EudraCT-number: 2013-003421-28
Trial name: HINKL
Trial Code: TUD-HINKL1-059

## 1. Name of Sponsor/Company

Technische Universität Dresden (TUD)
01062 Dresden
To be represented by the Coordinating Investigator,
Prof. Dr. med. Martin Bornhäuser
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## 2. Name of Finished Product

CD3-negative/ CD56-positive NK cells from HLA-haploidentical family donors

## 3. Name of Active Substance

CD3-negative/ CD56-positive NK cells from HLA-haploidentical family donors

## 4. Individual Study Table: Referring to Part of the Dossier (Volume, Page)

Not applicable.

## 5. Title of Study

Randomised controlled phase-2 trial to determine the efficacy of adoptive immunotherapy with haploidentical natural killer cells in high-risk acute myeloid leukemia

- The HINKL Trial -

This sponsor-protocol-version includes:

sponsor-protocol-version-date: Version 1-0, 06.12.2013
sponsor-protocol-version-date: Version 2-0, 23.01.2014
sponsor-protocol-version-date: Version 3-0, 11.06.2014

## 6. Investigators

Prof. Dr. med. Martin Bornhäuser (coordinating investigator)

## 7. Study centres

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## 8. Publication (reference)

Michaelis SU, Mezger M, Bornhäuser M, Trenschel R, Stuhler G, Federmann B, Oevermann L, Kanz L, Handgretinger R, Bethge WA. 2014. KIR haplotype B donors but not KIR-ligand mismatch result in a reduced incidence of relapse after haploidentical transplantation using reduced intensity conditioning and CD3/CD19-depleted grafts. Ann Hematol 93:1579–1586. doi:10.1007/s00277-014-2084-2

Schonefeldt C, Sockel K, Wehner R, Sopper S, Wolf D, Wermke M, Thiede C, Oelschlagel U, Ehninger G, Bornhäuser M, Platzbecker U, Schmitz M. 2013. Azacytidine impairs NK cell activity in AML and MDS patients undergoing MRD-based pre-emptive treatment after allogeneic stem cell transplantation. Blood Cancer J 3:e136. doi:10.1038/bcj.2013.35

## 9. Studied period (years): date of first enrolment, date of last completed

Date of first enrollment: 30.09.2016
Date of last completed: 22.04.2017

## 10. Phase of development

Open, randomised, controlled, multicenter, phase-II trial

## 11. Objectives

The aim of the HINKL trial had been the hypothesis that haploidentical NK cells being transferred within the consoslidation therapy of high-risk AML in elderly patients not eligible for transplantation may reduced the incidence of relapse and thereby increase overall survival in the first year after therapy.

Primary Endpoint: 2-year overall survival.

Secondary Endpoints: time to relapse (TTR), cumulative incidence of relapse (CIR), relapse-free survival (RFS), yield and purity of NK cells (CD3-CD56+) after CD3 depletion and CD56 enrichment, NK cell recovery, NK cell chimerism and NK phenotype in the first 4 weeks after infusion.

Secondary safety endpoints: clinical performance (ECOG score), incidence and severity of acute GVHD, incidence of AEs and SAEs.

## 12. Methodology

Open, multicenter, single-arm phase-II trial.

## 13. Number of patients

Patients planned: 56
Patients screened: 3 (2 screening failures)
Patients analyzed/recruited: 0/1

## 14. Diagnosis and main criteria for inclusion

Inclusion criteria

(1) Newly diagnosed AML other than acute promyelocytic leukemia (APL) according to WHO criteria

(2) In AML defined by cytogenetic aberrations the proportion of blasts may be <20%

(3) Age ≥60 years

(4) Clinical performance corresponding to ECOG score 0-2

(5) High-risk karyotype, i.e. at least one of the following criteria:
   - o complex karyotype with ≥ 3 chromosomal aberrations
   - o inv(3)(q21q26) or t(3;3)(q21;q26), RPN1-EVI1
   - o t(6;9)(p23;q34); DEK-NUP214
   - o t(v;11)(v;q23); MLL rearranged, i.e. t(9;11)(p22;q23) are not eligible for inclusion (see exclusion criteria)
   - o -5 or del(5q); -7; abnl(17p)
   - o FLT3-ITD ratio >0.8

(6) <5% myeloblasts in bone marrow ≥21 days after beginning of most recent chemotherapy (induction or first consolidation). Screening with-in 21 days before start of treatment.

(7) maximal two preceding chemotherapy cycles (either two induction cycles or one induction + one consolidation cycle)

(8) Study inclusion (experimental or control intervention) latest 56 days after preceding chemotherapy

(9) Reconstitution of peripheral blood leukocytes following chemotherapy (total leukocytes >1.5 GPT/l; neutrophil granulocytes >0.5 GPT/l)

(10) No available HLA-matched (≥ 9 of 10 HLA-alleles) stem cell donor or unfit for allogeneic hematopoietic stem cell transplantation

(11) Potentially available haploidentical family donor (child/ sibling), willing and fit for NK cell donation

Exclusion criteria:

(1) AML with favorable risk cytogenetic features, i.e. t(15;17) or PML-RAR alpha transcript or t(8;21) or RUNX1 transcript or inv(16) or CBFa transcript

(2) AML with t(9;11)(p22;q23)

(3) AML with intermediate risk cytogenetic features, i.e. no high-risk cytogenetic features as defined in inclusion criteria and no favorable cytogenetic features as defined in exclusion criteria, FLT3-ITD ratio ≤0.8

(4) Persistent aplasia following preceding chemotherapy

(5) Relapsed or refractory AML

(6) Age <60 years

(7) Known pre-existing autoimmune diseases

(8) Any severe concomitant condition which makes it undesirable for the patient to participate in the study (e.g. end stage irreversible multi organ failure, HIV infection, uncontrolled active infections >°2 CTCAE V4-0)

(9) Any condition which could jeorpadize compliance of the protocol (e.g. severe pychological disturbances)

(10) Participation in another clinical trial (investigational drug therapy outside of this trial) during or within 4 weeks before study entry

## 15. Test product, dose and mode of administration, batch number

CD3-negative/ CD56-positive NK cells from HLA-haploidentical family donors

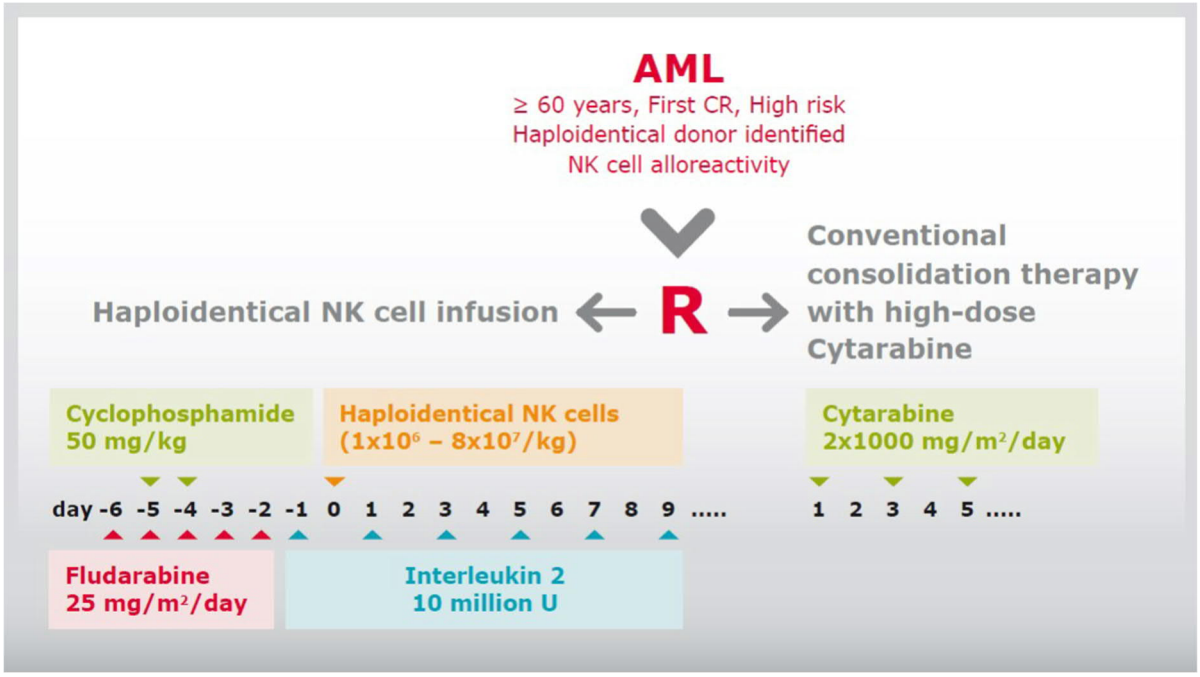


Figure 1: Design of the HINKL Trial

Manufacturer:

Certified GMP facilities

## 16. Duration of treatment

Duration of intervention per patient: about 4 weeks in the control arm (conventional consolidation), depending on the indidividual clinical course and about 3 weeks in the experimental arm plus an additional duration of follow up per patient of 2 years after randomization.

## 17. Reference therapy, dose and mode of administration, batch number

Conventional consolidation chemotherapy with high-dose cytarabine

See Figure 1

## 18. Criteria for evaluation: Efficacy, Safety

After initiation of the trial, 3 patients were screened. Unfortunately, only one patient could be included into the trial. This patient was randomized into the control arm and received standard intermediate-dose cytarabine. Although this

therapy was tolerated well, the patient experienced early relapse only 3 months after inclusion.
Although the trial was supposed to continue patient screening and accrual, the slope of activities to this end flattened out and no further patient could be included. The trial had to be stopped and follow-up of the included patient as well as all sign-off process with all legal entities was initiated.

The trial coordinators and the leading PI identified four major reasons for the delay in patient accrual:

1. While the time interval from submission of the trial dossier to the competent authorities was much longer than expected, novel therapeutic avenues for high-risk patient became available (e.g. hypomethylating agents, tyrosine kinase inhibitors, BCL-2 antagonists)

2. Potentially eligible patients were reluctant to be randomized to a potentially ineffective but toxic chemotherapy with cytarabine and not receiving the innovative cell-based therapy

3. Fitter patients until the age of 70 became eligible for less toxic transplant procedures (allogeneic SCT after reduced-intensity conditioning)

4. A renaissance of haploidentical transplantation with post-grafting Cyclophosphamide occurred and was offered at several centres to fitter patients.

## 19. Statistical methods

As the recruitment of the trial had been stopped prematurely, no further plans concerning later clinical and commercial applications of the procedures can be foreseen.

## 20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

Treatment outcome in acute myeloid leukemia (AML) is still unsatisfying, especially in cases with high-risk disease. The only curative treatment option is allogeneic hematopoietic cell transplantation (HCT). Give the high extramedullary toxicity of this approach, its use is currently still restricted to patients at younger age with a good performance status. In addition, successful allogeneic HCT requires a significant reduction in disease burden within induction therapy which is often not achievable in high-risk patients. Therefore, only a minor proportion of patients with high-risk AML qualifies for allogeneic HCT.

At the same time, several preclinical and clinical studies could demonstrate that the adoptive transfer of HLA-partially matched (haploidentical) Natural Killer cells (NK cells) from sibling donors after immunosuppressive pretreatment can contribute to control of the underlying disease as NK cells are able to attack and

eradicate myeloid neoplasms, Until now, no controlled prospective trial has confirmed the efficacy of this approach within a randomized trial design.

The HINKL trial was supposed to be the first randomized clinical trial of its kind, comparing the adoptive transfer of NK cells from a haploidentical donor with conventional cytarabine-based post-remission therapy in older patients with high-risk AML. The trial had been powered to detect a 2-year survival difference between the cell therapy arm and the respective control intervention. Unfortunately, the prolonged process of licensure of the investigational cell product and the 18 months it took for the trial to be approved by the competent authorities in Germany, a significant delay in trial activation occurred. Although, the first site could be initiated, only three patients were screened and only one patient could be randomized to the control intervention. In the meantime, the potential superiority of novel therapies, e.g. hypomethylating agents, bcl2-anatagonists and the increasing use of haploidentical allogeneic HCT even in older patients decreased the adherence of referal centres to the protocol. Accordingly, the trial had to be closed due to slow accrual. The speed of recruitment made the successful inclusion of 56 planned patients highly unlikely. Both the sponsor and the funding bodies were involved in the decision and agreed to close the trial and to finalize the follow-up of the included patient who unfortunately relapsed early and died from recurring AML.

In summary, the trial team had to realize that the high regulatory burden and the delays which have to be foreseen within academic investigator initiated trials make the execution of such a demanding trial difficult without involving pharmaceutical industry, at least in Germany. Current developments in the area of chimeric antigen receptor T cells (CAR T cells) confirm the notion that licensure of such an approach can only be achieved by larger internationally active pharmaceutical companies, mainly recruiting patients outside Germany.

**Date of report**

28.10.2019

Prof. Dr. med. M. Bornhäuser