number of all adverse events grade 3 to 5 per study arm
- Minimum, maximum and mean number of adverse events per patient per study arm
- Number and percentage of patients with at least one serious adverse event per study arm
- Absolute number of all serious adverse events per study arm
- Minimum, maximum and mean number of serious adverse events per patient per study arm
- Number and percentage of patients with at least one adverse event for which relatedness to the study therapy cannot be excluded
- Minimum, maximum and mean number of adverse events for which relatedness to the study therapy cannot be excluded
- Absolute numbers and percentages of patients with defined adverse events will be tabulated by CTCAE grade and study arm
- Absolute number and percentages of patients with defined adverse events of grades 3 to 5 will be tabulated by CTCAE grade and study arm

Following data will be listed patient-wise:

- Listing of all adverse events with study arm, subject identifier, description of adverse event, start date of study therapy, start date of adverse event, end date of adverse event, CTCAE grade, seriousness, relatedness to study drug, action taken, outcome of adverse event
- Serious adverse events will be listed in a separate list with the same parameters as described above for adverse events

All deaths will be listed with study arm, subject identifier, age, sex, weight, height, adverse event, adverse event duration, severity of adverse event, seriousness, relatedness of adverse event to study treatment, last study treatment and time since last study treatment

GvHD

In the transplant arm the proportion of patients with GvHD in all patients alive at the respective time point will be calculated based on non-missing values. Time points for evaluation are months 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, and 48. Grades of severity will be presented for GvHD of skin, gastrointestinal tract, liver, and total GvHD for all patients with GvHD at the respective time points. Absolute counts and percentage will be given.

Karnofsky index

Absolute numbers and percentage (based on non-missing values) will be presented for the re-evaluation visit and all follow-up time points (same as described in analysis of GvHD + visit 1 – re-evaluation) separately for each treatment arm. Shift tables will be presented illustrating change of Karnofsky index compared to the re-evaluation visit.

Duration of hospitalization

Duration of hospitalization during the preceding follow-up period is recorded in all follow-up visits. For analysis all values will be summed up. Missing values will be treated as zero values. This absolute cumulative number of days in hospital is analyzed as continuous variable as described in section 10.1.

To adjust for different survival times the duration of hospitalization in days is divided by the overall survival time in days. This proportion of days in hospital in all days alive since randomization will be analyzed as continuous variable as described in section 10.1. Comparison between both arms will be performed with the Mann-Whitney-U-Test.

10.6.1 Blood count

Laboratory values will be analyzed descriptively separately for each treatment arm and for all available time points as described in section **Fehler! Verweisquelle konnte nicht gefunden werden.**.

10.6.2 Clinical chemistry

Clinical chemistry will be analyzed descriptively separately for each treatment arm and for all available time points as described in section **Fehler! Verweisquelle konnte nicht gefunden werden.**.

10.6.3 Pregnancy test

Pregnancy test will be analyzed descriptively as categorical variable for all available time points as described in section **Fehler! Verweisquelle konnte nicht gefunden werden.**.

10.7 Evaluation of Exploratory Variables

Not applicable

10.8 Evaluation of Pharmacokinetic Variables

Not applicable

10.9 Evaluation of Other Variables

Treatment of GvHD

For treatment with immunosuppression and treatment with DLI absolute numbers and percentage will be given. Percentage will be based on the number of patients with GvHD and non-missing values at the respective time points.

Medication for treatment of GvHD is recorded with separate indicator variables for each substance. Absolute numbers and percentage will be presented. Percentage will be based on the number of patients with GvHD and non-missing values at the respective time points.

Time points for evaluation of treatment of GvHD are the same as described in section 10.6 (GvHD).

10.10 Special Analytic Issues

The study did not recruit the planned number of patients and the initially planned power will not be reached. The actually reached power will be calculated.

10.11 Interim Analysis

No interim analysis was planned and no interim analysis was performed.

11 Changes in the Planned Analysis

Change of primary endpoint from 4-year overall survival to 2-year overall survival. Due to slow patient accrual the study was closed prematurely. The follow-up period has been reduced. This reduction would have led to a substantial number of patients missing the binary endpoint ‘4-year overall survival’. Therefore it was decided to change the endpoint to 2-year overall survival, instead of imputing missing 4-year survival data points.

Adjusting variable for the multiple logistic regression model for analysis of primary endpoint and grouping variable for subgroup analyses d16-blast count: dichotomization clarified: initially </> 10% clarified to <10% vs. >=10%.

MRD-level excluded from multiple logistic regression model for analysis of primary endpoint, because not all patients have an MRD marker, but all patients must be included in the analysis according to the intention to treat (ITT) principle.

Grouping variable for subgroup analyses time from diagnosis to HSCT: dichotomization clarified: initially >90 vs. <90 days clarified to >90 vs. <= 90 days.

Overall survival as time-to-event variable added for descriptive analysis of survival time distributions

12 References

P. Grambsch and T. Therneau (1994), Proportional hazards tests and diagnostics based on weighted residuals. Biometrika*,* 81, 515-26

13 Version History and Review Log

Add number of new document version, version date and remarks (if applicable) in the table below.

Version	Version Date	Remarks
1-0	dd.mm.2020	Statistical Analysis Plan first version

Add information as requested in the table below. Any reviews without change of content must also be tracked.

Version reviewed	Review Date	Name of reviewer	Remarks

14 Planned tables and figures

14.1 Tables

14.1.1 Disposition of subjects

Table 1 Disposition of subjects

	Arm A	Arm B
Patients who consented		
Patients who consented and were eligible with respect to inclusion and exclusion criteria		
Patients who consented and were not eligible with respect to inclusion and exclusion criteria		
Eligible patients who were randomized		
Non-eligible patients who were randomized		

Eligible patients who were not randomized		
Patients who prematurely discontinued study treatment		

14.1.2 Demographic and Baseline Characteristics

Table 2 Demographic and baseline characteristics

	Arm A	Arm B
Number of patients, n		
Age (years)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Sex		
nval (%)		
nmiss (%)		
female, n/nval (%)		
male, n/nval (%)		
Disease status		
nval (%)		
nmiss (%)		
de novo AML, n/nval (%)		
AML with prior MDS, n/nval (%)		
treatment related AML, n/nval (%)		
Bone marrow blasts (%)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
FAB classification		
nval (%)		
nmiss (%)		
M0, n/nval (%)		
M1, n/nval (%)		
M2, n/nval (%)		
M4, n/nval (%)		
M4eo, n/nval (%)		
M5, n/nval (%)		
M5a, n/nval (%)		
M5b, n/nval (%)		
M6, n/nval (%)		
M7, n/nval (%)		
Karyotype		
nval (%)		
nmiss (%)		

normal, n/nval (%)		
aberrant, n/nval (%)		
CEBPa mutation		
nval (%)		
nmiss (%)		
wildtype, n/nval (%)		
mutated, n/nval (%)		
not analyzed, n/nval (%)		
NPM1 mutation		
nval (%)		
nmiss (%)		
wildtype, n/nval (%)		
mutated, n/nval (%)		
not analyzed, n/nval (%)		
FLT3 mutation		
nval (%)		
nmiss (%)		
wildtype, n/nval (%)		
ITD, n/nval (%)		
point mutation, n/nval (%)		
not analyzed, n/nval (%)		
FLT3-ITD ratio		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
CMV IgG		
nval (%)		
nmiss (%)		
positive, n/nval (%)		
negative, n/nval (%)		
not analyzed, n/nval (%)		
Blood group		
nval (%)		
nmiss (%)		
A Rh pos, n/nval (%)		
A Rh neg, n/nval (%)		
B Rh pos, n/nval (%)		
B Rh neg, n/nval (%)		
AB Rh pos, n/nval (%)		
AB Rh neg, n/nval (%)		
0 Rh pos, n/nval (%)		
0 Rh neg, n/nval (%)		
Donor type		
nval (%)		
nmiss (%)		
related, n/nval (%)		
unrelated, n/nval (%)		
HLA match of recipient and donor		
nval (%)		
nmiss (%)		
10/10, n/nval (%)		

9/10, n/nval (%)		
Stratum for randomization		
nval (%)		
nmiss (%)		
Stratum 1, n/nval (%)		
Stratum 2, n/nval (%)		
Stratum 3, n/nval (%)		
Stratum 4, n/nval (%)		
Stratum 5, n/nval (%)		
Stratum 6, n/nval (%)		
Stratum 7, n/nval (%)		
Stratum 8, n/nval (%)		

14.1.3 Response to induction

Table 3 Response to induction

	Arm A	Arm B
Bone marrow blasts after induction 1 (%)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Response to induction 1		
nval (%)		
nmiss (%)		
good response, n/nval (%)		
no good response, n/nval (%)		
Bone marrow blasts after induction 2 (%)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Remission status after induction 2		
nval (%)		
nmiss (%)		
MLFS, n/nval (%)		
CR, n/nval (%)		

14.1.4 Physical examination

Table 4 Physical examination

	Arm A	Arm B
Body height (cm)		
nval (%)		
nmiss (%)		

mean (SD)		
median (IQR)		
min – max		
Body weight (kg)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Pulse rate (BPM)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Systolic blood pressure (mmHg)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Diastolic blood pressure (mmHg)		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Karnofsky index		
nval (%)		
nmiss (%)		
100%, n/nval (%)		
90%, n/nval (%)		
80%, n/nval (%)		
70%, n/nval (%)		
60%, n/nval (%)		
below 60%, n/nval (%)		

14.1.5 Concomitant diseases / comorbidities

Table 5 Concomitant diseases / comorbidities

	Arm A	Arm B
Headache / migraine		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Osteoporosis		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		

Arthrosis		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Hypertension		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Gastrointestinal disease including inflammatory bowel disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Mild pulmonary disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Mild renal disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Metabolic disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Bleeding		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Coagulation disorder		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Asthma		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Arrhythmia		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Cardiac disease		
nval (%)		

nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Mild hepatic disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Cerebrovascular disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Obesity		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Diabetes		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Psychiatric disturbance		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Infection		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Rheumatologic disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Moderate pulmonary disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Heart valve disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Prior solid malignancy		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Moderate / severe hepatic		

disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
Severe pulmonary disease		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
HCT-CT comorbidity score		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
HCT-CI comorbidity score categorized		
nval (%)		
nmiss (%)		
0, n/nval (%)		
1-2, n/nval (%)		
>2, n/nval (%)		

14.1.6 Extent of exposure

Table 6 Extent of exposure

	Arm A	Arm B
allogeneic SCT as post remission therapy		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
allogeneic SCT as salvage therapy		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
chemo consolidation therapy performed		
nval (%)		
nmiss (%)		
no, n/nval (%)		
yes, n/nval (%)		
number of cycles of consolidation therapy		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		

14.1.7 Safety analyses

Table 7 Safety data

	Arm A	Arm B
Patients with at least one adverse event		
nval (%)		
nmiss (%)		
n/nval (%)		
Number of all adverse events grade 3 to 5		
n		
Number of adverse events per patient		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Patients with at least one serious adverse event		
nval (%)		
nmiss (%)		
n/nval (%)		
Number of all serious adverse events		
n		
Number of serious adverse events per patient		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		
Patients with at lest one adverse event for which relatedness to study therapy cannot be excluded		
nval (%)		
nmiss (%)		
n/nval (%)		
Number of adverse events for which relatedness to study therapy cannot be excluded per patient		
nval (%)		
nmiss (%)		
mean (SD)		
median (IQR)		
min – max		

Table 8 Adverse events

System organ class	Arm	N grade 1	% grade 1	N grade 2	% grade 2	N grade 3	% grade 3	N grade 4	% grade 4	N grade 5	% grade 5	N total	% total
SOC1	A												
SOC1	B												
SOC2	A												
SOC2	B												
…													
SOCX	A												
SOCX	B												

Table 9 Adverse events grades 3 to 5

System organ class	Arm	N grade 3	% grade 3	N grade 4	% grade 4	N grade 5	% grade 5	N total	% total
SOC1	A								
SOC1	B								
SOC2	A								
SOC2	B								
…									
SOCX	A								
SOCX	B								

Table 10 GvHD

	month 3	month 6	…	…	…	…	…	…	month 48
GvHD									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
GvHD total, severity									
nval (%)									
nmiss (%)									
1, n/nval (%)									
2, n/nval (%)									
3, n/nval (%)									
4, n/nval (%)									
5, n/nval (%)									
GvHD skin, severity									
nval (%)									
nmiss (%)									
1, n/nval (%)									
2, n/nval (%)									
3, n/nval (%)									

4, n/nval (%)									
5, n/nval (%)									
GvHD gastrointestinal, severity									
nval (%)									
nmiss (%)									
1, n/nval (%)									
2, n/nval (%)									
3, n/nval (%)									
4, n/nval (%)									
5, n/nval (%)									
GvHD liver, severity									
nval (%)									
nmiss (%)									
1, n/nval (%)									
2, n/nval (%)									
3, n/nval (%)									
4, n/nval (%)									
5, n/nval (%)									

Table 11 Karnofsky index

	Visit 1 re-evaluation	month 3	…	…	…	…	…	…	month 48
Karnofsky index									
nval (%)									
nmiss (%)									
100, n/nval (%)									
90, n/nval (%)									
80, n/nval (%)									
70, n/nval (%)									
60, n/nval (%)									
below 60, n/nval (%)									

Table 12 Shift table Karnofsky index

	month X						
Visit 1 – re-evaluation	n / row %	100	90	80	70	60	below 60
	100						
	90						
	80						
	70						
	60						
	below 60						

Table 13 Blood count

Arm X	Study entry	Visit 1 – re-evaluation	month 3	…	…	…	…	…	month 48
Hemoglobin (mmol/l)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
WBC (G/L)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Neutrophile count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Segmented neutrophile count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Band neutrophile count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Lymphocyte count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Monocyte count (%)									
nval (%)									
nmiss (%)									
mean (SD)									

median (IQR)									
min – max									
Eosinophile count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Basophile count (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Peripheral blasts (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Other (%)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Platelets (G/L)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									

Table 14 Clinical chemistry

Arm X	Study entry	Visit 1 – re-evaluation	month 3	⋮	⋮	⋮	⋮	⋮	month 48
Creatinine (µmol/l)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Total bilirubin (µmol/l)									
nval (%)									
nmiss (%)									
mean (SD)									

median (IQR)									
min – max									
ASAT (µmol/s*l)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
CRP (mg/dl)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									

Table 15 Treatment of GvHD, Immunosuppression, DLI

	month 3	month 6	⋮	⋮	⋮	⋮	⋮	⋮	month 48
Prednison									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Prednison dose (mg)									
nval (%)									
nmiss (%)									
mean (SD)									
median (IQR)									
min – max									
Methylpred. bolus									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Ciclosporin A									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Tacrolimus									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Sirolimus									
nval (%)									

nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Thalidomid									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
MMF									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Hydroxychloroquine									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
MTX po/iv									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Daclizumab									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
PUVA									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Photopheresis									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Pentostatin									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Everolimus									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
topical Tacrolimus									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
topical Steroids po									

nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
topical Steroids inhaled									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Physical therapy									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Other									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
Immunosuppression									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									
DLI									
nval (%)									
nmiss (%)									
Yes, n/nval (%)									
No, n/nval (%)									

14.2 Planned figures

- Consort diagram
- Event-free survival Kaplan-Meier curves
- Cumulative incidence of relapse curves
- Cumulative incidence of non-relapse mortality curves
- Overall survival Kaplan-Meier curves

14.3 Planned data listings (exemplary)

14.3.1 Prior therapy of AML

Arm	SUBJID	Treatment cycle	Medication	Start date of medication	Duration of treatment	Cumulative dose

14.3.2 Listing of all deaths

Arm	SUBJID	age	sex	height	weight	adverse event	adverse event duration	CTCAE grade of adverse event	serious adverse event	relatedness of adverse event to study therapy	last study treatment	time since last study treatment

14.3.3 Listing of all adverse events

Arm	SUBJID	adverse event	start date of study therapy	start date of adverse event	end date of adverse event	CTCAE grade	serious adverse event	related to study therapy	action taken	outcome

14.3.4 Listing of serious adverse events

Arm	SUBJID	adverse event	start date of study therapy	start date of adverse event	end date of adverse event	CTCAE grade	serious adverse event	related to study therapy	action taken	outcome