Summary of the Trial Report
[Synopsis according to ICH E3]

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

Name of Finished Product/Name of Active Substance:
Hematopoietic stem cells
Indication/Diagnosis:
Acute Myeloid Leukaemia
Phase of Development:
Not applicable
EudraCT-Number:
2007-003514-34
Registration-Number:
Not applicable
Date of report: 25.08.2021
Version: final 1.0

Trial start: 11.01.2010
End of Trial: 31.08.2020

Coordinating Investigator

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Sponsor

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Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and coordinating investigator

[redacted]

Biometry

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1 Name of the Sponsor/Company

Name of institution: European Society for Blood and Marrow Transplantation EBMT, Clinical Trials Office
Address: Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands

Representative of the Sponsor

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2 Name of Finished Product	3 Name of active Ingredient
not applicable	Hematopoietic stem cells
not applicable, treatment defined only by active substance	Fludarabine
not applicable, treatment defined only by active substance	Ciclosporin
not applicable, treatment defined only by active substance	Mycophenolate mofetil
not applicable, treatment defined only by active substance	Mitoxantron
not applicable, treatment defined only by active substance	Cytarabin

4 Individual study table

Not applicable.

5 Title of Study

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 Version 5.1 (07.11.2013) including amendments:
1. 04.11.2011
2. 03.07.2013
3. 07.11.2013

A list of the participating sites is included in the appendix.

6 Publications

The trial was registered at ClinicalTrials.gov Identifier: NCT00766779.

7 Studied period (in years)

Date of first enrolment: 11.01.2010

Date of last completed: 31.08.2020

Recruitment was stopped after DMC recommendation on August 1st 2017 since recruitment target would not have been reached within reasonable time. Patients who were registered but not yet randomized until August 1st 2017 were randomized or assigned to the observational arm after this date. The last patient was randomized on August 27th 2017 and follow-up and last patient last visit therefore determined to be on August 30th 2020.

8 Phase of Development

This trial is a phase III.

Primary objective:

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.

Secondary objectives:

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

9 Methodology

Figure 1 shows the trial design. Patients in first complete remission (CR1) after one or two induction cycles are registered for the study and search for a 10/10 matched donor is initiated. Meanwhile patients receive one cycle of consolidation therapy according to local protocols.

Patients who remain in remission, still pass all inclusion and exclusion criteria, and who have a 10/10 matched donor are randomised at a ratio of 2:1 between transplant ‘SCT arm’ (SCT is here used as a synonym for HCT) or further conventional treatment according to the local protocol ‘non-SCT arm’.
The randomization was stratified by centre, type of donor (marrow unrelated donors (MUD) versus HLA identical sibling) and cytological risk group (high risk vs. intermediate to low risk).

Patients randomised to the non-SCT arm had the option of a late transplant in case they achieve a second remission after a relapse.

Patients without a matched donor within 5 months (150 days) from diagnosis were allocated to an 'observation arm'. Patients otherwise not eligible for randomisation (e.g. refusal of SCT) were also allocated to the observation arm.

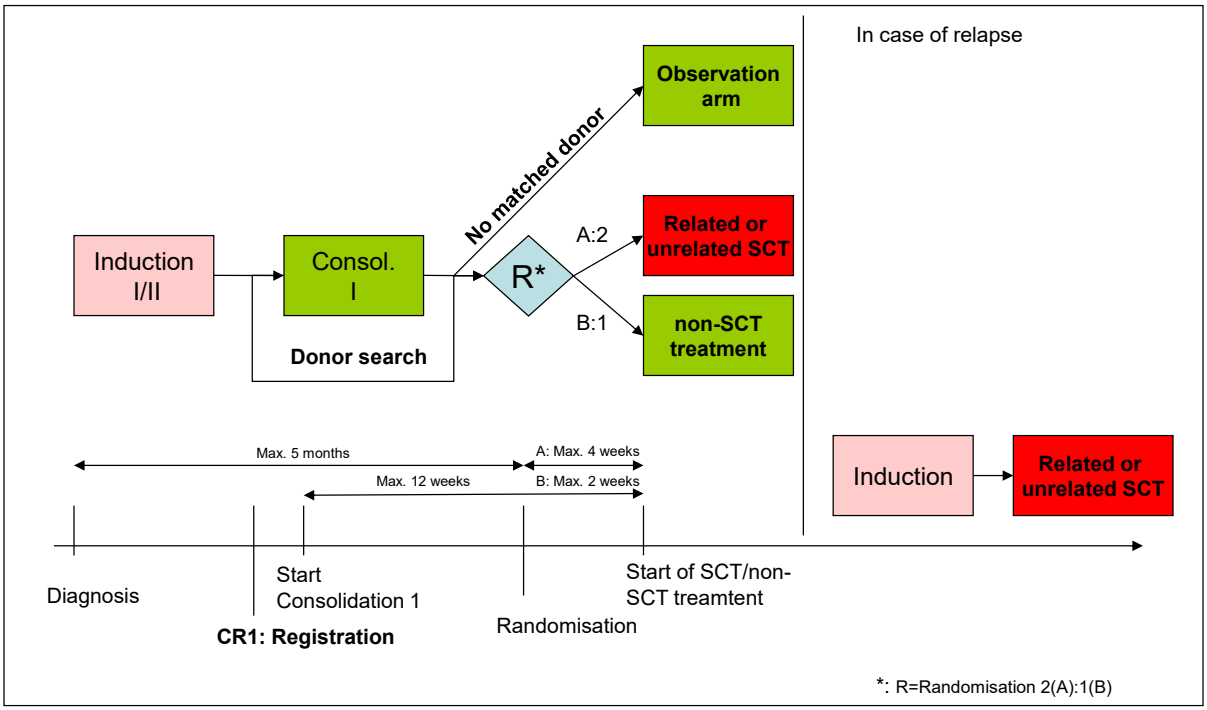


Figure 1

The data were reviewed by a data monitoring committee at several timepoints during the trial.

Key assumptions in the original protocol were too optimistic: The screening failure rate between registration and randomisation was higher than expected and LFS in general was lower than expected. The accrual rate was much lower than expected. Originally the sample site target was N = 231 randomised patients with expected accrual time of less than 4 years.

Accrual started in January 2010. In 2014 (on occasion of the first interim analysis) with N = 76 patients randomised, it became clear the target sample size was unattainable within a reasonable period.

In addition OS and LFS curves crossed, such that the envisaged analysis relying on the proportional hazard assumption became inadequate.

A conditional power analysis in 2014 showed that reasonable power would be achieved already with N=150 randomised patients. This recalculation took the observed higher LFS event rate into account and assumed switching to restricted mean survival methods, which are adequate when curves cross and have higher power in these cases.

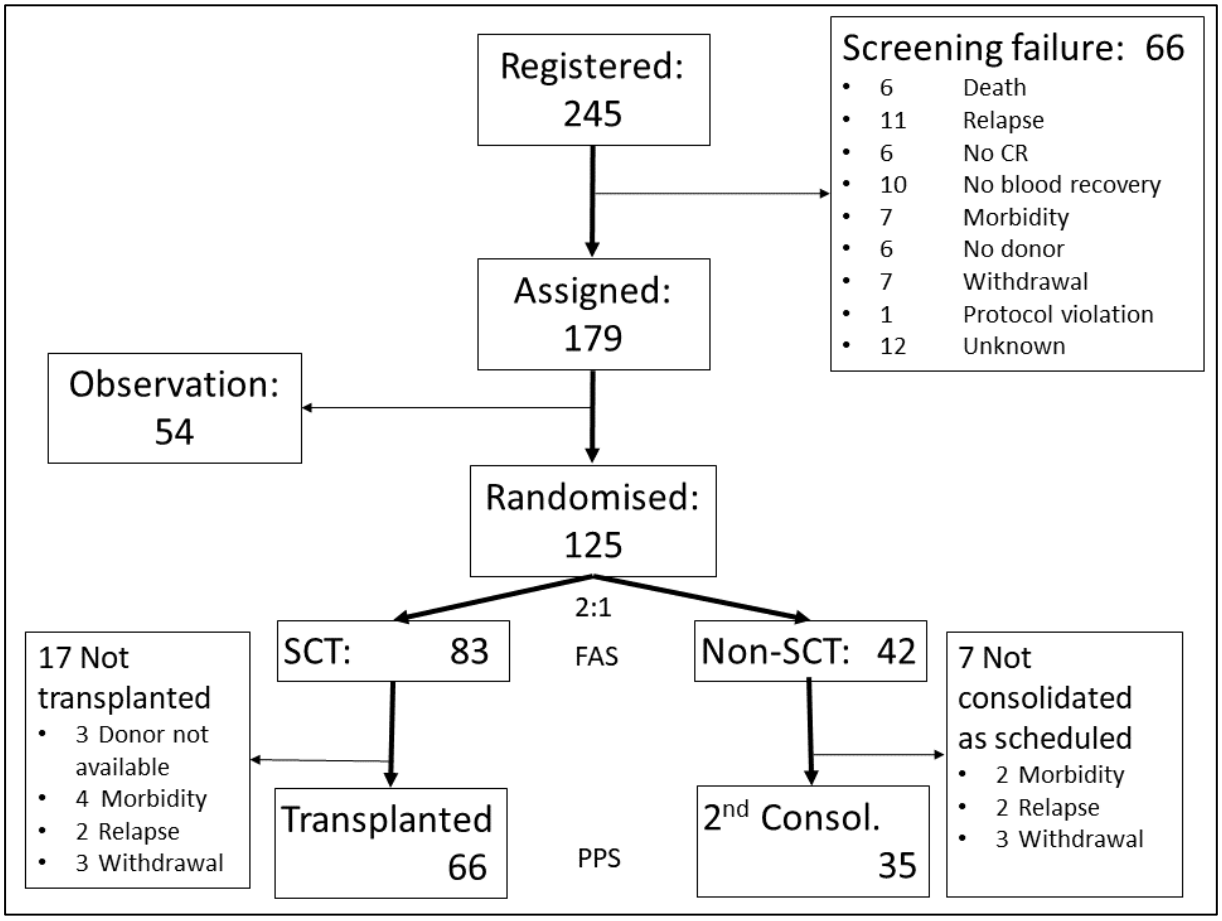
Eventually, accrual was stopped by the DMC in 2017 at N=125 due to slow recruitment fading away.

In addition in 2014, we decided to skip the planned second interim analysis. The first interim analysis was done at an alpha = 0.0002 level. Thus, the false-positive error of the final analysis is practically not affected (Peto-Heybittle). Therefore, we present the final analysis using a nominal alpha = 5% significance level.

10 Number of patients (planned and analysed)

Planned number:	231 randomised patients (Ratio 2:1)
Registered/screened subjects:	245
Randomised subjects	125
Analysed patients (ITT):	125
Analysed patients (PPS):	104

For details see the CONSORT-flow diagram:



11 Diagnosis and main criteria for inclusion

Inclusion criteria at registration:

- 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

Exclusion criteria at registration:

- 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 eldery AML study.
    - Documentation for the HCT vs CT in eldery AML study is not compromised. Second hand data from foreign study is not accepted

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:

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 109/l or 1500/mm³, transfusion independent platelet count ≥ **50** x 109/l (i.e. 48 h after last transfusion) and no leukemic blasts in the peripheral blood and no dysplasia
    - AND platelet count must be increasing
- Matching (10/10: HLA-A, -B, -C, DRB1 and DQ) related or unrelated donor is available

Exclusion criteria at randomisation:

- Patient has undergone more than one consolidation cycle
- More than 5 months (>150 days) after diagnosis
- Organ dysfunction
    - Patients with creatinine clearance < 50 ml/min
    - Cardiac ejection fraction < 40%
    - 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

  - 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 met all of the inclusion criteria and none of the exclusion criteria after the first consolidation cycle AND were not randomised were treated off study but were 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.

12 Information on the Test Product

	Dose	Mode of Administration	Batch numbers
Hematopoietic stem cells			not applicable
Fludarabine	3 days, 30 mg/m2 mg/m2	intravenous use	not applicable, treatment defined only by active substance
Ciclosporin	Related stem cell donor: day -3 to day 84 (minimum), then tapered at 8% per week Unrelated Stem cell donor: day -3 to day 183 (minimum), then tapered at 8% per week 12.5 mg/kg/day	intravenous use, oral use	not applicable, treatment defined only by active substance
Mycophenolate mofetil	Related stem cell donor: for 27 days Unrelated Stem cell donor: for 40 days, then decrease of dose by 500 mg every 2 weeks 45 mg/kg/day	intravenous use, oral use	not applicable, treatment defined only by active substance
Mitoxantron	2 days 10 mg/m2/day	Intravenous use	not applicable, treatment defined only by active substance
Cytarabin (Ara-C)	3 days 500 mg/m2/day	Intravenous use	not applicable, treatment defined only by active substance

13 Duration of Treatment

Conditioning Regimen

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

Ciclosporin (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 stoped. 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).
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/mm3 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.
Fludarabine	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.
Peripheral blood stem cells of the donor (PBSC)	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 106/kg CD34+) on day 0 of the treatment regimen. • Each patient may receive up to 2 intravenous infusions of donor T-cells given at intervals outlined in the trial protocol (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 x 107 CD3+ cells/kg and the remaining cells in aliquots of 1x108 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 ³ grade II acute GvHD. 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.

14 Reference Therapy

Patients randomized in Arm B were scheduled to receive further consolidation according to an upfront specified trial site protocol. This treatment should start at latest 2 weeks after randomization to the nonSCT-arm. If no consolidation protocol was available, the following optional schedule was to be be considered:

Mitoxantrone 10 mg/m² 30 min Infusion d 1 + 2
Ara-C 500 mg/m² q12hrs. 1h infusion d 1 + 3 + 5.

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

Batch numbers: Not applicable, since the treatment in the reference (non-SCT) arm is only a recommendation and local protocols should be used. The recommended treatment is only defined by active substance.

15 Criteria for Evaluation

15.1 Efficacy

The primary efficacy endpoint Leukaemia Free Survival (LFS) is defined as the time from randomisation to the first of the following three events:

- Haematological relapse
- Initiation of additional anti-leukaemic therapy (this includes DLI)
- Death from any cause

Modulation of immunosuppression does not count as an event.
Secondary efficacy endpoints

- Overall survival (OS): Time from randomisation to death from any cause.
- Components of LFS
  - Cumulative incidence of Treatment related mortality (TRM) defined as any death without documented evidence of a prior haematological relapse. (For consistency with the definition of LFS, we include prior initiation of additional anti-leukaemic therapy in the definition of TRM.
  - Cumulative incidence of relapse

15.2 Safety

Incidence, severity and duration of acute and chronic Graft versus Host Disease (GvHD)
(Note: TRM is already capture as a secondary efficacy endpoint, see above)

16 Statistical Methods/analysis procedures

In the original study protocol, the analysis and the sample size calculation was based on the log-rank test and cox regression. This turned out to be inadequate, since the underlying proportional hazard assumption is massively violated: Overall Survival (OS) and Leukaemia Free Survival (LFS) curves cross. This means in particular that the hazard ratio, which underlies the planned analysis as a measure of difference, is ill defined, and the power considerations in the protocol are obsolete.

Non-proportional hazards should have been envisaged: LFS is a composite endpoint - you have to survive and remain relapse free. It is - and was - well known from data in younger patients that Allo-SCT (as compared to conventional consolidation chemotherapy) reduces the hazard of relapse (Graft versus Leukaemia (GvL) effect), but increases the hazard of dying in

remission – both by acute treatment related mortality and increases long-term mortality risk of infection and chronic Graft versus Host Disease (cGVHD).

With crossing time to event curves, the answer to the apparently simple question “What is better for the patients?” becomes dependent on the time horizon. With a short-term perspective, conventional consolidation may be preferable due to increased Treatment Related Mortality (TRM) with Allo-SCT; long-term, better AML control with Allo-SCT may lead to more long-term remissions.

During the conduct of the trial, new adequate statistical methods became available that

a) can be applied to crossing survival curves,
b) provide a meaningful and easy to understand measure of difference, and
c) allow describing the dependence on the time horizon.

Andersen, Per Kragh; Hansen, Mette Gerster; Klein, John P. (2004): Regression analysis of restricted mean survival time based on pseudo-observations. In: Lifetime data analysis 10 (4), S. 335–350. DOI: 10.1007/s10985-004-4771-0.

Klein, John P.; Gerster, Mette; Andersen, Per Kragh; Tarima, Sergey; Perme, Maja Pohar (2008): SAS and R functions to compute pseudo-values for censored data regression. In: *Computer methods and programs in biomedicine* 89 (3), S. 289–300. DOI: 10.1016/j.cmpb.2007.11.017.

Andersen, Per Kragh; Perme, Maja Pohar (2010): Pseudo-observations in survival analysis. In: *Statistical methods in medical research* 19 (1), S. 71–99. DOI: 10.1177/0962280209105020.

Royston, Patrick; Parmar, Mahesh K. B. (2011): The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. In: *Statistics in medicine* 30 (19), S. 2409–2421. DOI: 10.1002/sim.4274.

Royston, Patrick; Parmar, Mahesh K. B. (2013): Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. In: *BMC medical research methodology* 13, S. 152. DOI: 10.1186/1471-2288-13-152.

A'Hern, Roger P. (2016): Restricted Mean Survival Time: An Obligatory End Point for Time-to-Event Analysis in Cancer Trials? In: *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 34 (28), S. 3474–3476. DOI: 10.1200/JCO.2016.67.8045.

Royston and Parmar (2011) have proposed a new ‘standard’ method of analysis which can be applied when proportional hazards fail and which makes the notion of dependence on the time horizon explicit. Instead of using the log hazard ratio as a measure of difference (which is ill defined without hazard proportionality), they propose to use the difference in mean survival time within a specified time horizon.

The restricted mean survival is directly interpretable and can be communicated to a patient. E.g. “Your life expectancy over the next two years with treatment A is 11 months; choosing treatment B increases your life expectancy by two months.” (Royston & Parmar 2011).

The restricted mean survival is estimated as the area under the survival curve integrated up to a given time horizon. Confidence intervals for both point estimates and differences in restricted mean survival can be obtained using a recently improved method (Klein 2008, Andersen 2010), which also allows for multivariate linear regression models.

Corresponding tests can be used in clinical trials, but require specification of a time horizon.

The restricted mean Leukaemia Free Survival (RLFS) estimates the mean expectancy of time alive and in remission up to a specified time horizon.

For testing we focus primarily on a time horizon of 60 months, which is implied by the original study protocol: The study was planned based on 5-year LFS rates. Follow up within the study was required for 5 years. Therefore, the pertinent time horizon for testing is set to 60 months.

This change of the measure of difference and of the method of analysis was proposed to the DMC in 2014 in a detailed document, when these problems became apparent on occasion of the first planned interim analysis.

In addition, we describe differences in restricted mean survival graphically for varying time horizons with corresponding two-sided confidence intervals.

Instead of Cox regression, which would require proportional hazards, we use linear Restricted Mean Survival regression adjusting for cytological risk and type of donor.

The Full Analysis Set (FAS) for the primary analysis follows the intent-to-treat principle and includes all randomized patients.The data from patients who rescinded their consent to participate are retained until the date at which they withdrew from the trial. However, one patient was excluded from the FAS who was erroneously randomised already after being transplanted ("protocol deviation" in CONSORT Flowchart).

The Per Protocol analysis set (PPS) consists of all randomised patients who actually received the post-randomisation treatment to which they were randomised. The PPS serves for sensitivity analysis, approximating a contrafactural world in which treatment could be given as per protocol. The PPS analysis is intended as a test for robustness of the confirmatory analysis and is auxiliary in nature.
\newline \newline
A special case are older patients in the Non-SCT arm who were not scheduled for further consolidation as per local protocol. These patient are included in the PPS as they were sheduled for no 2nd consolidation as per protocol.

17 Summary/Conclusion

Abstract

An EBMT 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

Background: Allogeneic stem cell transplantation (HCT) is a well-established, curative treatment in young AML patients, however associated with treatment related mortality and chronic Graft versus Host Disease. The role of Allo-HCT in elderly patients is controversial.

Objective: Do AML patients between 60 and 75 years of age who have achieved a complete remission and received one cycle of conventional consolidation chemotherapy profit from Allo-HCT as compared to further conventional consolidation?

Methods: In an open label, international, EBMT multicentre, phase III trial, patients with a sibling or unrelated 10/10 matched donor after their first consolidation were randomised in a ratio of 2:1 to either HCT or nonHCT consolidation (according to local protocols). Relapsing patients in the nonHCT arm could be transplanted as part of their second line therapy.

Primary efficacy endpoint was Leukaemia Free Survival (LFS) defined as time from randomisation to haematological relapse, initiation of additional anti-leukemic therapy (including Donor Lymphocyte Infusions (DLI)) or death from any cause. Follow-up was required for five years. Original sample size calculations were based on 5-year rates and the logrank test. However, because the proportional hazard assumption turned out to be violated, arm differences are described as difference in Restricted Mean Leukaemia Free Survival on a time horizon of 5 years. The original sample size target of N = 231 was recalculated at the first interim analysis and set to N = 150. The analysis followed the intent to treat principle with additional per protocol analysis (PPS).

Results: From 2010-01-11 to 2017-08-24 a total of 245 patients were registered when achieving first complete remission. 125 were eventually randomised. The first patient was randomised on 2010-02-23, the last patient on 2017-10-11. Median follow-up was 62 months. Of 83 patients in the HCT arm, 66 actually received a transplant, while 35 of 42 patients in the nonHCT arm received consolidation as planned per local protocol. There were 28 deaths without prior relapse (TRM) all in the HCT arm. From 66 transplanted patients, 8 experienced grade 3 or more aGvHD and 25 developed extensive GvHD.

Overall Survival curves crossed at about 18 months due to early treatment related mortality. OS 5-year rates were 31.3% (95% CI [22.6 ; 43.2]) in the HCT arm and 27.1% (95% CI [15.9 ; 46.4]) in the nonHCT arm. On a time horizon of 60 months, there was no difference (HCT-noHCT) in restricted mean Overall Survival (-0.8 months (95% CI [-9.2 ; + 7.6]) p = 0.853 in the FAS). However, 23 of 34 relapsed nonSCT patients received an Allo-HCT in second line.

LFS 5-year rates were 28.8% (95% CI [20.4 ; 40.6]) in the HCT arm and 8.9% (95% CI [3.1 ; 25.7]) in the nonHCT arm. The difference in the primary endpoint Restricted Mean Leukaemia Free Survival was significant with 8.9 months (95% CI [1.3 ; 16.6]) favouring HCT (p = 0.022 in the FAS).
Results for OS and FPS in FAS or PPS in univariate or multivariate analysis adjusting for the stratification factors cytological risk and donor type were all similar and consistent.

Conclusion: In elderly AML patients, SCT is beneficial for LFS when a time horizon of five years appears adequate for the individual patient.

18 Appendix

18.1 List of Investigators/Study Centres

Center ID	TRIAL SITE	Site has recruited patients	Name	First Name	Function	only applicable in Germany: German Drug Law version
A-001	Medizinische Universität Wien	no	Greinix	Hildegard	Principal Investigator	n.a.
A-002	Hanusch Krankenhaus der Wiener Gebietskrankenkasse	no	Keil	Felix	Principal Investigator	n.a.
AU-001	Alfred Health	yes	Patil	Sushrut	Principal Investigator	n.a.
CH-001	Hôpitaux Universitaire Genève	yes	Chalandon	Yves	Principal Investigator	n.a.
CH-002	Universitätsspital Basel	yes	Heim	Dominik	Principal Investigator	n.a.
CH-003	UniversitätsSpital Zürich	no	Schanz	Urs	Principal Investigator	n.a.
CH-004	Kantonsspital Aarau AG	no	Cantoni	Nathan	Principal Investigator	n.a.
CH-005	Inselspital Bern	no	Pabst	Thomas	Principal Investigator	n.a.
CH-007	Kantonsspital Luzern	yes	Gregor	Michael	Principal Investigator	n.a.
D-001	Universitätsklinikum Leipzig	yes	Bourgeois	Malvina	Investigator	before 10/2012
			Lange	Thoralf	Investigator	before 10/2012
			Nehring-Vucinic	Claudia	Investigator	before 10/2012
			Niederwieser	Dietger	Investigator	after 10/2012
			Niederwieser	Dietger	Principal Investigator	before 10/2012
			Trawinski	Henning	Investigator	before 10/2012
			Basara	Nadezda	Investigator	before 10/2012
			Tänzer	Julia	Investigator	before 10/2012
D-002	Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden	yes	Balaian	Ekaterina	Investigator	before 10/2012
			Bornhäuser	Martin	Investigator	before 10/2012
			Ordemann	Rainer	Investigator	before 10/2012
			Parmentier	Stefani	Investigator	before 10/2012

Center ID	TRIAL SITE	Site has recruited patients	Name	First Name	Function	only applicable in Germany: German Drug Law version
			Platzbecker	Uwe	Investigator	before 10/2012
			Schaich	Markus	Investigator	before 10/2012
			Schetelig	Johannes	Investigator	after 10/2012
			Schetelig	Johannes	Principal Investigator	before 10/2012
			Röllig	Cristoph	Investigator	before 10/2012
D-003	Robert-Bosch-Krankenhaus Stuttgart	yes	Aulitzky	Walter-Erich	Investigator	before 10/2012
			Bacchus-Gerybadze	Liza	Investigator	before 10/2012
			Kaufmann	Martin	Investigator	after 10/2012
			Kaufmann	Martin	Principal Investigator	before 10/2012
D-004	Berlin Charité	no	Uharek	Lutz	Principal Investigator	before 10/2012
			Notter	Michael	Investigator	before 10/2012
			Blau	Igor-Wolfgang	Investigator	before 10/2012
			Gerbitz	Armin	Investigator	before 10/2012
			Nogai	Axel	Investigator	before 10/2012
			Friedrichs	Birte	Investigator	before 10/2012
			Müßig	Arne	Investigator	before 10/2012
			Rieger	Kathrin	Investigator	before 10/2012
			Notter	n.a.	Investigator	before 10/2012
			Blau		Investigator	before 10/2012
			Gerbitz		Investigator	before 10/2012
			Rieger		Investigator	before 10/2012
			Friedrichs		Investigator	before 10/2012
			Müßig		Investigator	before 10/2012
			Nogai		Investigator	before 10/2012
			Ganepola		Investigator	before 10/2012
			Göldner		Investigator	before 10/2012

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D-005	Universitätsklinikum der Ernst-Moritz-Arndt-Universität Greifswald	no	Busemann	Christoph	Investigator	before 10/2012
			Dölken	Gottfried	Principal Investigator	before 10/2012
			Gudzuhn	Andrej	Investigator	before 10/2012
			Kiefer	Thomas	Investigator	before 10/2012
			Koberstein	Volker	Investigator	before 10/2012
			Krüger	William	Investigator	before 10/2012
			Neumann	Thomas	Investigator	before 10/2012
			Schmidt	Christian Andreas	Investigator	after 10/2012
			Wilfert	Hanna	Investigator	before 10/2012
D-007	Universitätsklinikum Heidelberg	no	Conzelmann	Michael	Investigator	before 10/2012
			Dengler	Jolanta	Investigator	before 10/2012
			Dreger	Peter	Investigator	before 10/2012
			Hegenbart	Ute	Investigator	after 10/2012
			Hegenbart	Ute	Principal Investigator	before 10/2012
			Krämer	Alwin	Investigator	before 10/2012
			Luft	Thomas	Investigator	before 10/2012
			Schmitt	Thomas	Investigator	before 10/2012
			Schönland	Stefan	Investigator	before 10/2012
			Bellos	Frank	Investigator	before 10/2012
D-008	Universitätsklinikum Jena	yes	Eigendorff	Ekkehard	Investigator	before 10/2012
			LaRosee	Paul	Investigator	before 10/2012
			Sayer	Herbert	Investigator	before 10/2012
			Sayer	Herbert	Principal Investigator	before 10/2012
			Schilling	Kristina	Investigator	before 10/2012
			Schmidt	Volker	Investigator	before 10/2012
			Scholl	Sebastian	Investigator	after 10/2012

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			Scholl	Sebastian	Investigator	before 10/2012
			Theuer	Claudia	Investigator	before 10/2012
			Pester	Frank	Investigator	before 10/2012
D-009	Universitätsklinikum Kiel	no	Gramatzki	Martin	Principal Investigator	before 10/2012
			Günther	Andreas	Investigator	before 10/2012
D-010	Universitätsklinikum Münster	yes	Krug	Utz	Investigator	before 10/2012
			Stelljes	Matthias	Investigator	after 10/2012
			Stelljes	Matthias	Principal Investigator	before 10/2012
			Groth	Christoph	Investigator	before 10/2012
			Wenning	Doris	Investigator	before 10/2012
			Mesters	Rolf	Investigator	before 10/2012
			Müller-Tidow	Carsten	Investigator	before 10/2012
			Kessler	Torsten	Investigator	before 10/2012
			Silling	Gerda	Investigator	before 10/2012
			Berkemeier	Almut	Investigator	before 10/2012
D-011	Klinikum der Universität Regensburg	no	Reichle	Albrecht	Principal Investigator	before 10/2012
			Reichle	Albrecht	Investigator	after 10/2012
			Holler	Ernst	Investigator	before 10/2012
			Edinger	Matthias	Investigator	before 10/2012
			Vogelhuber	Martin	Investigator	before 10/2012
			Hahn	Joachim	Investigator	before 10/2012
			Mayer	Stefanie	Investigator	before 10/2012
			Grube	Matthias	Investigator	before 10/2012
			Hautmann	Anke	Investigator	before 10/2012
			Landfried	Karin	Investigator	before 10/2012
			Beier	Fabian	Investigator	before 10/2012

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D-012	Universitätsklinikum Rostock	yes	Große-Thie	Christina	Investigator	before 10/2012
			Junghanß	Christian	Investigator	after 10/2012
			Junghanß	Christian	Principal Investigator	before 10/2012
			Jost	Kirsten	Principal Investigator	before 10/2012
D-013	Universitätsklinikum Tübingen	yes	Bethge	Wolfgang	Investigator	after 10/2012
			Bethge	Wolfgang	Principal Investigator	before 10/2012
			Faul	Christoph	Investigator	before 10/2012
			Vogel	Wichard	Investigator	before 10/2012
			Wirths	Stefan	Investigator	before 10/2012
D-015	Ernst-von-Bergmann Klinikum Potsdam	yes	Breywisch	Frank	Investigator	before 10/2012
			Jakob	Christian	Investigator	before 10/2012
			Maschmeyer	Georg	Investigator	after 10/2012
			Maschmeyer	Georg	Principal Investigator	before 10/2012
			Peinert	Stefan	Investigator	before 10/2012
D-016	Universitätsklinikum Aachen	yes	Akin	Sema	Investigator	before 10/2012
			Brümmendorf	Tim	Investigator	after 10/2012
			Brümmendorf	Tim	Principal Investigator	before 10/2012
			Crysandt	Martina	Investigator	after 10/2012
			Jost	Edgar	Investigator	before 10/2012
			Willop	Stefan	Investigator	before 10/2012
D-017	Otto-von-Guericke-Universität, Universitätsklinikum Magdeburg AöR	yes	Gehring	Sonja	Investigator	before 10/2012
			Hanus	Lynn	Investigator	before 10/2012
			Heinicke	Thomas	Investigator	after 10/2012
			Heinicke	Thomas	Principal Investigator	before 10/2012
			Ionita	Ana Maria	Investigator	before 10/2012
			Krogel	Christian	Investigator	before 10/2012

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			Schalk	Enrico	Investigator	before 10/2012
			Steinhagen	Imke	Investigator	before 10/2012
			Boger	Bianka	Investigator	before 10/2012
			Heidel	Florian	Investigator	before 10/2012
			Hütten	Heiko	Investigator	before 10/2012
D-018	Klinikum Chemnitz gGmbH	yes	Hänel	Mathias	Investigator	after 10/2012
			Hänel	Mathias	Principal Investigator	before 10/2012
			Herbst	Regina	Investigator	before 10/2012
			Morgner	Anke	Investigator	before 10/2012
			Rönitz	Marcus	Investigator	before 10/2012
			Thiel	Andreas Stefan	Investigator	before 10/2012
			Wittke	Ulrike	Investigator	before 10/2012
D-019	Klinikum Augsburg, II. Medizinische Klinik	no	Rank	Andreas	Investigator	after 10/2012
FR-001	CHU de Nantes, Hôtel Dieu	yes	Chevallier	Patrice	Investigator	n.a.
			Chevallier	Patrice	Principal Investigator	n.a.
			Delaunay	Jacques	Investigator	n.a.
			Guillaume	Thierry	Investigator	n.a.
			Mohty	Mohamad	Principal Investigator	n.a.
FR-002	Centre Antoine Lacassagne Nice	no	Gastaud	Lauris	Principal Investigator	n.a.
FR-003	Centre Hospitalier Sud Amiens - Maladies du Sang	yes	Marolleau	Jean-Pierre	Principal Investigator	n.a.
FR-006	CHU du Haut Lévêque	no	Pigneux	Arnaud	Principal Investigator	n.a.
FR-007	Centre Hospitalier (CH) Saint Quentin	no	Garidi	Reda	Principal Investigator	n.a.
FR-008	Institut Paoli-Calmettes Marseille	no	Furst	Sabine	Principal Investigator	n.a.

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FR-009	Hopital Saint Antoine Paris	no	Rubio	Marie	Principal Investigator	n.a.
FR-010	Hôpital d'instruction des armées Percy	no	Malfuson	Jean-Valére	Principal Investigator	n.a.
FR-011	Hospitalier et universitaire (CHU) de Nice	no	Legrand	Faezeh	Principal Investigator	n.a.
FR-012	Centre hospitalier et universitaire (CHU) de Limoges	no	Turlure	Pascal	Principal Investigator	n.a.
NL-001	Academisch Ziekenhuis bij de Universiteit Amsterdam	yes	Biemond	B.	Principal Investigator	n.a.
NL-002	VU University Medical Center	yes	Janssen	J.J.W.M.	Principal Investigator	n.a.
NL-003	University Hospital Maastricht	yes	Schouten	Harry	Principal Investigator	n.a.
NL-004	Erasmus MC Rotterdam	yes	Cornelissen	Jan	Principal Investigator	n.a.
			de Greef	G. E.	Investigator	n.a.
NL-005	University Medical Centre Utrecht	yes	Petersen	E.	Principal Investigator	n.a.
NL-006	University Medical Centre Groningen	no	Huls	G.	Principal Investigator	n.a.
NL-007	Isala Ziekenhuis Zwolle	yes	Dompeling	Elizabeth Christina	Investigator	n.a.
			van Marwijk Kooy	M.	Principal Investigator	n.a.