A Randomized Phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older Patients with AML in first Complete Remission

HCT vs CT in elderly AML

PROTOCOL

EudraCT Number 2007-003514-34

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Confirmation of Trial Protocol / Signature page

A Randomized Phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older Patients with AML in first Complete Remission

EudraCT Number 2007-003514-34

The signatories declare that they agree to conduct their responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented.

Approved by the following

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signature

2 X 1.13

date

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12 NOV 2013

date
Protocol Agreement / Signature page for Investigator

A Randomized Phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older Patients with AML in first Complete Remission

EudraCT Number 2007-003514-34

Herewith I declare that I have read and understood the protocol and agree to conduct the study accordingly. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product and their duties.

Investigator (stamp)                     signature                     date
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## 2 Synopsis

### 2.1 English

**Title**  
A Randomized Phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older Patients with AML in first Complete Remission

**Acronym**  
HCT vs CT in elderly AML

**Indication**  
Acute myelogeneous leukemia

**Inclusion Criteria**
- Age ≥ 60 years and ≤ 75 years
- primary or secondary AML as defined by WHO or refractory anemia with excess of blasts (RAEB)
- First complete remission following one or two cycles of induction chemotherapy
- Chemotherapy was administered according to current participating cooperative group protocols
- Karnofsky score ≥ 70
- Written informed consent

**Exclusion Criteria**
- AML FAB M3
- HIV positivity
- Participation in another clinical trial without prior consent of the coordinating investigator, patients may exceptionally take part in a further study only if
  - The second study exclusively concerns induction therapy
  - Consolidation cycle one and two are given according to the accredited study group policy
  - No investigational drugs are used post registration for the HCT vs CT in elderly AML study.
  - Documentation for the HCT vs CT in elderly AML study is not compromised. Second hand data from foreign study is not accepted

**Trial design**  
Two armed, controlled, randomised, open, multicentre, phase III trial:
Haematopoietic stem cell transplantation (HCT/SCT) after reduced intensity conditioning or conventional chemotherapy as a consolidation treatment for elderly patients with AML in complete remission.

**Primary Objectives**  
Efficacy of allogeneic related or unrelated hematopoietic cell transplantation (HCT) after reduced intensity conditioning as a consolidation treatment for elderly patients with AML in complete remission.

**Secondary objectives**  
Safety and toxicity of allogeneic related and unrelated

---

HCT vs CT in elderly AML  
final 5.1, 2013-11-07 incl amendments 01-03  
EBMT
hematopoietic cell transplantation (HCT) after reduced intensity conditioning as a consolidation treatment for elderly patients with AML in complete remission.

**Therapy / Interventions**

Patients with a matched sibling or with an unrelated donor, who have entered CR1, will be eligible for randomisation in a 2 (SCT): 1 (nonSCT) fashion. Patients without a donor will receive post-remission therapy as scheduled at the local trial site.

**Trial Duration**

6 months trial therapy per patient, 5 years of follow-up

**Primary endpoint** / Leukaemia free survival

**Secondary endpoints / outcomes**

- Overall survival
- Cumulative incidence of relapse
- Treatment related mortality
- Time series of blood parameters post therapy respectively transplant
- Incidence of myelosuppression
- Incidence of grades 2-4 acute GvHD after transplant
- Incidence of grades chronic extensive GvHD after transplant

**Biometry**

Analysis on an ITT basis and as treated,
Primary endpoint: Logrank test,
Secondary endpoints: Logrank test for time-to-event data, chi-square tests for frequencies;
Further descriptive statistics

**Number of Patients**

231 patients at randomization

**Planned start and end of recruitment**

Start of recruitment: 2010
Expected end of recruitment: 2015
Titel


Acronym

HCT vs CT in elderly AML

Indication

Akute myeloische Leukämie

Einschlusskriterien

- Alter ≥ 60 Jahre and ≤ 75 Jahre
- Primäre oder sekundäre AML nach WHO-Definition oder Refractory Anemia with Excess of Blasts (RAEB)
- Erste vollständige Remission nach ein oder zwei Zyklen Induktionschemotherapie
- Die Induktions- und erste Konsolidierungstherapie wird nach den Vorgaben der lokalen Studiengruppen verabreicht
- Karnofsky score > 70
- Schriftliche Einwilligung

Ausschlusskriterien

- AML FAB M3
- HIV-Test positiv
- Teilnahme an einer anderen klinischen Prüfung ohne die vorangehende Einwilligung des Leiters der klinischen Prüfung. Patienten dürfen nur an einer weiteren klinischen Prüfung teilnehmen, wenn:
  o Die zweite Studie betrifft nur die Induktionstherapie
  o Die Konsolidierungstherapie wird nach den Vorgaben der lokalen Studiengruppen verabreicht
  o Nach der Randomisation werden in der HCT vs CT in elderly AML-Prüfung keine Prüfpräparate eingesetzt
  o Die Dokumentation für die HCT vs CT in elderly AML-Prüfung wird primär
durchgeführt und ist nicht gefährdet. Daten aus einer anderen klinischen Prüfung werden nicht akzeptiert.

**Studiendesign**
Zweiarmige, kontrollierte, randomisierte, offene, multizentrische, Phase III-Prüfung: Hämatopoetische Stammzelltransplantation (HCT/SCT) nach reduzierter Konditionierung oder konventionelle Chemotherapie als Konsolidierungstherapie für ältere AML-Patienten in erster vollständiger Remission.

**Primäre Studienziele**
Effektivität allogener hämatopoetischer Stammzelltransplantation verwandter oder unverwandter Spender nach reduzierter Konditionierung als Konsolidierungstherapie für ältere AML-Patienten in erster vollständiger Remission.

**Sekundäre Studienziele**
Sicherheit und Toxizität hämatopoetischer Stammzelltransplantation (HCT) von verwandten bzw. fremden Spendern nach intensitätsreduzierter Konditionierung als Konsolidierung für ältere AML-Patienten in kompletter Remission.

**Therapie / Intervention**
Patienten in vollständiger Remission, für die ein passender Geschwisterspender oder unverwandter Spender gefunden wurde, werden im Verhältnis 2:1 in die zwei Studienarme Transplantation (SCT) oder konventionelle Chemotherapie (nonSCT) randomisiert. Patienten ohne passenden Spender erhalten eine Post-Remissionstherapie entsprechend den lokalen Vorgaben.

**Studiendauer**
6 Monate Prüftherapie und 5 Jahr Follow-up pro Patient

**Primärer Endpunkt**
leukämiefreies Überleben

**Sekundäre Endpunkte**
- Totales Überleben,
- Kumulative Relapse-Inzidenz,
- Behandlungs-bedingte Mortalität,
- Zeitreihen der Blutparameter nach Therapie bzw. Transplantation,
- Inzidenz von Myelosuppression,
- Inzidenz akuter GvHD (Grade 2 – 4) nach Transplantation,
- Inzidenz chronischer GvHD nach Transplantation.

**Biometrie**
Analyse auf ITT-Basis und als tatsächlich behandelt, primärer Endpunkt: Logrank Test, sekundäre Endpunkte: Logrank test für Überlebenszeitdaten, Chi-quadrat-Tests für Häufigkeiten weiterhin: deskriptive Statistik

**Anzahl Patienten**
231 Patienten werden randomisiert

**Geplanter Beginn und Ende der Rekrutierung**
Start: 2010
Ende: 2015
2.3 Schema of the Study

Figure 1: schema of the study

Note: Induction, Consolidation and non-SCT treatments will be administered as confirmed per study group protocol
3 Rationale

The majority of patients with acute myelogenous leukaemia enter complete remission following induction therapy, but relapse despite consolidation and maintenance therapy[1-5]. In response, post-remission treatment has been progressively intensified and results improved either by high-dose post-remission therapy with autologous hematopoietic cell transplantation (HCT) or by allogeneic HCT, which has the highest curative potential for patients with AML[6-8]. Given the toxicity of dose intensification and of allogeneic HCT, however, only younger patients profit from this treatment approach.

3.1 AML in older patient group

[reviewed in [9-11]

AML occurs predominantly in adults and its incidence increases with age. Epidemiological analyses reveal that the median age of affected patients is approximately 65 years [12]. However the median age in clinical studies of patients with AML tends to be lower, likely due to a reluctance of physicians to offer older patients the participation in clinical trials that use intensive cytotoxic therapy. The high early death rate reported from chemotherapy studies for AML in the 1980s might be one explanation for this. Nonetheless, chemotherapy-based antileukemic therapy is clearly superior to supportive care in the treatment of AML in elderly patients.

Löwenberg et al. reported a randomized study which showed that intensive remission induction therapy had a clearly higher survival rate (17% at 2 years) than a primary watch and wait strategy followed by mild palliative treatment with hydroxyurea and cytarabine (0% at 2 years) [13]. Several prospective randomized studies have been reported during the last 10 years in which the question of chemotherapy intensity for elderly patients with AML was investigated [14-22]. The results from these studies confirmed that elderly patients with AML benefit from intensive rather than reduced dose induction therapy. There was a decrease of early death rates from 41% in 1985 to 20% in 1995 which may in part be due to improvements in supportive care. Currently, in elderly patients with AML, complete remission (CR) rates between 40 and 60% can be achieved with acceptable treatment related mortality (TRM). However, after achieving CR, long term leukemia-free survival (LFS) remains poor due to early relapse and below 20% at 5 years with a median survival of approximately 9-10 months. In a current study of the Ostdeutsche Studiengruppe für Hämatologie (OSHO) using a standard induction regimen (Idarubicin 12 mg/m^2/d days 1-3 and Ara-C 240 mg/m^2/d days 1-7) 70% CR were achieved in 81 patients with an early death rate of 14%. However, despite two consolidation courses of intensive chemotherapy, LFS at 2 years was only 15%. The high early relapse rate in elderly patients with AML might reflect, in comparison to the younger patients, an increased frequency of leukemias with poor prognostic karyotypes or high multi-drug resistance gene 1 (mdr-1) expression [23;24].

In order to improve long term results in elderly patients, new approaches are needed. Although myeloablative high dose therapies have been effective in younger patients this is not feasible in older patients because of the high treatment related mortality (TRM) of this approach.

Reduced intensity conditioning (RIC) in elderly patients with AML

With the aim of overcoming the age limits and the high TRM (which, depending on histocompatibility, age, comorbidities and disease specific factors ranges between 10 and 70% in patients below 50 years of age after unrelated HCT, or those below 55 years of
age after related HCT) treatment protocols have been adapted to reduce morbidity and mortality[25-30]. Specifically, since the preparative regimen is inevitably linked to morbidity and TRM, RIC regimens have been developed with the aim of obtaining donor engraftment and using Graft versus Leukemia (GvL) effects rather than maximal chemotherapy as a mean of eradicating the underlying malignancies.

The approach to establish chimerism using low-dose Total body irradiation (TBI) based regimens was initially developed in pre-clinical studies performed at the Fred Hutchinson Cancer Research Center in Seattle, USA in a dog model[31]. Following these experimental study a phase I study was performed in humans with the intention to induce chimerism in hematological diseases[30]. The approach was further tested in protocols using unrelated donors [32].

The minimal conditioning regimen involving Fludarabine and low-dose TBI followed by immunosuppression with cyclosporine (CSP) and MMF was associated with very low hematological and non-hematological toxicities, without new onset of alopecia and, in some of the patients, without a requirement for red blood cell or platelet transfusions. Neutropenia is very moderate or does not even fall below 500/µL, so that infections during the early post-transplant period are rare. As a direct consequence even outpatient transplants became feasible, provided that an adequate infrastructure is available. The reduction in myelosuppression has meant that patients previously considered ineligible for HCT have now become eligible for allogeneic HCT, and that age has largely disappeared as a limiting factor.

Since December 1997, more than 1000 transplants with low-dose TBI based regimens have been carried out in patients with a variety of hematologic malignancies, solid tumors and non-malignant diseases not eligible for conventional transplants. Of 819 patients analysed in detail 59% are alive and 41% died. Causes of death included relapse/progression in 25%, (Graft versus Host Disease) GvHD and infections in 11%, infections in 2% and miscellaneous in 3% of the patients (R. Storb personal communication).

In a currently published study involving 122 patients with AML and treated with the same conditioning patients in CR1 and CR2 had better OS and LFS than patients in later stages of the disease[33]. In addition, a lower incidence of relapse and a high OS in unrelated compared to related RIC-HCT was described. In CR1 patients given related or unrelated grafts the OS was 44% and 63% respectively[33]. Furthermore, a non-relapse mortality (NRM) of 10% and 27% at two years was observed for related and unrelated RIC-HCT respectively, the most frequent causes of NRM being acute and chronic GvHD (approx. 10% in related and unrelated HCT) and infections without GvHD in unrelated transplants (11%). Relapse of the malignancy remained the major cause of death in AML patients. Relapse was dependent upon the stage of the disease and was 47% in patients with related donors and 33% in patients with unrelated donors. The durability of remission in patients after RIC-HCT was tested with molecular analyses in a variety of diseases including CML and AML. This has confirmed that not only cytogenetic remissions but also long lasting molecular remissions can be induced with purely immunological effects. In this study we analyzed the value of (donor lymphocyte infusion) DLI for treating relapse or low donor chimerism. DLIs were given for relapse/persistent disease to 14 of the 122 patients, of whom, 12 patients (8.3%) had received related grafts, and two patients (1.6%) received unrelated grafts. Thirteen of the 14 patients died from relapse between 1 and 595 days after DLI. One patient is alive in remission. DLIs were given for low-level donor chimerism to seven of the 122 patients (5.7%). One patient died of liver GvHD, two patients relapsed, and four patients are alive in remission. DLIs were unsuccessfully administered to two patients with pending graft rejection.
Initial data from a preceding HOVON/SAKK/OSHO study in patients with age 50-60, 60-70 and 70-80 and with related donors have demonstrated the feasibility of establishing allogeneic engraftment in older patients with hematologic malignancy. The results did not indicate the slightest effect of age on outcome in 83 patients. Full allogeneic engraftment has been consistently and safely achieved with an immunosuppressive conditioning program incorporating low-dose TBI and post-grafting immunosuppression with CSP and MMF. The evaluation of the HOVON/SAKK/OSHO study is in progress. The two year OS and leukemia free survival data are looking promising but follow up is still limited. Evidently, the availability of related donors in this age group is quite limited which precludes most patients to proceed and receive an allogeneic HCT. At most 20% of the patients in this age group have an identical family donor. Transplants from unrelated donors provide an opportunity for allogeneic HCT in these patients. This seems of interest because accumulating data confirm the feasibility of the procedure towards the age of 75 years and beyond, and preliminary results suggest equivalent or even better outcome than after transplants from related donors. The more potent graft-versus-Leukemia effect in unrelated HCT suppressing the risk of leukemia recurrence and the lower early TRM using the reduced conditioning regimen seem to contribute to the beneficial effects. In this study, we set out to test the role of allogeneic HCT from unrelated donors using low-dose TBI and postgrafting immunosuppression with CSP and MMF in a prospective comparison with chemotherapy. Only such a study approach will directly address the comparative value of this form of allogeneic HCT in this age group of patients with AML. Conventional chemotherapy will offer a probability of OS in the range of 10-15% at 2 years. Consolidation therapy with unrelated HCT may allow for an increase of OS and LFS in elderly patients with AML.

3.2 Proposal

Allografting using high dose regimens has been shown to reduce relapse of AML in patients at all stages of disease and is the only curative treatment for many patients. Older patients however do not tolerate the high-dose regimens. Phase I/II studies using related and unrelated donors have shown that allogeneic HCT is feasible with minimal toxicity in older AML patients and that patients may remain long term disease free after allogeneic transplantation.

In the present protocol we plan to analyse the role of allogeneic HCT from related and unrelated donors in comparison to chemotherapy in patients between 60-75 yrs of age in CR1 after one or 2 induction cycles followed by one consolidation therapy. Patients with a donor will be randomized in a head-to-head comparison between chemotherapy and treatment with Fludarabine, 200 cGy TBI and allogeneic HCT followed by immunosuppression with CSP and MMF. According to Figure 1 patients are enrolled in this trial as soon as they achieve CR1 after induction chemotherapy. Induction and first consolidation are not unified over all trial sites, each participating study group or trial site should declare its induction and consolidation protocol they will use during this trial upfront. However, if a trial site or study group is not committed to a special regimen, chemotherapy protocols from HOVON or OSHO can be provided. The second consolidation cycle (arm B) will be administered according to the confirmed protocols. If a center or study group is not committed to a special regimen, consolidation protocols from HOVON or OSHO can be provided.
4 Study objectives

4.1 Primary
To evaluate leukaemia free survival (LFS) for older patients after allogeneic SCT in AML/RAEB in CR using matched or unrelated donors in comparison to conventional chemotherapy.

4.2 Secondary
To evaluate:

- Overall Survival
- Cumulative incidence of relapse
- TRM and complications
- Incidence of myelosuppression (ANC < 500/mm³ for > 2 days, platelets < 20,000/mm³ for > 2 days) after initial PBSC infusion
- Incidence of grades 2-4 acute GvHD after transplant
- Incidence of grades chronic extensive GvHD after DLI
5 Trial Design and description

5.1 Trial design
The trial is designed as a open-label, randomized, phase III, two-armed, multi-centre trial. The schema of the trial is shown in chapter 2.3.

Patients who are diagnosed with AML, underwent one or two cycles of induction chemotherapy and reached complete remission are screened for eligibility for this trial. After registration at CR1 a donor search is started to evaluate the availability of a related (sibling) or unrelated donor for a hematopoetic stem cell transplant (SCT).

Patients with a matched sibling or with an unrelated donor, will be eligible for randomisation in a 2 (SCT): 1 (nonSCT) fashion.

Patients without a donor will be enrolled in an observation arm and receive post-remission therapy as scheduled by the trial site.

5.2 Requirements for participating investigators and trial sites
The common qualification criteria required by ICH-GCP and the German drug law will be assessed by the ethics committees involved before start of the trial. There are no further specific requirements concerning the trial sites.

5.3 Trial sites and number of trial subjects
The participating trial centers (according to the recent information received) are located in Germany, the Netherlands, Switzerland, France and Spain and are associated to the EBMT. A total of 231 patients will be randomised.

5.4 Expected duration of trial
Patients are registered as soon as they reach the first complete remission and are randomised as soon as they find a matching donor. The stem cell transplant takes place 4 weeks after randomisation the treatment in the conventional chemotherapy arm starts 2 weeks after randomisation. Patients are followed until year 5 after start of the respective trial treatment, such that the trial duration per patients adds up to approximately 5.5 years depending on the period in which a donor can be located. The recruitment period is estimated to require approximately five years.
6 Patient selection

Participation in this trial is broken down to two time points of eligibility checks: registration (after reaching CR1) and randomisation (successful donor search).

6.1 Inclusion criteria at registration

Patients must meet ALL of the following criteria:

- Age ≥ 60 years and ≤ 75 years
- primary or secondary AML as defined by WHO or refractory anemia with excess of blasts (RAEB)
- First complete remission following one or two cycles of induction chemotherapy
- Chemotherapy was administered according to current participating cooperative group protocols
- Karnofsky score ≥ 70 (see Appendix D. - Karnofsky performance scale)
- Written informed consent

6.2 Exclusion criteria at registration

Patients will be excluded for ANY ONE of the following reasons:

- AML FAB M3
- HIV positivity
- Participation in another clinical trial without prior consent of the coordinating investigator, patients may exceptionally take part in a further study only if
  - The second study exclusively concerns induction therapy
  - Consolidation cycle one and two are given according to the accredited study group policy
  - No investigational drugs are used post registration for the HCT vs CT in elderly AML study.
  - Documentation for the HCT vs CT in elderly AML study is not compromised. Second hand data from foreign study is not accepted

6.3 Inclusion criteria at randomisation

All registered patients who meet the inclusion criteria and do not meet any of the exclusion criteria after the first consolidation cycle are randomised if they have a 10/10 matched donor:

- Patient is registered in this trial
- Complete remission must be confirmed after first consolidation cycle according to the response criteria enlisted in appendix B with the following exception regarding the peripheral blood recovery (B1):
  - Peripheral Blood Recovery (PBR): ANC ≥ 1.0 x 10^{9}/l or 1500/mm$^3$, transfusion independent platelet count ≥ 50 x 10^{9}/l (i.e. 48 h after last
transfusion) and no leukemic blasts in the peripheral blood and no dysplasia
  o AND platelet count must be increasing
- Matching (10/10: HLA-A, -B, -C, DRB1 and DQ) related or unrelated donor is available

6.4 **Exclusion criteria at randomisation**
The exclusion criteria must be checked before and as close in time as possible to randomization!

- Patient has undergone more than one consolidation cycle
- More than 5 months (>150 days) after diagnosis
- Organ dysfunction
  o Patients with creatinine clearance < 50 ml/min
  o Cardiac ejection fraction < 40%
  o Severe defects in pulmonary function testing (defects are currently categorized as mild, moderate and severe) as defined by the pulmonary consultant, or receiving supplementary continuous oxygen
  o Liver function tests: total bilirubin > 2x the upper limit of normal, SGOT and SGPT 4x the upper limit of normal
- Patients with poorly controlled hypertension
- Participation in another clinical trial without prior consent of the coordinating investigator

**Note:** Patients who meet all of the inclusion criteria and none of the exclusion criteria after the first consolidation cycle AND are not randomised are treated off study but are documented in the observation arm. The observation group comprises e.g. patients who do not have a 10/10 matched donor or withdraw consent to be randomised. Data from the observation arm will help to assess the external validity of the trial results.

Treatment in the observation arm is at the discretion of the treating centre. Documentation in the observation arm is reduced: Data on LFS and type of further treatment will be collected. Detailed documentation of the course of treatment is not required.
7 Donor search

7.1 Patients with related donors

Patients with related, HLA genotypically identical donors in CR1 undergo RIC-HCT after induction therapy and first consolidation therapy. Donors must be medically fit to undergo apheresis procedure (which has to meet institutional guidelines for apheresis). In addition, donors must consent to G-CSF administration and leukapheresis and have adequate veins for leukapheresis or agree to placement of central venous catheter (femoral, subclavian).

7.2 Patients with unrelated donors

In patients without a family donor an unrelated search is initiated as soon as CR1 (for definition see Appendix B – Response criteria for AML and MDS) has been reached (usually after first induction).

Centers have to use unrelated donors with 10/10 allele match (HLA-A, -B, -C, DRB1 and DQ). High resolution typing in HLA - class I and class II is used to identify a donor. Previous studies did show that the use of bone marrow instead of peripheral blood hematopoietic cells as a stem cell source has a significant negative impact on engraftment (rejection rate app. 40%), therefore only peripheral blood stem cell donors are accepted. CMV and blood group recipient-donor combination did not influence OS or LFS, therefore no restrictions are applied. In case of more available donors maximal match should be used as first priority followed by CMV status and blood group. Sex combinations were not shown to influence outcome after 200 cGy TBI based regimens and are therefore not considered an important donor selection criterion.

Timing is an important aspect in the conduct of the study. Considering that HCT was performed at median of 76 days after last therapy, HCT should be done within 12 weeks after start of the last chemotherapy[33]. If no donor has been identified within 5 months after diagnosis, the non-transplant approach of treatment that is applied at the local institution will be pursued.

For details see[33]. As soon as a donor has been identified (Appendix C – Eligibility guidelines for donor PBSC apheresis) and the patient has been randomized for HCT, a work -up meeting international and institutional guidelines is started and the transplant scheduled at least 2 weeks after blood counts normalized following the first consolidation cycle.

7.3 Exclusion criteria (donor)

- Participation in another clinical trial without prior consent of the coordinating investigator
- Monozygotic identical twin
- Age ≤ 18 years
- Pregnancy
- Infection with HIV
- Inability to achieve adequate venous access
- Known allergy to G-CSF
- Current serious systemic illness

7.4 Patients without donor

If the donor search is negative at the possible last time point of randomisation (i.e. 5 months after the date of diagnosis, see section 2.3), the patient will not be randomised and are enrolled in an observation arm where treatment and outcome of these patients are documented as described above (see 6.4).
8 Registration and randomisation

8.1 Patient information and informed consent

A conference will be held with the patient, his or her family and - if applicable - the related donor to discuss this study and alternative treatments available for the treatment of the underlying disease. All potential risks associated with the use of TBI, immunosuppressive drugs and DLI should be discussed as objectively as possible. It should be explained that patients offered this protocol have a projected long term survival of < 20% if treated with conventional chemotherapy only.

If applicable, the procedure for collecting peripheral blood mononuclear cells and toxicities of G-CSF will be explained to the donor. The donor should be counseled as to the risks of treatment with G-CSF and be informed that leukapheresis at several time points will be necessary.

Informed consent from the patient and – if applicable – from the donor will be obtained.

The investigator must explain to each trial subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail to each trial subject. Each trial subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician. The patient should be provided with enough time to think about the participation in the study.

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

The Patient Information and Consent Form

A generic patient information leaflet/consent form (PIL/Consent form) is provided with the protocol. This is a sample and should be amended as required to conform to local requirements and will be translated into local language as necessary. Local versions should be appropriately version controlled.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s):

A properly signed and personally dated informed consent form is required for each patient before any trial specific procedure. After the study has been fully explained the patient should be given ample time to read the consent forms and ask questions. Written informed consent will always be obtained from the patient and/or his/her guardian or legal representative prior to study participation.
The informed consent process should be recorded in source documents (date of information and consent, parties present).

The investigator is responsible for checking entries made by the patient on the consent form, and to request correction immediately in case of missing, illegible or incorrect dates. The person taking the patient consent should sign and date both consent forms to confirm he/she provided information to the subject.

All entries on the consent forms must be permanent (no pencil).

The Informed Consent form will be updated by the Investigator-Sponsor whenever important new information becomes available that may be relevant to subject’s consent. This may be a result of amendments to the protocol, new information regarding the trial medication alternative treatments. Revised versions must be approved by the relevant ethics committee(s).

The revised consent form must be signed by subjects who are entered in the trial and not yet completed, if these changes are relevant to the subject’s willingness to continue participation. In particular, if the consent form is updated with new safety information, a new version of the informed consent form must be provided to all subjects in a timely manner as soon as written ethics approval is obtained.

Patient withdrawal of consent from the study should be explicitly documented in the source documents.

The Informed Consent form is to be found in the Investigator Site File. The signed Informed Consent has to be duplicated to provide one version to the participant and one for the trial site which has to be filed in the Investigator Site file.

The informed consent of the patient must also refer specifically to the assessment and processing of data on the patients’ health. The patient is to be informed explicitly on the purpose and extent of the assessment and the use of his/her personal data, especially the health-related data.

### 8.2 Procedure for registration and randomisation

All eligibility criteria will be checked and each patient will be given a unique patient study number.

All study centres will register the eligible patients via the completed and signed CRF registration form to the ZKS Leipzig – KKS (KKS) Data Management as per contact details on the form. The KKS will send a confirmation of the registration if all registration criteria are met.

Patients with a donor (HLA-identical family donor or an unrelated donor) who meet all inclusion criteria for randomisation will be randomised at latest 150 days after date of diagnosis to the SCT arm or non-SCT arm of the study in a proportion of 2:1. Patients without a donor will be enrolled in the ‘observation arm’.

In both cases (donor search successful/not successful) the patient’s data is submitted to the KKS via the CRF randomisation form as per contact details on the form.
9 Treatment Plan

All patients in CR1 after induction cycle 1 or 2 without a matched family donor will undergo unrelated donor search. One cycle of Consolidation therapy and supportive therapy, as per relevant study group protocol may be administered to every patient during the search interval.

All patients who remain in remission and who have a donor will be randomised to the ‘SCT arm’ (SCT is here used as a synonym for HCT) or to the conventional treatment in the ‘non-SCT arm’ at a ratio of 2:1.

Patients randomised to the non-SCT arm will have the option of a late transplant in case of relapse and attainment of a second complete remission.

Patients without a related or unrelated donor within 5 months (150 days) from diagnosis are allocated to the nonSCT treatment in a third ‘observation arm’.

9.1 SCT-Arm: Hematopoietic cell transplantation after reduced intensity conditioning (RIC)

9.1.1 Conditioning regimen

The conditioning regimen is composed of administration of Fludarabine, Cyclosporine, Mycophenolate mofetil and total body irradiation.

9.1.2 Cyclosporine (CSP)

- CSP is given at 6.25 mg/kg p.o. b.i.d by day -3 to day +180 for unrelated HCT and to day 84 for related HCT, then be tapered at 8% per week to be discontinued unless GvHD develops. If a decrease of CD34+ cells occurs CSP will be tapered earlier and after MMF has been stopped. If there is nausea and vomiting at anytime during CSP treatment drug should be given intravenously at 1.5 mg/kg b.i.d.
- Blood pressure, renal function (creatinine), electrolytes and magnesium will be followed at least three times per week while receiving CSP.
- Dose Adjustments: CSP whole blood "trough" levels (i.e., just prior to the next dose) will be evaluated on day +1 and adjusted if necessary to maintain blood levels that target the upper end of therapeutic range. Further CSP determinations should be performed on a twice weekly basis until CSP is stopped unless high levels are detected, or toxicity is suspected in which case more frequent monitoring will be performed as clinically indicated. In this group of patients, close monitoring of renal function is essential. Dose reductions for high levels without toxicity should be conservative e.g. 25%, to avoid inadequate immunosuppression, particularly in the first month post-transplant.
- Drugs that may affect CSP levels include: dilantin, phenobarbital (may lower CSP levels), steroids, fluconazole, ketoconazole, cimetidine (may increase CSP levels).
9.1.3 Mycophenolate mofetil (MMF)

- Oral administration of MMF will be at 15 mg/kg t.i.d. (45 mg/kg/day) from the evening of day 0 (i.e. first dose to follow PBSC infusion). MMF administration will be stopped on day +27 in patients with related donors and will be tapered by day +40 in patients with unrelated donors by 500 mg every 14 days.

- Guidelines for MMF dose adjustment: The major adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, and vomiting. If in clinical judgment of the attending physician the observed toxicity is related to MMF administration, a dose adjustment may be made. Based on previous organ transplant studies, dose adjustments are likely to occur because of hematopoietic or gastro-intestinal adverse effects. Dose adjustments will not be made for hematopoietic toxicity unless severe neutropenia (ANC < 100/mm$^3$ for > 5 days). In the event of gastrointestinal toxicity that requires medical intervention including medication for control of persistent vomiting or diarrhea that is considered to be due to MMF, a 20% dose reduction will occur first and if there is no improvement, MMF will be reduced a further 20%. For severe G.I. toxicity related to MMF (severe refractory diarrhea, or overt gastrointestinal bleeding), the MMF may be temporarily stopped. Patients should be evaluated by a Gastroenterology consultant and discussed with the principal investigator before stopping MMF.

9.1.4 Total Body Irradiation (TBI)

TBI with reduced intensity is performed in a single dose application exposing the total body with a dose of 2 Gy. It is the aim of the conditioning regimen to damage the malignant and normal host stem cell to obtain engraftment and an antitumor effect. The irradiation applied to the total body including the skin is well tolerated and only a fraction of the dose given during conventional stem cell transplantation. The total dose applied is within the tolerance of the organs at risk in terms of acute toxicity. However, stochastic late effects on somatic cells can occur. These include radiation induced second malignancies as solid tumours with a latency period of approximately 20 years or a second leukaemia after a latency period of 5 years. According to UNSCEAR 1977 the risk will be estimated between 0.4 - 1 % of events. The selected radiation technique has to assure a maximum dose homogeneity. It is therefore a prerequisite to provide an individual treatment planning based on systematic dosimetry, CT localisation considering the tissue heterogeneities and variation in volume and shape of the body. In order to assure a precise treatment it is necessary to provide verification procedure and documentation of all relevant parameters. An in vivo dosimetry for all patients such TLD with checked dose application is recommended. The detailed application, treatment planning, dosimetry and quality assurance of TBI should be based on the recommendations of the guidelines for total body irradiation of the Society for Medical Physics and the German Society for Radiation Oncology.
9.1.5 Donor PBSC and transplant

On days -4, -3 and –2 Fludarabine will be administered with a dosage of 30 mg/m²/day i.v.
On day 0 the conditioning is continued with total body irradiation (TBI) 2.0 Gy at 6-7 cGy/min followed by infusion of the peripheral blood stem cells of the donor (PBSC).
TBI has to be administered between 11.00 a.m. and 2.00 p.m. to avoid proximity to CSP/MMF administration.

The PBSC graft should contain at least 4 x 10⁶ /kg CD34 and 3 x 10⁸ /kg CD3+ cells.
All patients will receive unmodified G-CSF mobilized PBSC (> 4 x 10⁵/kg CD34+) on day 0 of the treatment regimen. The regimen is summarized in Table 2.

Table 1: Conditioning schema and immunosuppression schedule:

<table>
<thead>
<tr>
<th>Day Number</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>0</th>
<th>+1</th>
<th>+28</th>
<th>+40</th>
<th>+56</th>
<th>+84</th>
<th>+180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>TBI</td>
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<td></td>
<td></td>
<td>200</td>
<td>cGy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cell Infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSP related</td>
<td>START</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>TAPER^B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF Related HCT</td>
<td>START^A</td>
<td>→</td>
<td>→</td>
<td>STOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSP unrelated</td>
<td>START</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>TAPER^B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF Unrelated HCT</td>
<td>START^A</td>
<td>→</td>
<td>→</td>
<td>Reduction of 500mg /14 days</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

^A The first dose of MMF is to be given 5-10 hours after the stem cell infusion

^B Taper will be a 8% dose reduction per week x 11 weeks
9.1.6 Immunosuppression

For related HCT:

Day –3: Commence CSP at 6.25 mg/kg p.o. b.i.d. and continue according to CSP levels. Taper starts on day +84 by 8% dose/week.

Day 0: Commence MMF at 15 mg/kg p.o. t.i.d. to day +27. Termination of immunosuppression is dependent upon the presence of GvHD and CD34+ chimerism.

For unrelated HCT:

Day –3: Commence CSP at 6.25 mg/kg p.o. b.i.d. and continue according to CSP levels. Taper starts on day +180 by 8% dose/week.

Day 0: Commence MMF at 15 mg/kg p.o. t.i.d. to day +40. Then decrease dose by 500 mg every two weeks. Termination of immunosuppression is dependent upon the presence of GvHD and CD34+ chimerism.

CSP doses will be given both at 9.00 a.m. and 9.00 p.m. Since significant nausea may accompany this immunosuppression and particularly in the days after TBI, regular scheduled antiemetic therapy is recommended for all patients for at least one week after the transplant.
Special management recommendations (during and post-transplant)

Post-transplant growth factors and neutropenia
It is recommended that patients do not receive growth factors while receiving MMF. They may be given (G-CSF preferably) in case of severe persistent neutropenia (ANC <100/mm$^3$ for > 5 days) or if patients are neutropenic (ANC < 500/mm$^3$) with active infection. If ANC drops to < 500/mm$^3$ then prophylactic broad spectrum antibiotics should be given, e.g. p.o. ciprofloxacin.

Infection prophylaxis
Patients will receive prophylaxis for PCP, HSV and candida as per standard practice manual with the modification that PCP prophylaxis will be discontinued 1 year post-transplant, or 1 year after the last DLI was given, unless the patient is receiving treatment for chronic GVHD (prophylaxis should be extended). Standard CMV prophylaxis and monitoring should commence at the time of transplant and should continue until at least 90 days post-DLI (last dose given). CMV practice should be as for regular allografts. Patients who do not engraft can discontinue this infection prophylaxis at 3 months post-transplant. Standard toxoplasmosis prophylaxis should be started at the time of hematological reconstitution after transplantation and should be continued until day +60.

Treatment of Acute GVHD grade ≥2
♦ CSP 6.0 mg/kg p.o. b.i.d. If there is concern of GI absorption use IV route (1.5 mg/kg b.i.d.), if patient is not on cyclosporine. Optimise CSP levels if patient is already on CSP.
♦ Prednisone (2 mg/kg) to be added if severe and progressive GvHD and no GvHD response to CSP by 72 hours, or at 1 week with less severe GvHD and no GvHD response to CSP. Prednisone should be given at 2 mg/kg for 2 weeks and then tapered over 6 weeks.
♦ OKT3 1 Amp. i.v. will be given if GvHD is not improving within 5 days after start Prednisone and will be continued until resolution of symptoms.
♦ If GvHD is confined only to the gut, Budesonid 3 mg t.i.d. is given.

Treatment of clinical extensive chronic GVHD
CSP daily and prednisone (1mg q.o.d.) and antibiotic prophylaxis with Pen-VK and twice weekly Bactrim.

9.1.7 Monitoring and treatment of Relapse
Patients are monitored for CD34$^+$ chimerism in patients with CD34$^+$ AML blasts according to the summary and time plan for evaluations (see section 9.3). Cells obtained from bone marrow aspirations are sorted by FACS or beads and subsequently analyzed either by FISH or VNTR. In case of chimeric or molecular relapse defined as the increase or positivity of the molecular marker beyond day 28 or CD34$^+$ donor cell decrease of more than 5%, immunosuppression is reduced within eight weeks starting with MMF first. In case of hematological relapse defined as reappearance of blast in the marrow >5% or appearance of blasts in the peripheral blood, immunosuppression is withdrawn immediately and, if no GvHD is appearing within 2 weeks, DLI of the donor infused.
9.1.8 Indication for post-transplant donor PBSC infusion

If there is evidence of relapse and the patient is off immunosuppression without GvHD, DLI or chemotherapy and DLI may be given. The EBMT relapse protocol might be used. There is no sufficient evidence that DLI is effective in increasing low-level chimerism except for relapse. Therefore we do not recommend the administration of DLI to achieve full donor chimerism.

Doses, Collection and Administration of Donor PBSC

The following describes a plan for collection and sequential administration of donor PBSC in a dose escalation scheme designed to avoid using higher doses of T-cells than that required to eradicate the malignant clone:

- Each patient may receive up to 2 intravenous infusions of donor T-cells given at intervals outlined in Table 4.
- Donors will undergo leukapheresis and collection of non-mobilized PBSC on the day of the first DLI.
- Immunophenotyping (CD3, CD4, CD8) of the PBSC product will be performed by the cryobiology laboratory. After determining the CD3+ cell content the first dose of T-cells will be infused. Residual cells will be cryopreserved for future infusion in 1 aliquot of $3.2 \times 10^7$ CD3+ cells/kg and the remaining cells in aliquots of $1 \times 10^6$ CD3+ cells/kg.
- PBSC will be collected using standard leukapheresis techniques. Donors should undergo vein to vein collections or if PBSC cannot be collected by a vein to vein technique, a percutaneous Mahurkar catheter will be inserted. Collections will be performed first thing in the morning to allow immunophenotyping of the product to determine appropriate volume of cells to be infused and cryopreserved. For DLI using fresh PBSC, infusion will take place in the afternoon of the day of the PBSC collection. Infusions of cryopreserved PBSC should be performed as per standard practice for infusions of cryopreserved PBSC.
- Unirradiated donor PBSC will be administered by i.v. infusion over 30 minutes.
- Tylenol, Demerol, morphine or Benadryl may be administered (as needed) for chills. Steroids should be avoided whenever possible.

- Patients who develop acute GvHD that requires therapy may not receive additional DLI on this protocol. Note: After initiating T-cell infusions patients should only be treated with immunosuppression for $\geq$ grade II acute GvHD.

Table 2. Administration of DLI for relapse: Dose and interval of donor T-cell infusions for related HCT and for unrelated HCT (cell dose 1 log less)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Day post-disease progression - criteria</th>
<th>CD3+ cells/kg patient weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>14 days after stop immunosuppression and no evidence of GVHD</td>
<td>$1 \times 10^7$ (related) or $1 \times 10^6$ (unrelated)</td>
</tr>
<tr>
<td>#2</td>
<td>No response after 4 weeks of dose level #1</td>
<td>$3.2 \times 10^7$ (related) or $3.2 \times 10^6$ (unrelated)</td>
</tr>
</tbody>
</table>
Myelosuppression after DLI

Patients with myelosuppression will be managed as follows:
- rhG-CSF (5µg/kg/day s.c.) will be started in patients with a hypoplastic marrow and a ANC of <500/mm³.
- Thrombocytopenic patients will receive platelet transfusion as per standard care.
- Prophylactic broad spectrum antibiotics e.g. ciprofloxacin, while ANC < 500/mm³.

9.2 nonSCT-Arm: The non-transplant treatment approach for consolidation

Patients randomized in Arm B (non-SCT) will receive a chemotherapy as second consolidation cycle. The consolidation or maintenance therapy has to be administered according to a upfront specified trial site protocol. This treatment should start at latest 2 weeks after randomization to the nonSCT-arm. If no consolidation protocol is available, the following optional schedule may be considered:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>10 mg/m²</td>
<td>30 min infusion</td>
<td>1 + 2</td>
</tr>
<tr>
<td>Ara-C</td>
<td>500 mg/m²</td>
<td>q12hrs. 1h infusion</td>
<td>1 + 3 + 5</td>
</tr>
</tbody>
</table>

If the local trial protocol designates no second consolidation cycle as for instance described in the HOVON study group for patients >65 years, it is allowed to leave out the second consolidation cycle for the correspondent patient population.

9.2.1 Relapse treatment in the nonSCT-Arm

In case of hematological relapse patients receive induction chemotherapy according to study group protocols. If no induction protocol is available the following combination might be used:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarubicin</td>
<td>12 mg/m²</td>
<td>30 min infusion</td>
<td>1 + 2</td>
</tr>
<tr>
<td>Ara-C</td>
<td>500 mg/m²</td>
<td>q12 hrs. 1h infusion</td>
<td>1 + 3 + 5</td>
</tr>
</tbody>
</table>

As soon as the second CR is reached patients may receive either a related SCT or unrelated SCT from their donor as described above.
### 9.3 Study Conduct – Summary and time plan for evaluations

Table 3: Time plan for evaluations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>1, 3 Baseline / CR1</th>
<th>2 Randomisation</th>
<th>4 First Consolidation</th>
<th>7a a Allograft: days -3 to 0</th>
<th>7b nonSCT treatment (to be documented after consolidation)</th>
<th>8a Post therapy SCT arm: days 28, 56, 84, 100</th>
<th>8b Post therapy nonSCT arm: days 28, 56, 84, 100</th>
<th>9 Follow up: days 180 and 270; months 12, 18, 24, 36, 48 and 60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Data</strong></td>
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HCT vs CT in elderly AML  final 5.1, 2013-11-07 incl amendments 01-03  EBMT

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<table>
<thead>
<tr>
<th>Assessment</th>
<th>1, 3 Baseline / CR1</th>
<th>2 Randomisation</th>
<th>4 First Consolidation</th>
<th>7a Allograft:</th>
<th>7b nonSCT treatment (to be documented after consolidation)</th>
<th>8a Post therapy SCT arm:</th>
<th>8b Post therapy nonSCT arm:</th>
<th>9 Follow up: days 180 and 270; months 12, 18, 24, 36, 48 and 60</th>
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</thead>
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<tr>
<td>Haematology / Biochemistry</td>
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<td>x</td>
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<td>x</td>
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<td>d0-d28 daily, d29-d56 weekly</td>
<td>d0-d28 daily, d29-d56 weekly</td>
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<td>x</td>
<td>x</td>
<td>d0-d28 daily, d29-d56 weekly</td>
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</tr>
</tbody>
</table>

1. After induction-therapy, prior to consolidation and prior to transplantation
2. Bone Marrow Biopsy including cellularity and blasts, BMB is desirable, but not mandatory
3. Molecular Marker: BCR-ABL, PML-RAR, AML1-ETO, FLT3-ITD (internal tandem duplication), NPM1 mutation, MLL-PTD (partial tandem duplication), CEBPA mutation
4. Chimerism: Peripheral Blood: CD3 donor cells, Myeloid donor cells, Total Chimerism; Bone Marrow: CD34+ donor cells, Total chimerism (see section 9.7)
5. Serological status: Antibodies: HIV, CMV, EBV, HBVs, HBVc, HCV, Toxoplasmosis, Direct Coombs; Antigens (if applicable): HBVs, HBVe, HCV
6. Haematology including: Haemoglobin, Platelets, WBC; Biochemistry including: Creatinine, Bilirubin, Serum β2-microglobulin, Alanine transaminase (ALT/SGPT), Aspartate transaminase (AST/SGOT), Alkaline phosphatase (ALP)
7. At diagnostics, at CR1 (prior to Registration) and after 1st consolidation (prior to Randomization)
8. Transplantation shall be performed as soon as possible after randomization of the subject. If, in exceptional cases, SCT is performed > 4 weeks after randomization: bone marrow biopsy/aspiration has to be repeated to prove patient is still in CR
9.4 **On study evaluations**

9.4.1 1-Registration / 3-Baseline (CR1)

See local practice manual for details of routine pre-allografting workup. Required data for the baseline evaluation are the following. Some of the data are already required at the time point of registration and refer to the diagnosis and date of CR1 as remarked on the CRF forms.

Medical History: A complete history with full details of the patients prior to treatment and response
- Careful physical exam with determination of (amongst others):
  - Comorbid Conditions
  - Karnofsky score
- Eligibility (inclusion/exclusion criteria) for registration
- Informed consent
- Disease Classification
- Involvement of organs/organ systems
- Information on induction cycle I and – if applicable – induction cycle II. Therefore each trial site should inform and update the ZKS Leipzig – KKS about the applied local treatment schema. A form is provided.

**Blood and bone marrow:**
Unilateral bone marrow aspirate is mandatory, biopsy is desirable but not mandatory.

- Disease Status: date of diagnosis
- White blood count
- Bone marrow: cellularity, blasts (%)
- Molecular Biology:
  - BCR-ABL, PML-RAR, AML1-ETO, FLT3-ITD (internal tandem duplication), NPM1 mutation, MLL-PTD (partial tandem duplication), CEBPA mutation
- Cytogenetics/PCR

9.4.2 2-Randomisation

- Eligibility (inclusion/exclusion criteria) for randomisation
  - Donor availability
  - Registration
  - Complete remission
- Information on consolidation cycle I

Please note: Please complete the CRF-form also for patients for whom no donor is available at the latest possible time point for randomisation. These patients are enrolled in the observation arm. Documentation for the observation arm is carried out parallel and a possible later transplant e.g. can be documented in the follow-up form.
9.4.3 4-First Consolidation
The following data have to be documented at the end of consolidation cycle I.

- Karnofsky score
- Information on consolidation cycle I, schema
- Bone marrow: cellularity, blasts (%) [investigation has to be repeated if SCT is performed > 4 weeks after randomization]
- Cytogenetics/PCR after first consolidation
- Molecular biological markers (absent/present)
- Confirmation of enduring complete remission
- Blood Analyses (CRF form “BA”):
  
  o Haematology:
    - Haemoglobin
    - Platelets
    - WBC
    - Reticulocytes
    - Neutrophils
    - Lymphocytes
    - Eosinophils
    - Basophils
    - Blasts
  
  o Biochemistry:
    - Creatinine
    - Bilirubin
    - Serum β₂-microglobulin
    - Alanine transaminase (ALT/SGPT)
    - Aspartate transaminase (AST/SGOT)
    - Alkaline phosphatase (ALP)

9.4.4 SCT-arm: 7a-Allograft, day -3 to day 0

Transplantation shall be performed as soon as possible after randomization of the subject. If, in exceptional cases, SCT is performed > 4 weeks after randomization: bone marrow biopsy/aspiration has to be repeated to prove patient is still in CR.

Bone marrow investigation: cellularity, blasts (%) [investigation has to be repeated if SCT is performed > 4 weeks after randomization]

The following data have to be documented on day 0 in the SCT-Arm:

- Karnofsky score
- Serological Status:
  - HIV
  - CMV
  - EBV
  - HBVs
  - HBVe
  - HCV
  - Toxoplasmosis
  - Direct Coombs
- Blood Analyses: Haematology and biochemistry, please see 9.4.3
- Information on stem cell graft (concentration of CD34⁺ cells)
- Information on applied conditioning regimen and immunosuppression
9.4.5 nonSCT-arm: 7b-nonSCT Treatment
The following data have to be documented at the end of consolidation cycle II.

- Karnofsky score
- **Serological Status:** (prior to consolidation II)
  - HIV
  - CMV
  - EBV
  - HBVs
  - HBVe
  - HBVc
  - HCV
  - Toxoplasmosis
  - Direct Coombs

- Information on consolidation cycle II, schema
- Blood Analyses: Haematology and biochemistry, please see 9.4.3

9.4.6 SCT-arm: 8a-Post therapy (days 28, 56, 84, 100)
- Karnofsky score
- Blood and bone marrow:
  - Bone marrow: cellularity, blasts (%)
  - Cytogenetics/PCR
  - Molecular biological markers (absent/present)
- Supportive Therapy:
  - G-CSF
  - fresh frozen plasma (FFP)
  - Thrombocyte concentrate
  - red packed cells
- Chimerism in peripheral blood, in bone marrow
- Immunosuppression/-modulation
- **Blood Analyses:** Haematology and biochemistry, please see 9.4.3:
  - Days 0-28 daily
  - Days 29-59 weekly

If applicable:
- Adverse Events that have arisen since the last documentation (TOX form)
- GvHD status, acute (grade)/chronic (aGvHD/cGvHD form)

9.4.7 nonSCT-arm: 8b-Post therapy (days 28, 56, 84, 100)
- Karnofsky score
- Blood and bone marrow:
  - Bone marrow: cellularity, blasts (%)
  - Cytogenetics/PCR
  - Molecular biological markers (absent/present)
- Supportive Therapy:
  - G-CSF
• fresh frozen plasma (FFP)
• Thrombocyte concentrate
• red packed cells

- **Blood Analyses:** Haematology and biochemistry, please see 9.4.3:
  - Days 0-28 daily
  - Days 29-59 weekly

If applicable:
- Adverse Events that have arisen since the last documentation (TOX form)

## 9.5 Follow up

### 9.5.1 9-Follow up

This form needs to be completed on days 180, 270, month 12, 18, 24, 36, 48, 60 and in case of relapse or DLI application

- Karnofsky score
- Disease Status (CR / Relapse)
- Treatment of AML since last documentation:
  - autologous/allogeneic SCT
  - palliative/curative chemotherapy
- Information on administered DLI
- Appearance of secondary malignancies
- Late toxicities
- Blood Analyses: Haematology and biochemistry, please see 9.4.3

If applicable:
- GvHD status, acute/chronic (aGvHD/cGvHD form)

Every effort should be made to obtain information on patients who do not attend a scheduled appointment, to obtain at least minimal efficacy and safety data.

- All relapses have to be reported within 2 weeks
- All deaths (including its causes) have to be reported immediately after one becomes aware of the event, latest within 3 days

### 9.6 Documentation of study termination, toxicities, GvHD

Documentation of study terminations of patients differentiates if the patient has been randomised yet or not respectively enrolled in the observation arm. The corresponding forms for study termination are:

- 5-Death/Study termination **prior** to assignment to study arm
- 6-Death/Study termination **after** assignment to study arm

With completion of these forms the reasons for study termination can be stated:

- Death
• Withdrawal of consent
• Investigator choice (only prior to assignment)
• Relapse
• Loss to follow up

Adverse Events will be documented on the Toxicity form (TOX), serious adverse events will be documented on an SAE-form (see also section 10.2).

In the case of emerging GvHD, these will be documented on the acute GvHD-form (aGvHD) or the chronic GvHD-form (cGvHD).

### 9.7 Post-transplant evaluation of chimerism

Chimerism will be evaluated according to the above shown schedule (section 9.3) in the peripheral blood and for CD 34\(^+\) cells in the bone marrow.

Therefore, myeloid (CD45\(^+\)) and lymphoid (CD3\(^+\)) PB cell populations will be sorted, and chimerism will be evaluated using PCR to amplify microsatellites. Mixed chimerism is determined by variable number tandem repeats (VNTR) PCR technique or by FISH in sex recipient-donor mismatches. CD34\(^+\) cells are sorted by FACS or immunomagnetic methods from the bone marrow and evaluated for donor or host origin. The results are given in % donor cells.

**Evaluation prior to DLI**

- LTFU evaluation including chronic GvHD evaluation
- T-cell and CD34\(^+\) chimerism

**Evaluation after DLI**

- History and physical exam to assess GvHD weekly until day 90 after the last DLI, thereafter monthly or as clinically indicated.
- CBC and LFT's weekly until day 90 after the last DLI, thereafter monthly or as applicable.
- Bone marrow aspirations for pathology, flow cytometry, and chimerism studies at day 56 after each DLI. Bone marrow biopsy to pathology at day 56.
- Heparinized blood sample 20 ml to chimerism laboratory on days 28 and 56 for chimerism studies of T-cells and granulocytes.
- At day 90 after the last DLI chronic GvHD screening.
- At one year anniversary from the last DLI, LTFU evaluation will be performed including: chronic GvHD evaluation.

### 9.8 Study Pathology

Not applicable.
10 Reporting of Adverse Events and Serious Adverse Events

10.1 Definitions of Adverse Events

Adverse Event (AE)
This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment. An AE is therefore described as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study treatment, whether or not related to the study treatment.

Adverse Reaction (AR)
This is defined as all untoward and unintended responses to a study treatment related to any dose administered. A causal relationship between the study treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE)
This is defined as any untoward medical occurrence or effect in a patient treated on a study protocol which does not necessarily have a causal relationship with the study treatment, that also, at any dose:
- Results in death
- Is life threatening
- Results in persistent or significant or disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above)

Suspected Serious Adverse Reaction (SSAR)
This is defined as an adverse reaction, the nature or severity of which is consistent with the known study treatment information (e.g. Summary of Medicinal Product Characteristics (SmPC), Investigator Brochure (IB) or Investigator Medicinal Product Dossier (IMPD)).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
This is defined as an adverse reaction, the nature or severity of which is not consistent with the known study treatment information. (e.g. Summary of Medicinal Product Characteristics (SmPC), Investigator Brochure (IB) or Investigator Medicinal Product Dossier (IMPD)).
A serious event or reaction is not defined as a SUSAR when:
- it is serious but expected
- it does not fit the definition of an SAE, whether expected or not

10.2 Procedures for Adverse Event Reporting

All adverse events that occur between day 0 (start of trial therapy) and day 100 must be recorded using the toxicity form. Those adverse events meeting the definition of a serious adverse event must be reported immediately using the Serious Adverse Event Report
Investigators must record in the CRF and the patient notes their opinion concerning details of nature, onset, duration, severity and any relationship to the investigational product. Medical terminology should always be used to describe any event. Investigators should avoid vague terms such as “sick”.

**Adverse Event Term**
An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v4.0 (CTCAE), available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

**All deaths** occurring on study, except if it is one of the following expected adverse events, must be reported as an SAE and on the CRFs. For all deaths, available autopsy reports should be pseudonymized with the patient-ID and sent to the coordinating investigator following to the notification.

**Expected adverse events**
The following adverse events, for the purposes of this clinical trial, will be considered as expected events that are disease/transplant related and do not require reporting as an SAE even if they fulfill the SAE-criteria mentioned above:

- Rejection
- Relapse (documentation: form 6)
- GvHD (documentation: forms aGvHD/cGvHD)
- Infection (documentation: form TOX)
- Toxicities (documentation: form TOX, where applicable: additional documentation on SAE-form)

These events should still be recorded on the corresponding CRF-forms as designated above.

**Severity**
Severity for each adverse event, including any lab abnormality, will be determined by using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE, se above) as a guideline, wherever possible. In those cases where the CTCAE criteria do not apply and where there is no accepted alternative grading system e.g. Bearman Scale, severity should be defined according to the following criteria:

**Mild**
Awareness of sign or symptom, but easily tolerated

**Moderate**
Discomfort enough to cause interference with normal daily activities

**Severe**
inability to perform normal daily activities

**Life Threatening**
Immediate risk of death from the reaction as it occurred.

**Death**
**Causality**
Relationship to study treatment will be determined as follows:

**None**
No relationship between the experience and the administration of the study treatment; related to other etiologies such as concomitant medications or patient’s clinical state.

**Unlikely**
The timing renders a causal relationship unlikely and concomitant disease or other products can serve as a plausible explanation.

**Possible**
Plausible timing, but could be explained by concomitant diseases or other products, information on withdrawal is incomplete or unclear.

**Probable**
A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected treatment. The reaction cannot be reasonably explained by the known characteristics of the patient’s clinical state or other modes of therapy administered to the patient.

**Definitely**
An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s).

**Expectedness**
An expectedness assessment needs to be conducted for all Serious Adverse Events and recorded appropriately on the Assessment-Sheets by the principle investigator. Expectedness of the event to the medicinal product will be determined as follows:

**Expected**
The event is listed in the SmPC/IB or the study protocol as expected.

**Unexpected**
The event is not listed in the SmPC/IB or in the study protocol, or the severity of the event is greater than that listed in the SmPC/IB or the study protocol (e.g. mild nausea is listed as expected in the SmPC/IB/study protocol but the event is moderate or severe nausea).

**Reporting of serious adverse events (SAE)**
As Sponsor, the EBMT is responsible for pharmacovigilance. Events defined as serious must be reported by fax to the ZKS Leipzig - KKS, using the Serious Adverse Event Report form, immediately after observing or learning of the event.

ZKS Leipzig - KKS / Pharmacovigilance
Universitaet Leipzig
Zentrum für Klinische Studien Leipzig - KKS
Härtelstr. 16-18,
04107 Leipzig
Telefon: +49/341/97-16129
Fax: +49/341/97-16278
E-mail: pharmacovigilance@zks.uni-leipzig.de

The following attributes must be assigned when reporting:
- Detailed description of the event
- Adverse event term (see Adverse Event Term section for details)
- Date of onset and date of resolution (if available)
- Severity of the event (see Severity section for details)
- Assessment of relatedness to the protocol treatment (see Causality section for definitions) and action taken
- Other suspect drugs/devices

Outcome

The ZKS Leipzig – KKS will forward all SAEs to the coordinating investigator (legal representative of the EBMT):

Dietger Niederwieser
Dept. of Hematology, Oncology and Hemostasiology,
Univ. of Leipzig, Johannisallee 32 A, 04103 Leipzig, Germany
Tel. +49 (0) 341 97-13050 or +49 (0) 341 97-13133
Fax. +49 (0) 341 97-13059 or +49 (0) 341 97-13139
dietger.niederwieser@medizin.uni-leipzig.de

Substitutes:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telefon</th>
<th>E-Mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD Dr. med. habil. Thoralf Lange</td>
<td>+49 (0) 341 97-13026 (DECT: 13858)</td>
<td><a href="mailto:Thoralf.lange@medizin.uni-leipzig.de">Thoralf.lange@medizin.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Dr. med. Wolfram Pönisch</td>
<td>+49 (0) 341 97-13063 (DECT: 13824)</td>
<td><a href="mailto:Wolfram.poenisch@medizin.uni-leipzig.de">Wolfram.poenisch@medizin.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Dr. med. Haifa Kathrin Al-Ali</td>
<td>+49 (0) 341 97-13125 (Beeper: 13125)</td>
<td><a href="mailto:Haifakathrin.al-ali@medizin.uni-leipzig.de">Haifakathrin.al-ali@medizin.uni-leipzig.de</a></td>
</tr>
</tbody>
</table>

The coordinating investigator is responsible for the assessment of every SAE regarding causal relationship and expectedness. This medical assessment is documented on an Assessment-Sheet which will be sent to the ZKS Leipzig - KKS within 2 days after receipt of the SAE at the principal investigator.

The ZKS Leipzig - KKS will proceed with the immediate data entry of the SAE-CRF and the assessment-sheet, as well as the MedDRA-coding.

**Query process and closure of open Adverse Events**
Queries regarding all open Adverse Events will be asked in the following frequency:

1. 2 weeks after receipt of SAE-CRF
2. 2 weeks after first query
3. 1 week after second query
All Serious adverse events will be followed up until resolution. The investigator will be asked to provide interim and follow-up reports, as necessary, if the SAE has not resolved at the time of initial report. The case will be closed if the outcome is declared as "recovered", "recovered with sequelae", or "fatal" and the stop date is known.

Even though there is no information about outcome and stop date after the third query it will be discussed with the principle investigator if there will be further queries or if the case will be closed without this information.

Investigators may receive an Investigator Notification from the EBMT trials office via the ZKS Leipzig - KKS at any time for any serious unexpected adverse reactions, which the Independent Data Monitoring Committee for the study deem necessary. These should be processed according to the local regulations.

10.3 Annual Safety Report

The Sponsor writes an annual (or upon request) safety report (following the “detailed guidance on the collection, verification and presentation of adverse events reports arising from clinical trials on medicinal products for human use). The ASR is prepared by the coordinating investigator in cooperation with the project management at the ZKS Leipzig - KKS and the corresponding biometrician. This report comprises a detailed risk-benefit-analysis, a line listing of all serious adverse reactions (SARs) registered during the report period of the ASR as well as an aggregate summary tabulation containing all documented SAEs in the course of the trial. The ZKS Leipzig - KKS submits this report detailing the safety of the tested medicinal products to the leading ethics committee as well as to the competent regulatory authorities.

Until the cut-off date for the annual safety report all data concerning SAEs, have to be present at the sponsor.

The cut-off date is the date of the first authorization of the clinical trial by the competent regulatory authority. All data obtained up to this time point will be included in the ASR. Beginning with the cut-off date, there is a time-limit of 60 days for the preparation and submission of the ASR to the competent regulatory authorities and the leading ethic committees.

10.4 Periodic SUSAR Reports for Ethic Committees

Because of the procedures concerning SUSAR-reporting (see 10.5) it is necessary that:

All SUSARs from other Member States are periodically reported at least every 6 months as a line listing accompanied by a brief report by the sponsor highlighting the main points of concern. These periodic reports should only include SUSARs reported within the period covered by the report.

The listing of SUSARs is prepared by the principal investigator in cooperation with the project management at the ZKS Leipzig - KKS and the corresponding biometrician. The sponsor submits the listing to all concerned ethics committees and a copy to the concerned competent authorities.
10.5 Expedited reporting of SUSAR

The ZKS Leipzig - KKS submits all information available about a SUSAR immediately, latest within 15 calendar days after the event becomes known, to the responsible leading ethics committee, the competent regulatory authorities, and to all primary investigators.

In the case of death or a life-threatening condition caused by a SUSAR the responsible leading ethics committee, the competent regulatory authorities, and all primary investigators must be informed by the sponsor within 7 calendar days after the event becomes known. Additional information has to be given within 8 further calendar days.

The primary investigator passes down all relevant information concerning the occurred SUSAR to all participating trial investigators in his trial centre. These have to acknowledge the receipt of the information by signing a signature list. The competent regulatory authority obtains an electronic report of the SUSAR, if possible. The leading ethics committee will be informed paper-based by the CIOMS-I form. The principal investigators will be informed by e-mail concerning SUSARs by using the CIOMS-I form. EBMT will also be informed about the occurrence of any SUSAR with the CIOMS-I form.

10.6 Toxicities

Peripheral blood stem cell transplant

Based on the clinical studies published to date we expect the initial treatment with PBSC transplant to be associated with relatively minor side effects. Since only approximately 1000 patients have received this treatment protocol we cannot be absolutely certain as to the potential risks. Side effects include low blood count, infections, bleeding, and failure of the donor stem cells to grow. Supportive care with red cell and platelet transfusions and antibiotic therapy may be necessary. GvHD (inflammation of skin, liver and gastrointestinal system), may also occur and require treatment with immune suppressing drugs. In addition, organ damage may occur as a result of radiation or the treatment with immune suppressing drugs. There is a risk that the patient will reject the donor’s PBSC and that donor cells will not be detected after transplant. The dose of radiation used is not being expected to cause permanent marrow suppression in the event that graft rejection occurs.

Total body irradiation

TBI may cause nausea, vomiting, diarrhea, temporary hair loss, and painful swelling of the saliva glands for a few days. TBI may kill normal bone marrow cells in addition to the cancer cells. The dose of TBI used in this protocol is approximately one-sixth of that used in conventional transplant protocols, and severe side effects from the TBI are not expected. TBI has been associated with causing sterility and there is a risk of major genetic damage to any children begeted soon after transplantation.

Fludarabine

Fludarabine is a drug used to treat blood cancers. It has been used in stem cell transplants to try to reduce the risk of rejection. Its main side effects include lowering of blood counts and infections. In early studies some patients who received high doses experienced nerve damage, but in doses used in this study this side effect would not be expected. Hemolytic anemia has occurred in some patients with chronic lymphocytic leukemia who received fludarabine.
**Mycophenolate mofetil**

MMF is a relatively new drug used for suppressing the immune system and it has not been used frequently in bone marrow or peripheral blood hematopoietic cell transplantation. Preliminary studies here indicate that this drug is reasonably well tolerated in the transplant setting. There are a small number of patients who have received solid organ transplants and had reversible fall in their red cell or white cell count while receiving MMF. The blood counts will be watched closely and, if significant decrease is noted, dose adjustments or stopping MMF may be indicated. Other uncommon side effects include nausea, vomiting, diarrhea, and abdominal discomfort. Cases of intestinal bleeding have also been reported.

**Cyclosporine**

The immediate effects of this drug may include nausea or vomiting when given orally. Other side effects include the possibility of developing high blood pressure (hypertension), shaking of the hands (tremor), increased hair growth and possibly an effect on mental function. These effects are generally reversible upon decreasing the dose of the drug. An occasional patient has had a seizure but it is unclear whether cyclosporine, other drugs, or a combination of drugs was responsible. Some patients given intravenous cyclosporine for the treatment of GvHD experienced painful sensation in hands or feet or both. The pain subsided with the improvement of the GvHD or when the cyclosporine was switched from the intravenous to the oral form.

Patients may experience a change of liver or kidney function, in which case, the dose may be reduced or possibly even stopped for a while. This effect on kidneys seems to increase when other drugs which might cause kidney problems are given at the same time, especially certain antibiotics. Occasionally the kidney damage is severe enough to require the use of an artificial kidney machine (hemodialysis). During treatment cyclosporine blood levels will be monitored to determine if there are increased risks of side effects that warrant changing the dose.

**Donor lymphocyte infusion**

Approximately 15-20% of patients receiving unmodified DLI have died of complications related to GvHD or myelosuppression and additional patients suffer from long term morbidity due to persistent GvHD. Risks appear related to T-cell dose and may be reduced through use of low doses of T-cells as proposed in this study.

The major toxicities associated with DLI have been the development of acute and/or chronic GvHD and severe suppression of the blood counts. These effects do not usually develop until 1-4 weeks after treatment. GvHD has occurred in approximately 50% of patients and may involve the skin (rash, discoloration, and tightness); gastrointestinal tract (nausea, vomiting, and diarrhea); abnormal liver function tests, lung injury, dry mouth and dry eyes, weight loss, and hair loss. GvHD may be mild or severe and may require prolonged treatment with drugs to suppress inflammation and immune reactions. This complication may be life-threatening. A condition of low blood counts has been observed in up to 40% of patients who have received DLI. This appears to be due to an immunologic effect of the donor cells against the host marrow, and the state may last several weeks. If this develops, there is a risk of bleeding from low platelet counts and infection due to low white cell counts. Intensive supportive care with red cell and platelet transfusions and antibiotic therapy may be necessary. It would also be treated with growth factors to speed up bone marrow recovery.
Graft-versus-Host Disease
The major toxicity associated with allografting or infusion of donor PBSC is GvHD. GvHD has occurred in > 50% of patients.

Diagnosis of GVHD: Skin involvement will be assessed by biopsy with percentage of body surface area involved recorded. Gi symptoms suspicious for GvHD will be evaluated by biopsy as indicated. Acute GvHD (Appendix E – Grading of acute GvHD) and chronic GvHD will be graded according to established criteria.

Myelosuppression
Myelosuppression (aplasia) has occurred in approximately 35% of relapsed leukemia patients given unmodified DLI. It occurs most frequently in patients with CML and is uncommon after DLI for AML. Myelosuppression will be defined as a decrease in ANC to <500/mm³ and/or platelet count to ≤ 50,000/mm³. If myelosuppression occurs a bone marrow aspirate and biopsy will be performed to exclude disease progression. Samples should be sent for chimerism analysis by FISH or VNTR.

Rejection
Rejection implies the loss of the donor stem cell graft after transplantation in the recipient and is defined as absence of donor T-cell chimerism. Rejection may occur without any increase of donor T-cells (primary rejection) or after a short period of engraftment and decline thereafter (secondary rejection).

G-CSF
G-CSF may be used in aplasia and life-threatening infections.

Grading of Toxicities
Toxicities will be scored according to the NCI Common Toxicity Criteria, version 4.0 (see section 10.2) and documented on the toxicity form (TOX). Any toxicities observed that are not addressed in the NIH CTCAE version 4.0 should be graded:

1 = mild
2 = moderate
3 = severe
4 = life-threatening.
11 Premature termination

It is planned that the study will be terminated after completion of the last follow-up, i.e. after the last recruited patient has completed the 5 years follow-up.

11.1 Premature termination of protocol treatment

Reasons premature termination of trial treatment are (see also section 9.6):

Prior to randomisation:

1. Death
2. Withdrawal of consent
3. Investigator choice
4. Patient lost to follow up
5. Haematological relapse

After assignment to treatment arm:

1. Death
2. Withdrawal of consent
3. Major protocol violation

Premature termination should be avoided. In case of a premature termination of therapy, reasons/circumstances and if applicable the final status have to be documented. If the patient does not withdraw the consent for further follow-up, he or she should be followed up as planned.

There is no plan for further treatment.

11.2 Premature closure of a trial site

Premature closure of a trial site has to be considered if:

- The recruitment rate is not sufficient
- The conduct of the study is not compliant with the protocol, or
- The data quality is not sufficient

The premature closure of a site will be decided by the sponsor and the coordinating investigator after consultation with the responsible biometrician and the steering committee.

Principal investigators may terminate his/her participation in the study. If this occurs they should provide a written statement of the reasons for terminating participation and should provide the coordinating investigator with all available and up-to-date study data.

The trial steering committee may also decide to terminate participation of an investigator or study centre for the following reasons:

- Breach of agreement
- Serious non-compliance to ICH-GCP standards
- Insufficient patient recruitment

If a participating centre closes, or is closed, prior to termination of the whole trial, the
EBMT expects that data from patients already entered into the trial will be reported as per protocol. Details on further treatment and follow-up of patients on study have to be discussed with the coordinating investigator.

11.3 Premature termination of the trial

The trial may be prematurely terminated, if in the opinion of the steering committee and/or the Independent Data Monitoring Committee, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.

In case of the following situations, a premature termination of the trial has to be considered:

- Serious adverse drug reactions / not justifiable toxicity
- Substantial changes in risk-benefit considerations
- New insights from other trials
- Insufficient efficacy
- Insufficient recruitment rate

The Data Monitoring Committee will monitor the study conduct and the safety aspects of the trial on a regular basis, and will give recommendations to the Steering Committee/the coordinating investigator/the sponsor whether to stop the trial or to change the trial protocol. The coordinating investigator/the sponsor will then decide on the actions to be taken. According to the German drug law (§42a), the trial may be suspended or prematurely terminated by decision of the competent federal authority (Paul-Ehrlich Institut).
12 Statistical considerations

This is an open parallel group randomised clinical trial.

12.1 Randomisation algorithm

Patients with donor are randomized according to the Pocock minimisation procedure (1975) in proportion 2 to 1 into SCT and nonSCT-arm, respectively. The randomization will be stratified by centre, type of donor (marrow unrelated donors (MUD) versus HLA identical sibling) and risk group (high risk vs. intermediate to low risk).

We expected an annual accrual of about 60 patients.

12.2 Endpoints

Definitions

*Treatment related mortality* (TRM): Any death without documented evidence of haematological relapse

*Leukaemia free survival* (LFS): Time from randomisation to the first of the following three events:
- Haematological relapse
- Initiation of additional anti-leukemic therapy (this includes DLI)
- Death from any cause
  (Modulation of immunosuppression does not count as an event.)

*Hematopoietic reconstruction:* White blood cell count > 1000 for 2 and more days after transplantation or conventional treatment

*Relapse:* Presence of >5% blasts in the bone marrow or blasts in the peripheral blood after CR

Primary endpoint

The primary efficacy endpoint is leukaemia free survival (LFS)

Secondary endpoints

- Overall Survival
- Cumulative incidence of relapse
- Treatment related mortality (TRM)
- Haematopoietic reconstruction (rejection / poor graft function, respectively)
- Time course of blood parameter after transplant or conventional chemotherapy.
- Incidence of myelosuppression (ANC <500 for 2 and more days, platelets <20,000 for 2 and more days) after transplantation
- Incidence acute GvHD (grades 2-4) after transplant
- Incidence of grades chronic extensive GvHD after transplant
12.3 Statistical hypotheses

The null hypothesis for the primary endpoint is

\[ H_0: \text{HCT and CT patients have the same leukaemia free survival} \]

\[ \text{versus} \]

\[ H_1: \text{HCT and CT patients differ in leukaemia free survival} \]

The clinical question is essentially one-sided since additional toxicity and costs for HCT would only be justified in case of clear clinical benefit. Nevertheless, we formally use a standard two-sided test procedure since we cannot exclude a priori that HCT leads to an unfavorable result regarding leukemia free survival than CT.

12.4 Sample size discussion

12.4.1 Consideration on effect size

Elderly AML-patients treated with conventional chemotherapy have a 5yr-leukaemia free survival of about 10-15% only (e.g. Löwenberg 2009). However, in this study randomisation takes place after achieving a complete remission and remaining relapse free during the first consolidation cycle. Conditioning on being in remission after the first consolidation, we expect a 5 year leukemia free survival of about 25%.

Leukaemia free survival rates reported with reduced intensity conditioning in related and unrelated donor settings vary between 35 and 60% at about two years (Hegenbart 2006, Basara 2009). We consider a 5year-leukemia free survival rate of 45% and thus a difference of 20% compared to conventional chemotherapy both realistic and worth detection.

12.4.2 Level of significance and power

The two-sided significance level is fixed at \( \alpha = 5 \% \) for tests and confidence intervals. Concerning the primary endpoint the trial is designed to achieve a nominal power of 90%. The sequential procedure reduces power to about 85%.

12.4.3 Drop outs after registration and after randomisation

Patients are registered for this trial after reaching CR1 after successful induction treatment. Patients are randomised only if they are still in complete remission after maximal one consolidation cycle and have a matching donor as described above. We expect that 30 % of registered patients will have no donor. Further 10 % will not qualify for randomisation because of early relapse or delays or withdrawals.

Rare patients with a donor randomised to conventional treatment will withdraw from the study and insist on having a transplant. All effort will be made to follow-up on such patients and include them into the intention to treat analysis.

We expect less than 5% loss to follow up in randomised patients since AML patients remain in close contact to their treating physicians.
12.4.4 Sample size and power calculation

Sample size of the study is based on the Logrank test and the following assumptions:
- 5 year event-free survival for CT = 25%
- 5 year event-free survival for SCT = 45%
- Power 90%
- Randomization of SCT versus CT in a 2:1 ratio (SCT = 67%)

Assuming proportional hazards and using the sample size formula of Freedman (1982) results in a sample size $N = 220$ or about 135 events. A total sample size $N = 231$ (SCT: 154, CT: 77) is required taking into account 5% loss to follow up after randomisation.

With 60 patients per year recruiting will take 3.85 years.

In order to randomise 231 patients
- 257 patients with donor
- 367 in CR1 and
- 733 at diagnosis, respectively
are required (compare 12.4.3).

12.5 Analysis methods

12.5.1 Analysis population
Analysis is performed on an intention to treat basis (ITT) and as treated analysis.

12.5.2 Planned methods for analysis

The primary endpoint will be analysed with the logrank-test. In addition, a Cox regression adjusting for type of donor (MUD versus HLA identical sibling) and risk group (high risk vs. intermediate to low risk) will be provided. Study group effects will be explored. Overall survival will be analysed analogously.

For the cumulative incidence of TRM and relapse standard methodology (Pepe et al. 1993) for competing risks will be used.

For baseline parameters descriptive statistics are calculated. Continuous measurements are described by mean ± SD, if roughly normally distributed. Otherwise median (interquartile range) are appropriate. Comparison of means is done for approximate normal distributed variables by t-test and by Mann-Whitney U test for skew distributed variables. Categorical factors are described by absolute and relative frequencies. and compared with the chi-square or Fisher’s exact test.

Details will be specified in the statistical analysis plan prior to the first interim analysis.
12.6 Safety monitoring

Complexity of allogeneic stem cell transplantation requires a biometrical safety monitoring in two directions:
- Treatment related mortality,
- Anti-leukaemic efficacy

12.6.1 Treatment related mortality

We would be concerned if the true incidence of TRM exceeded 20% within 100 days and 30% within one year of transplant, respectively. We will monitor TRM using an alarm trigger rule detailed below whenever a TRM event is reported. In case alarm is triggered, the DMC will be consulted whether the trial can be continued.

Alarm will be activated if the Bayesian posterior probability of a TRM rate \( p \geq 0.2 \) (0.3) is more than 80%. For every number \( N \geq 10 \) (10, 11, 12, …) of patients at 100 days (one year) after transplantation we calculated the corresponding number \( M \) of transplant-related deaths, for which this probability passes the 80% threshold. From a frequentist point of view, this closely corresponds to the first \( M \), where the 80% lower confidence bound for the TRM probability exceeds 20% (30%).

For example, an alarm concerning d100 TRM will be triggered if the critical ratio is 4/10, 5/15, 6/20, 7/25, 8/30, 9/35 and 11/40 or higher.

We simulated the frequentist properties of this procedure: Based on assumed probabilities of TRM we generated trials and estimated the probability of alarm. Results are given in the following table:

<table>
<thead>
<tr>
<th>Day 100 TR mortality (N=146 in transplant arm)</th>
<th>Assumed TRM probability</th>
<th>0.1</th>
<th>0.2</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Alarm</td>
<td></td>
<td>0.051</td>
<td>0.593</td>
<td>0.913</td>
<td>0.993</td>
<td>1.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 365 TR mortality (N=146 in transplant arm)</th>
<th>Assumed TRM probability</th>
<th>0.1</th>
<th>0.2</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Alarm</td>
<td></td>
<td>0.004</td>
<td>0.108</td>
<td>0.290</td>
<td>0.601</td>
<td>0.892</td>
</tr>
</tbody>
</table>

Determination of the denominator \( N \) requires further specification in practice:

(1) Bad news travel first: SAE reports of death are reported immediately. But documentation of transplantation and d100 follow-up may lag. To counteract this potential bias we will assume that patients without SAE information are alive at the date of analysis.

(2) Day of transplantation is defined day 0 concerning TRM risk. Information on date of transplant may also be delayed. Patients randomized to SCT, but without documentation of transplant will be assumed to be at risk starting 28 days after randomisation. Patients known to have relapsed before transplant or not to have received a transplant are excluded.
(3) Relapse and TRM have to be considered as competing risks. We will estimate the cumulative incidence of TRM using standard methodology (Pepe et al. 1993).

(4) In order to connect to the alarm trigger rule discussed above an effective sample size $N_{eff}$ will be used: Let $k$ be the number of documented TRM events, $\hat{p}$ the estimate of cumulative incidence at d100 (d365) $N_{eff}$ is calculated as $N_{eff} = \{k / \hat{p}\}$ where $\{x\}$ denotes the lowest integer greater than or equal to $x$.

12.6.2 Anti-leukaemic efficacy in the transplant arm

LFS with current approaches for AML in 1st CR in patients > 60 years is approximately 51% at 1 year with a relapse risk of 50% in related and 16% in unrelated. If after 20 patients have been transplanted the 1-year LFS appears < 40% as determined by upper limit to one-sided 90% CI, the treatment may be deemed to lack efficacy. This would require 4 or fewer leukaemia-free survivors at one year among the first 20 patients. Termination of the study will be considered after reviewing other parameters including relapse rate, and TRM.

12.7 Interim analyses

An O'Brian and Fleming group sequential plan with two interim analyses after about 1/3 and 2/3 of the expected events and a final analysis is used. The significance boundaries using the Lan-deMets alpha spending approach were calculated by the R-package GroupSeq (http://r-project.org). About 135 events are expected (compare 12.4.4.).

<table>
<thead>
<tr>
<th>Fraction of events</th>
<th>lower Bounds</th>
<th>upper</th>
<th>alpha (per analysis)</th>
<th>alpha (cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.33</td>
<td>-3.71</td>
<td>3.71</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>0.67</td>
<td>-2.51</td>
<td>2.51</td>
<td>0.0119</td>
<td>0.0121</td>
</tr>
<tr>
<td>1.00</td>
<td>-1.99</td>
<td>1.99</td>
<td>0.0379</td>
<td>0.0500</td>
</tr>
</tbody>
</table>

We performed a simulation assuming annual accrual of 60 patients and leukaemia free survival according to the assumptions in 12.4.4. The first (second) interim analysis is expected after about 2.4 years (3.9 years) respectively.

The interim analyses will compare SCT and CT group on an intention-to-treat basis in exactly the same way as the final analysis. They use the significance boundaries given in the table.

12.8 Final analysis

Final analysis will be performed if the information regarding the final endpoint is complete. That is if every patient has either died or has been observed for about 3 years.

All patients are followed up for 5 years in order to get long time results irrespective of whether the trial was stopped early or not.
13 Notification to local authorities

Prior to enrolment of the first patients into the trial the sponsor, his legal representatives/contractors and all investigators are responsible for notification of his/her participation in the trial to the local regulatory authority, according to the German drug law (AMG §67 (1) and the requirements of the GCP-V §12). According to §67 (3) AMG and §§ 12,13 GCP-V the sponsor, his legal representatives/contractors and all investigators are also responsible to notify the local regulatory authority of amendments, premature terminations of trial arms or of the whole study and the regular trial termination.

14 Publication policy

The trial is registered at clinicaltrials.gov. The final publication of the trial results will be written by the coordinating investigator on the basis of the statistical analysis performed. A draft manuscript will be submitted to the ZKS Leipzig - KKS and all co-authors (and the sponsor) for review. After revision by the Data Centre, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal. Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the datamanager in charge of the trial, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomised treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered/randomised in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomised treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published.
15 Data Handling and record Keeping

15.1 Case Report Forms (CRF)

The CRF will be prepared by the ZKS Leipzig - KKS and printed on 3-part, no carbon required (NCR) paper. The ZKS Leipzig - KKS receives the original CRF pages and two copies are retained at the trial site.

All entries in the CRFs must be made clearly with black ball-point pen, to ensure the legibility in self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, in a way that it can still be seen, and placing the revised entry beside it. The revised entry must be initialled and dated by trial staff authorized to make CRF entries. Correction fluid may not be used.

The principal investigator or one of the investigators will review the CRF for completeness and accuracy, sign and date all relevant CRF pages and any changes therein.

The signatures serve to attest that the information contained in the CRF is true and has not been falsified. In case of a major correction or missing data, the reason for it has to be given. The investigator must assure completion, review and approval of all CRFs. At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRF. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

Immediately after assessment of the data and the corresponding CRF forms will be completed and will be sent to the ZKS Leipzig - KKS for data entry and analysis.

As source data are regarded:

- all data contained in the patient’s medical record
- all laboratory data provided by the local laboratory

15.2 Data Management

Once the CRFs are transferred to ZKS Leipzig - KKS, their receipt is recorded and the original copy is placed in central files by the responsible data management staff for processing.

For creation of the study database, the study management software eResearch will be used. The database will be validated according to the Standard Operating Procedures (SOPs) of the ZKS Leipzig - KKS prior to data capture.

Data items from the CRFs are entered into the study database by double data entry. The information entered into the database is systematically checked by data management staff, using error messages printed from validation programs and database listings. Obvious errors will be corrected by ZKS Leipzig - KKS personnel.

Other errors or omissions will be entered on data query forms, which will be returned to the investigational site for resolution. A copy of the signed query is to be kept with the CRFs, and once the original is received at ZKS Leipzig - KKS the answered queries will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be made after entering data from each visit. An audit trail of all
changes in the contents of the study database will be automatically recorded. Once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between the coordinating investigator, the biometrician and the data manager.

15.3 Archival storage

The investigators have to arrange the retention of the subject identification codes for at least 10 years after the completion or termination of the trial (or 15 years if data will be used for regulatory affairs). Patient files and other source data shall be kept for the maximum period of time permitted by the hospital.

The coordinating investigator or other owner of the data shall retain all other documentation pertaining to the trial for at least 10 years. These procedures shall include:

- the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational therapy used.
- standard operating procedures
- all written opinions on the protocol and procedures,
- final report,
- case report forms,
- audit certificate(s), if available.
- all other relevant documents of the trial master file, according to the ICH-GCP guideline

Any changes of data ownership have to be documented. All data have to be made available if requested by relevant authorities.
15.4 *Forms and procedures for collecting data*

Table 4: CRF forms

<table>
<thead>
<tr>
<th>Form nr</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Registration</td>
</tr>
<tr>
<td>2</td>
<td>Randomisation</td>
</tr>
<tr>
<td>3</td>
<td>Baseline</td>
</tr>
<tr>
<td>4</td>
<td>Consolidation I</td>
</tr>
<tr>
<td>5</td>
<td>Death/Study Termination prior to assignment to study arm</td>
</tr>
<tr>
<td>6</td>
<td>Death/Study Termination after assignment to study arm</td>
</tr>
<tr>
<td>7a</td>
<td>Allograft SCT-arm</td>
</tr>
<tr>
<td>7b</td>
<td>nonSCT-arm</td>
</tr>
<tr>
<td>8a</td>
<td>Post therapy SCT-arm</td>
</tr>
<tr>
<td>8b</td>
<td>Post therapy non SCT-arm</td>
</tr>
<tr>
<td>9</td>
<td>Follow up</td>
</tr>
<tr>
<td>BA</td>
<td>Blood analyses</td>
</tr>
<tr>
<td>aGvHD</td>
<td>acute Graft versus Host Disease</td>
</tr>
<tr>
<td>cGvHD</td>
<td>chronic Graft versus Host Disease</td>
</tr>
<tr>
<td>TOX</td>
<td>Toxicities, adverse events</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse events</td>
</tr>
</tbody>
</table>

A schedule for completion will be included in the instruction together with the full set of CRFs.
16 Quality Assurance

16.1 Monitoring of Trial Data
An independent data monitoring and safety committee (DMC) will be established. The DMC will receive annual reports on the status of the trial. The DMC will be convened whenever the statistical safety monitoring as described in section 12.6 raises any safety concern or an interim analysis indicates a difference in efficacy. The DMC then recommends whether the trial should stop or how it should proceed.

On-site Monitoring of Study Sites
Each participating Co-operative Group will have responsibility for monitoring the patients entered into the study by that group. In adherence to GCP and EU Law, each centre will be initiated and monitoring visits to participating centres will be conducted during the study and at the end of the study before final data analysis. The details of each groups monitoring plan will be available in the form of a work practice document. In addition further monitoring will be done by statistical methods.

16.2 Audit & Inspection
In accordance with applicable laws participating centres will allow direct access for monitoring, audit and inspection by appropriate EBMT personnel and direct access for inspection by government and European regulatory authorities. Access will be granted to all trial related documentation and sites (including trial master file, patient files, clinics, laboratories and pharmacy). The EBMT maintains the right to perform audits during the active phase of the clinical trial and/or after the trial has been completed. There are two types of audits:

1) Routine audit: A systematic examination of trial-related activities and documents to assure compliance with the trial protocol, EBMT standard operating procedures (SOP), and national/local regulations. For routine audits there is a random selection process of centres. The principal investigator of a selected centre will be given a 3 months notice period prior to the proposed audit visit.

The aim of a routine audit is to:
- inspect the trial facilities
- ensure that the trial is conducted in accordance with ICH-GCP guidelines, the principles in the Declaration of Helsinki and relevant regulatory requirements
- ensure that the site staff adhere to the protocol and SOP’s
- review the informed consent process
- review the SAE identification and reporting process
- aid in identifying and correcting problem areas and provide suggestions to improve performance, if required

The principal investigator will receive an audit report within 4 weeks of the site visit.

2) “For-cause” audit: Where there is evidence or suspicion of non-compliance with
important aspect(s) of the trial requirements. The notification period is dependent on the reason(s) triggering the audit.

In case of a for cause audit a letter is sent to the Principal Investigator outlining:

- the reason(s) for the for-cause audit
- any hold that has been placed on the protocol related research
- all of the documents that are to be reviewed
- interviews that will be conducted
- planned inspections of the facilities (primarily how data is stored, drug storage, accountability, destruction etc.)
- who will come and perform the audit
- when the audit will likely occur

The principal investigator will receive an audit report within 2 weeks of the site visit.
17 ETHICS & ADMINISTRATION

Good Clinical Practice
The study will be conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice (ICH-GCP) and the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected.

The sponsor’s Trial Master File will be maintained at the coordinating investigator’s Office. Each participating site will maintain a site file as per local Standard Operating Procedures (SOPs). This study file should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

All trial related documents and files must be kept for a minimum of 15 years and for selected items as specified in the German § 14 Transfusionsgesetz, at least 30 years.

Ethical Considerations
The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The ethics committee(s) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where ethics approval has been obtained. The investigator will provide the relevant ethics committee(s) with the final version of the protocol, patient information and consent forms, any other written information given to patients, safety updates, annual progress reports, and any revisions to the study protocol or any other trial documentation.

Patient Confidentiality
In order to maintain patient privacy, all data capture records, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The full patient name should never be used in any correspondence with the Sponsor or on the case record forms.

The investigator will grant monitor(s) and auditor(s) from the EBMT and/or Regulatory Authorities direct access to the patient’s original medical records for verification of data gathered on the data capture records and to audit the data collection process. Direct access includes examining, analysing, verifying, and reproducing any recorded data and reports that are important to the evaluation of the monitoring. The investigator is obliged to inform the patient that his/her trial-related records will be viewed without violating their confidentiality and that the collected information will only be made publicly available to the extent permitted by the applicable laws and regulations.

All data will be stored electronically in an anonymous manner and handled strictly confidential. There will be no possibility of conclusion. The investigators are obliged to keep all study data and information confidential and to use those data only in context with the persons involved in the trial conduct. Study material or information developed in this trial must not be available to third parties, except for official representatives of the sponsor or regulatory authorities.

Data will be processed in the ZKS Leipzig - KKS, according to the written safety concept of this institution. Access to the data will be strictly limited to authorized persons. Loss of data
is excluded due to extensive back-up procedures. All legal requirements concerning data protection and confidentiality will be respected. All authorized persons are sworn to secrecy.

In the case of withdrawal of consent the stored data will be checked for further use. Data not necessary any longer are deleted immediately. Collected personal data will be stored in an anonymous manner after reaching the study aim 10 years at the latest, if there are no other regulatory or contractually archiving periods.

Declaration to data protection
During data entry, handling and analysis in the Zentrum für Klinische Studien Leipzig – KKS, Universität Leipzig, Härtelstr. 16-18, 04107 Leipzig all requirements of the data protection act will be take into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorized access.

Protocol Compliance
The investigator will conduct the study in compliance with the protocol given approval/favourable opinion by the ethics committee(s), the appropriate Regulatory Authority(ies) and, if required, institutional department(s) such as Research & Development Department. Changes to the protocol will require approval from the study Steering Committee and written ethics committee approval/favourable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The ethics committee(s) may provide, if applicable Regulatory Authority(ies) permit, expedited review and approval/favourable opinion for minor change(s) in ongoing studies that have the approval /favourable opinion of the ethics committee(s). The investigator will submit all protocol modifications (non-compliance) to the EBMT trials office and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents. And an explanatory note to file, signed by the Principle Investigator, placed in the site file.

Insurance and liabilities
As the trial sponsor the EBMT offers insurance coverage to cover the liability of participating investigators. The EBMT deals solely with HDI-Gerling Insurance Company. All EBMT insurance is coordinated through the Prospective Clinical Trials Committee (PCTC) Administrator in London.

The participating patients are insured by the following insurance company:

HDI Gerling Industrie Versicherung
Überseering 10a
22297 Hamburg

The number of the insurance police is: 70-006678966-2. A copy of the insurance policy and the insurance conditions will be filed in the investigators file.
18 Appendix

18.1 References

Reference List


24. Leith CP, Kopecky KJ, Godwin J, McConnell T, Slovak ML, Chen I-M et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to...


36. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Statistics in Medicine 1982, 1:121-129

37. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Statistics in Medicine 1993, 12:737-751

18.2 Glossary of abbreviations
(in alphabetical order)

AE  Adverse Event
ALT  Alanine Amino Transferase
AML  Acute Myelogenous Leukaemia
ANC  Absolute Neutrophil Count
Ara-C  Cytarabine, cytosine arabinoside
AST  Aspartate Amino Transferase
BM  Bone Marrow
BMT  Bone Marrow Transplant
BUN  Blood urea nitrogen
Ca  Calcium
CALGB  Cancer and Leukaemia Group B
CFC  Colony Forming Cells
CI  Confidence interval
CMV  Cytomegalovirus
CR  Complete Remission
CRF  Case Report Form
CSP  Cyclosporine
CT  Computerized Tomography
CTC  Common Toxicity Criteria
DFS  Disease Free Survival
DLI  Donor Lymphocyte Infusion
DLT  Dose Limiting Toxicity
DNR  Daunorubicin
DSMB  Data and Safety Monitoring Board
ECG  Electrocardiogram
ECOG  Eastern Cooperative Oncology Group
EFS  Event Free Survival
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FAB</td>
<td>French American British (cytological classification)</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluroreszenz-in-situ-Hybridisierung</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GvHD</td>
<td>Graft versus Host disease</td>
</tr>
<tr>
<td>GvL</td>
<td>Graft versus Leukemia</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro intestinal</td>
</tr>
<tr>
<td>GO</td>
<td>Gemtuzumab Ozogamicin</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematopoietic (Stem-)Cell Transplantation</td>
</tr>
<tr>
<td>Ht</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte histocompatibility antigen</td>
</tr>
<tr>
<td>HOVON</td>
<td>Dutch/Belgian Hematology-Oncology Cooperative Group</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ILLN</td>
<td>Institutional Lower Limit of Normal</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prognostic Score System (for myelodysplastic syndromes)</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to Treat</td>
</tr>
<tr>
<td>IULN</td>
<td>Institutional Upper Limit of Normal</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>KKS</td>
<td>ZKS Leipzig – KKS</td>
</tr>
<tr>
<td>LD50</td>
<td>Lethal Dose 50%</td>
</tr>
<tr>
<td>LFS</td>
<td>Leukemia Free Survival</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean Corpuscular Volume</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean Corpuscular Hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean Corpuscular Hemoglobin Concentration</td>
</tr>
<tr>
<td>MDR</td>
<td>Multi Drug Resistance</td>
</tr>
<tr>
<td>MDR-1</td>
<td>Multi Drug Resistance-1 gene</td>
</tr>
<tr>
<td>MDS</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>MMF</td>
<td>Mycophenolate Mofetil</td>
</tr>
<tr>
<td>MUD</td>
<td>Marrow Unrelated Donor</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multiple Gated Acquisition</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PAS</td>
<td>Periodic Acid Schiff</td>
</tr>
<tr>
<td>PB</td>
<td>Peripheral Blood</td>
</tr>
<tr>
<td>PBSC</td>
<td>Peripheral Blood Stem Cell</td>
</tr>
<tr>
<td>PBR</td>
<td>Peripheral Blood Recovery</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response</td>
</tr>
<tr>
<td>RAEB</td>
<td>Refractory Anemia with Excess of Blasts</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>RAEB in transformation</td>
</tr>
<tr>
<td>RIC</td>
<td>Reduced Intensity Conditioning</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAKK</td>
<td>Swiss Group for Clinical Cancer Research</td>
</tr>
<tr>
<td>SCT</td>
<td>see HCT</td>
</tr>
<tr>
<td>TBI</td>
<td>Total Body Irradiation</td>
</tr>
<tr>
<td>TRM</td>
<td>Treatment Related Mortality</td>
</tr>
<tr>
<td>VNTR</td>
<td>Variable Number of Tandem Repeats</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
### 18.3 Appendix A - FAB classification of AML

Cytological criteria for the diagnosis of acute myeloid leukemia: French-American-British-(FAB) classification

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>&lt; 3% of blasts positive for Sudan Black B or Myeloperoxidase ♦ at least one of the following myeloid markers present: CD13, CD33, CD15, CDw65 ♦ in absence of lymphoid markers CD3 and CD22</td>
</tr>
<tr>
<td>M1</td>
<td>Blasts ≥ 90% of bone marrow nonerythroid cells (i.e. excluding also lymphocytes, plasma cells, macrophages and mast cells) ♦ Maturing granulocytic cells (i.e. promyelocytes towards polymorphonuclear cells) ≤ 10% of nonerythroid cells ♦ (pro)monocytes ≤ 10% of nonerythroid marrow cells</td>
</tr>
<tr>
<td>M2</td>
<td>Blasts 30-89% of bone marrow nonerythroid cells ♦ Maturing granulocytic cells (i.e. promyelocytes to polymorphonuclear cells) &gt; 10% of nonerythroid cells ♦ Monocytic cells (i.e. monoblasts to monocytes) &lt; 20% of nonerythroid cells</td>
</tr>
<tr>
<td>M2E</td>
<td>Analogous to M4E, but lacking clear monocytic differentiation</td>
</tr>
<tr>
<td>M3</td>
<td>Promyelocytes (most hypergranular) &gt; 30% of bone marrow nucleated cells</td>
</tr>
<tr>
<td>M3V</td>
<td>Promyelocytes (hypogranular or microgranular) &gt; 30% of bone marrow nucleated cells</td>
</tr>
<tr>
<td>M4</td>
<td>Granulocytic cells (myeloblasts to polymorphonuclear cells) ≥ 20% of nonerythroid cells plus one of the following criteria ♦ Monocytic cells (monoblasts to monocytes) ≥ 20% of nonerythroid cells Or ♦ Peripheral blood monocytes ≥ 5 x 10⁹/l Or ♦ Elevated urinary lysozymes ≥ 3 x normal value</td>
</tr>
<tr>
<td>M4E</td>
<td>Same as M4, but with ≥ 5% abnormal eosinophils (basophilic granulae)</td>
</tr>
<tr>
<td>M5A</td>
<td>Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts ≥ 80% of bone marrow monocytic component</td>
</tr>
<tr>
<td>M5B</td>
<td>Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts &lt; 80% of bone marrow monocytic component</td>
</tr>
<tr>
<td>M6</td>
<td>Erythroblasts ≥ 50% of bone marrow nucleated cells ♦ Blasts ≥ 30% of bone marrow nonerythroid cells</td>
</tr>
<tr>
<td>M7</td>
<td>&gt;30% of bone marrow nucleated cells are megakaryoblasts CD41 or CD61 positive or ♦ Platelet specific peroxidase reaction (electron microscopy) ♦ &lt; 3% of blasts positive for Sudan Black B or Myeloperoxidase</td>
</tr>
</tbody>
</table>
18.4 Appendix B - Response criteria for AML and MDS
HOVON-AML/MDS Response criteria (modified from CALGB-CRITERIA for AML and according to the International Working Group Criteria for MDS)

1 DISEASE STATUS CRITERIA
Note that the kind of cells considered equivalent to blasts and included in the calculation of last percentages depend on the FAB classification (Appendix A).

1.1 Bone Marrow
A1 cellular marrow with normal maturation of all cell lines and no evidence of dysplasia (*); and <5% blasts, and no Auer rods.
When erythroid cells constitute less than 50% of bone marrow nucleated cells, then the percentage of blasts is based on all nucleated cells; when there are ≥ 50% erythroid cells, the percentage of blasts should be based on the non-erythroid cells.
A2 in case of AML: cellular marrow with maturation of all cell lines; and blasts ≥ 5% but ≤ 15%
A2 in case of RAEB/RAEB-t: blasts decreased by ≥ 50% over pretreatment value, or change to a less advanced MDS FAB classification than pretreatment. The order from advanced to less advanced is: RAEB-t, RAEB, CMMOL, RA, RARS. Cellularity and morphology are not relevant
A3 Failure to meet criteria for A1 or A2

1.2 Peripheral Blood
B1 Peripheral Blood Recovery (PBR): ANC ≥1.5 x 10^9/l or 1500/mm³, transfusion independent platelet count ≥ 100 x 10^9/l (i.e. 48 h after last transfusion);
and no leukemic blasts in the peripheral blood and no dysplasia (*)
B2 Failure to meet the criteria for B1

(*) The presence of mild megaloblastoid changes may be permitted if considered to be consistent with chemotherapy effect. However, persisting pretreatment abnormalities (e.g. pseudo-Pelger-Hüet cells, ringed sideroblasts, dysplastic megakaryocytes) are not consistent with CR or PR.
1.3 Extramedullary Disease
C1 None
C2 Any

2 RESPONSE CRITERIA

2.1 Complete remission (CR)
Attainment of A1 marrow status and B1 peripheral blood recovery and C1 extra-medullary disease status without evidence of relapse within 28 days (for definitions see chapter 18.3).

2.2 Treatment failure
Subjects who do not enter CR following induction will be classified according to the type of failure (document on CRF):
• Partial response (PR): Subject only achieves A2 marrow status with B1 peripheral blood status and C1 extramedullary involvement as a best response in any induction cycle. The response of subjects who achieve A1B1C1 status and within 28 days relapse will be considered as PR.
• Induction resistance (RD): Subject has persistent leukaemia in the bone marrow with $\geq 15\%$ blasts and/or persistent blasts in the peripheral blood and/or persistent extramedullary disease
• Other induction failure (Ind.F.): Patients who do not meet any of the criteria for CR, PR or RD are classified as other induction failures. This includes patients who die before response could be ascertained or before PBR was achieved.

3 RELAPSE CRITERIA
Relapse after complete remission for patients with AML, RAEB / RAEB-t is defined as:
• recurrence of blasts in the marrow of $\geq 5\%$ (excluding increased blasts in the context of regenerating marrow)
• recurrence of leukemic blasts in the peripheral blood
• recurrence of leukemia at an extramedullary site
• recurrence of pre-treatment characteristic signs of morphological dysplasia
• recurrence of Auer rods

After stem cell transplant:
Hematological relapse is defined as reappearance of blasts in the marrow $>5\%$ or appearance of blasts in the peripheral blood.

Cytogenetic relapse is defined as reappearance of cytogenetic aberrations. Reappearance of patients CD34+ cells in the chimerism analysis after donor CD34+ cells have been detected is not considered as hematological relapse.
### Appendix C. - Eligibility guidelines for donor PBSC apheresis

<table>
<thead>
<tr>
<th>IMMUNIZATION</th>
<th>DONOR ELIGIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera</td>
<td>No wait</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>No wait</td>
</tr>
<tr>
<td>Flu</td>
<td>24 hour wait</td>
</tr>
<tr>
<td>Gamma globulin</td>
<td>No wait unless for hepatitis (immune serum globulin)</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>No wait unless given for hepatitis exposure</td>
</tr>
<tr>
<td>Measles (Rubella)</td>
<td>1 month wait</td>
</tr>
<tr>
<td>Mumps</td>
<td>2 week wait</td>
</tr>
<tr>
<td>Polio - Sabin (inj)</td>
<td>No wait</td>
</tr>
<tr>
<td>Plague</td>
<td>No wait</td>
</tr>
<tr>
<td>Rabies</td>
<td>1 year wait if given as treatment for bite.</td>
</tr>
<tr>
<td></td>
<td>2 week wait if given as prophylaxis (DMV's or zoo workers)</td>
</tr>
<tr>
<td>Smallpox</td>
<td>2 week wait</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>No wait</td>
</tr>
<tr>
<td>Typhoid</td>
<td>No wait</td>
</tr>
<tr>
<td>Typhus</td>
<td>No wait</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>2 week wait</td>
</tr>
</tbody>
</table>
### 18.6 Appendix D. - Karnofsky performance scale

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

**Liver**  
+1 moderate increase of SGOT$^b$ (150-750 IU) and bilirubin (2.0-3.0 mg/100 ml)  
+2 bilirubin rise (3-5.9 mg/100 ml) with or without an increase in SGOT  
+3 bilirubin rise (6-14.9 mg/100 ml) with or without an increase in SGOT  
+4 bilirubin rise to > 15 mg/100 ml with or without an increase in SGOT

**Gut**  
Diarrhea, nausea and vomiting graded +1 to +4 in severity. The severity of gut involvement is assigned to the most severe involvement noted.

**Diarrhea**  
+1 > 500 ml of stool/day  
+2 > 1,000 ml of stool/day  
+3 > 1,500 ml of stool/day  
+4 2,000 ml of stool/day
Severity of GVHD

Grade I  
+1 to +2 skin rash  
No gut involvement  
No more than +1 liver involvement  
No decrease in performance status

Grade II  
+1 to +3 skin rash  
+1 to +2 gastrointestinal involvement and/or  
+1 to +2 liver involvement mild decrease in performance status

Grade III  
+2 to +4 skin rash and +2 to +4 gastrointestinal involvement  
with or without +2 to +4 liver involvement  
Marked decrease in performance status with or without fever

Grade IV  
Pattern and severity of GVHD similar to grade 3 with extreme constitutional symptoms

*b Increases in SGOT temporally related to either the onset or worsening of the skin rash.