haematologica
Journal of the Ferrata Storti Foundation

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*Collaborative Groups: (EBMT), (OSHO), (HOVON-SAKK)*

*Received: May 17, 2024.*
*Accepted: August 1, 2024.*

*Citation: Dietger Niederwieser, Dirk Hasenclever, Wolfgang E. Berdel, Bart J. Biemond, Haifa Al-Ali, Yves Chalandon, Michel van Gelder, Christian Junghanss, Gosta Gahrton, Mathias Haenel, Ruediger Hehlmann, Thomas Heinicke, Andreas Hochhaus, Simona Iacobelli, Rien van Marwijk Kooy, Nicolaus Kroeger, Jeroen Janssen, Madlen Jentzsch, Frank Breywisch, Mohamad Mohty, Stavroula Masouridi-Levrat, Gert Ossenkoppele, Jacob Passweg, Wolfram Poenisch, Johannes Schetelig, Christoph Schliemann, Sebastian Schwind, Matthias Stelljes, Leo F. Verdonck, Vladan Vucinic, Bob Loewenberg, and Jan Cornelissen.*
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*Hematopoietic cell transplantation for older acute myeloid leukemia patients in first complete remission: results of a randomized phase III study.*
*Haematologica. 2024 Aug 8. doi: 10.3324/haematol.2024.285879 [Epub ahead of print]*

# Hematopoietic cell transplantation for older acute myeloid leukemia patients in first complete remission: results of a randomized phase III study

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Fundings:

Supported by the Deutsche Krebshilfe Grant 108830, Grant support for data management by KWF-Dutch Cancer Society (Grant-no. EMCR 2008-4332) and by the Swiss State Secretariat for Education, Research and Innovation (SERI) Switzerland

Acknowledgments:

The authors would like to acknowledge Michael Cross PhD for language cross reading, the transplantation center physicians, nurses, and data managers for their continued help and in their constant improvement in their patients' outcomes. We thank the local and central data managers for collecting patient data, in particular Yasmine Breitenstein, Schrock, Annett and Kalina Berit (study manager, data manager, Centre of Clinical Trials Leipzig), Marlies Groenendijk-Sijnke (study manager HOVON) and R. Hack, G. Droog-Bellis, M. Stals-Huls, D. van den Boom (Local data managers HOVON)

COI:

No potential conflict of interest relevant to this article was reported.
YC consulting fees for advisory board from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier; Travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz, Sanofi all via the institution; GG: Advisor Fujimoto Pharmaceutical corpora-tion. Japan; TH, Advisory Board: Eurocept; Travel grants: Eurocept, Stemline, JAZZ; Honoraria: Eurocept, JAZZ; AH, Research support from Novartis, BMS, Pfizer, and Incyte; CS, Honoraria: AbbVie, Astellas, AstraZeneca, BMS/Celgene, Laboratories Delbert, Jazz Pharmaceuticals, Novartis, Pfizer, Roche; Re-search support (institutional): Jazz, Boehringer Ingelheim, AngioBiomed; MH, Honoraria: Novartis, SOBI, Gilead Sciences, Falk Foundation; Consulting/Advisory Role – Novartis, BMS/Celgene, Gilead Sciences, Pfizer, Incyte, Sanofi/Aventis, Roche, Amgen, SOBI, Janssen; BL, Advisory Board: Servier, Astellas, Abbvie, Jazz, Kronos Bio, Stemline Pharmaceutics/Meranini; Shareholder, Consultancy CureVac SE
DN, DH, WB, BJB, HA-A, MG, CJ, RH, SI, RMK, NK, JJ, MJ, FB, MM, SM-L, GO, JP, WP, JS, SS, MS, VV, LFV and JC reported no conflict of interest

Contributions:
protocol writing: DN, DH, BL, JC; data contribution: DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP,WP, JS; CS; SS, MS, LFV, VV, BL, JC; data analy-sis: DN, DH, BL, JC; discussion results: DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP,WP, JS; CS; SS, MS, LFV, VV, BL, JC; manuscript writing: DN, DH, BL, JC; manuscript discussion and approval: DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP,WP, JS; CS; SS, MS, LFV, VV, BL, JC

Data sharing:
Individual participant data that underlie the results reported in this Article (text, tables, figures, and appendices) will be shared after de-identification to researchers who provide a methodologically sound and ethically approved proposal. Proposals can be submitted up to at least 36 months after Article publication. Proposals should be directed to dirk.hasenclever@imise.uni-leipzig.de; to gain access, data requestors will need to sign a data-access agreement.

Clinical trial registration: EudraCT-Number: 2007-003514-34

## Abstract

Given the selection of elderly patients with AML in first complete remission (CR1) the advantage of consolidation with allogeneic hematopoietic cell transplantation (HCT) over chemotherapy is still unclear.

Newly diagnosed AML patients in CR1 aged 60-75 years were registered and a donor search initiated. After one consolidation cycle, patients with a matched donor were randomized to HCT with fludarabine/low-dose total body irradiation and cyclosporine/mycophenolate mofetil immunosuppression or conventional non-HCT. Primary outcome was restricted mean leukemia-free survival (RM-LFS) up to five years.

Between 2010 and 2017, 245 patients (median age 67 years) were registered at CR1. After one consolidation, 26.9% of patients failed inclusion criteria. Of the 179 (73%) patients still on study, 75.4% had an HLA identical donor. Ten ineligible patients were excluded, and 125 randomized to HCT (n=83) or non-HCT (n=42).

The primary outcome RM-LFS up to 5 years was 24.5 months (95%CI:18.9-30.1) in the HCT and 15.6 months (95%CI:10.4-20.8) in the non-HCT arm (p=0.022) due to a decrease in cumulative relapse incidence from 91.1 (95%CI:80.7-100.0) after non-HCT to 37.8 (95%CI:27.2-48.4)% after HCT (p<0.0001). The secondary endpoints RM-OS up to 5 years was 27.8 months (95%CI:22.3-33.2) in the HCT as compared to 28.6 months (95%CI:22.2-35.0) in the non-HCT arm; non-relapse mortality at 5 years was 33.4% (95%CI: 23.0-43.9) with HCT and 0% without.

In older patients with AML in CR1 5-year RM-LFS is better with HCT than with non-HCT consolidation treatment. The long-term RM-LFS benefit did not translate into a better RM-OS during the study period.

## Introduction

Acute myeloid leukemia (AML) has a dismal prognosis in the continuously growing population of patients of higher age. Advances in supportive therapy have improved the proportion of patients who might benefit from a potentially curative treatment.[1–4] However, attempts to improve leukemia-free survival (LFS) by increasing therapy intensity have largely been unsuccessful, mostly because of very high relapse rates (>80%), resulting in average long-term survival rates of 20% or less.[2,5] For the time being long-term outcome perspectives have neither been significantly improved by more recent treatment approaches.[6–11]

Hematopoietic cell transplantation (HCT) has been shown to be the treatment modality with a high anti-leukemic potential, combining immunological anti-leukemia effects with preparative regimens of variable intensities.[12] For decades, HCT was restricted to younger and fit patients up to the age of 60 years. Since the beginning of the century, the use of HCT has been extended to adults of higher age (generally up to the age of 75 years) by employing reduced intensity conditioning (RIC) or non-myeloablative (NMA) preparative regimens.[13–16] Retrospective analyses and prospective studies in elderly patients have confirmed the potential of HCT to induce durable long term remissions.[16–19] On the basis of these clinical trials, the application of HCT at older age patients has risen substantially. Randomized studies have yet to be done so that a critical assessment of the comparative therapeutic value of HCT has not yet become available. This is relevant especially in patients of higher age since various selection factors (e.g, leukemia prognostic risk, comorbidities) in the older age segment may significantly influence the access to HCT. As a consequence, the selection of more favorable risk patients for HCT may profoundly impact on therapeutic outcome.

Here, we report the results of a prospective randomized study in patients with AML aged 60-75 years eligible for an intensive and low intensity induction treatment approach that were enrolled directly after achievement of first CR (CR1). The design enabled the assessment of the dropout rate of patients on consolidation and prior to HCT, the chance of identifying a matched donor, the logistics of performing HCT within a predetermined maximal interval from diagnosis, and the kinetics of relapse.

## Methods

### Trial design

This is an international, prospective, open, randomized, controlled trial to compare allogeneic HCT versus conventional consolidation therapy in elderly patients with AML in CR1. The study design is detailed in Figure S1.

Patients, 60-75 years of age, with newly diagnosed AML were treated with one or two induction therapies (Table S4A). After reaching CR1, patients were registered and subsequently HLA typed. A related/unrelated donor search was initiated and consolidation therapy started. After consolidation, patients were evaluated for comorbidity and hematological response. Eligible patients (see Table S1) with an HLA-identical related or 10/10 matched unrelated donor were randomized (2:1 ratio) to receive HCT within 4 weeks or non-HCT consolidation according to institutional treatment protocols (Table S4B) within 2 weeks after randomization. No additional chemotherapy was applied between randomization and HCT or non-HCT treatment. Randomization used Pocock minimization with center, type of donor (unrelated versus HLA identical sibling donors) and risk group at diagnosis (high-risk versus intermediate- to low-risk according to Grimwalde et al[20]) as strata. Patients randomized to non-HCT treatment maintained the fallback option of using their stem cell donor in the event of relapse. The trial was approved by the Ethics Committees of the participating institutions, registered (EudraCT-Number: 2007-003514-34) and informed consent obtained from each participant.

Trial procedures

HCT was performed after conditioning with fludarabine/200 cGy total body irradiation and cyclosporine /mycophenolate mofetil immunosuppression as previously described.[14,15] No ATG was used. Non-HCT consolidation was administered according to local protocols.

Outcomes

The primary endpoint was restricted mean (RM)-LFS, defined as time from randomization to the first of the following three events: hematological relapse, initiation of additional anti-leukemic therapy, or death from any cause. Secondary endpoints included cumulative incidence of relapse (RI), non-relapse mortality (NRM), overall survival (OS) and complications including graft-versus-host disease (GvHD).

Statistical Analysis

In the initial protocol, the analysis relied on the proportional hazard assumption by specifying a Cox regression adjusting for randomization strata. At the planned first interim analysis in 2014 based on data from 78 patients, the proportional hazard assumption was not applicable because of crossing curves. In addition, both the accrual rate and the overall LFS was markedly lower than expected. After extensive discussion

with the Data Monitoring Committee (DMC), the measure of difference in LFS was switched from the conceptually inadequate hazard ratio to the difference in 5-year restricted mean LFS (RM-LFS) recommended for situations with crossing curves [21–26] and estimates the mean expectancy of time alive and in remission up to a specified time horizon; this corresponds to the area under the LFS curve up to the time horizon. Accrual was stopped in 2017 at 125 randomized patients, the end of the trial was on August 31, 2020 and the latest follow-up information available on December 10, 2020.

RM-LFS estimation and regression analyses for LFS and OS were performed using the R-package "pseudo".[21–26] RI and NRM were analyzed using competing risk methods. The primary analyses follow the Intention to Treat (ITT) principle.

Additional information is given in supplemental materials.

**Results**

From 2010 to 2017, 245 patients in CR1 (median age 67 years) were registered in 25 trial sites in Germany, the Netherlands, Switzerland, France, and Australia (Figure 1 and Table S2).

There were 66 (27%) screening failures after first consolidation (Figure 1), 6 (9%) patients died, 26 (40%) were no longer in CR1 (relapse, non CR1, no hematological recovery), and 34 (51 %) patients exited the study due to morbidity, withdrawal of informed consent, no donor available, or for unknown reasons. Of 179 patients still in CR1 after consolidation, 135 (75%) had an HLA identical (related or 10/10 unrelated) donor. Ten patients with a suitable donor were not randomized and therefore allocated to the observation group: seven patients declined transplant; one patient was deemed unfit for transplant, and two patients were transplanted without randomization. The other 125 patients were randomized to HCT (n=83) or non-HCT (n=42), and 54 were assigned to observation (Figure 1). Mean time from diagnosis to randomization was 15 weeks, with 121/125 (97%) randomized within 5 months as *per protocol* (Figure S3A).

Patient characteristics at randomization were balanced in both groups with respect to age, gender, diagnosis of AML and RAEB, cytogenetic risk, major molecular characteristics, comorbidity indices, and donor type (Table 1). The integrated NRM risk score[28] showed an imbalance in the distribution with more frequent lower beneficial scores (0-3) in the non-HCT and higher risk scores (4+) in the HCT arm (p=0.01). Determination of detailed molecular markers revealed no significant imbalance between the two groups (Table S3).

The proportion of patients not receiving treatment according to randomization was 20.5% in the HCT (relapse n=7; morbidity n=4; withdrawal n=3; unavailable donor n=3) and 16.7% in the non-HCT arm (relapse n=2; morbidity n=2; withdrawal n=3; Figure 1). In total, 66 of the 83 patients in the HCT arm finally received

HCT. In the non-HCT arm 35 of the 42 patients local non-HCT therapy. In those transplanted, mean time from diagnosis to transplant was 4.5 months, with 62 of 66 (94%) within less than 6 months (Figure S3B).

The median follow-up time of surviving patients was 62 months. Figure 2A shows LFS in the ITT analysis. Kaplan Meier curves cross within the first year. Five-year LFS rates were 28.8% (95%CI: 20.4-40.6) in the HCT and 8.9% (95%CI: 3.1-25.7) in the non-HCT arm; the LFS rate difference at 5-years was +19.9% (95%CI: 6.2-33.6), favoring HCT.

The primary endpoint RM-LFS up to 5 years (i.e., the expected lifetime in CR1 on a time horizon of five years) was 24.5 months (95%CI: 18.9-29.8) in the HCT and 15.6 months (95%CI:10.4-20.8) in the non-HCT arm (Table 2). The difference in RM-LFS of +6.4 months (95%CI: 0.2-12.6) at 4 years (p=0.04) increased to +8.9 months (95%CI: 1.3-16.6) at 5 years (p=0.022) and +10.8 months (95%CI: 1.7-19.9) at 6 years (p=0.019) favoring HCT (Table 3). This treatment effect is confirmed in regression analysis as 9.5 months (95%CI: 2.1-17.0), when adjusting for stratification parameters, cytogenetic risk group and donor type (Table S5). No difference in LFS was observed between patients transplanted from related and unrelated donors (Figure S7). Analyses of LFS as per protocol revealed similar results.

Figure S8A depicts the dependence of the treatment effect in RM-LFS as a function of the time horizon. After an early disadvantage of HCT due to NRM in the first year, the benefit of HCT over non-HCT emerges starting at about 36 months and reaches statistical significance after 48 months.

The study does not allow for a robust analysis of molecular AML subsets. The distribution of NPM1 mutated AML in both treatment groups was not significantly different (28.4 versus 45.7%, respectively; p=0.12). Proportions of continuous CR, relapse and NRM among NPM1 mutated and NPM1 wild type patients between HCT and non-HCT treatment groups were too small to allow for a meaningful analysis (Table S6). The distributions of FLT3-ITD-positive patients were neither different in the HCT and non-HCT treatment groups (21.3 versus 16.7%; p=0.75 Table 1), respectively. TP53 mutant was present in 6 of 24 patients tested and distributed equally between the two arms (three in each).

LFS events were either AML relapse, NRM or initiation of anti-leukemic treatment. Cumulative incidence curves of relapse with NRM as a competing risk show a potent anti-leukemic effect after HCT treatment (Figure 2C). Almost all patients in the non-HCT arm relapsed early with a 5-year RI of 91.1% (95%CI: 80.7-100.0). In contrast, RI in the HCT was 37.8% (95%CI: 27.2-48.4) at 5 years [HR 3.1 (95%CI: 1.93-4.98), p<0.0001].

On the other hand, NRM was exclusively observed in the HCT arm with a 5-year NRM cumulative incidence (with RI as a competing risk) of 33.4% (95%CI: 23.0-43.9) (Figure 2D). Cumulative incidence of NRM, broken down by the integrated NRM score[28] was 25.0% (95%CI: 6.9-43.1) in patients with lower score (0-3) versus 45.7% (95%CI:30.2-61.2) in higher scores (4+) (Figure S4).

Relapses were the predominant cause of death in both treatment groups, i.e. 50.9% in the HCT and 100% in the non-HCT group. Infections (22.8%; bacterial 19.3% and viral 3.5%) and GvHD (10.5%; Table S7) were the most frequent cause of death after relapse in the HCT arm. Cumulative incidence of acute GvHD grade III-IV was noted in 13.1% and chronic GvHD in 33.5% at 5 years (Figures S5 and S6).

OS survival curves cross at about 20 months (Figure 2B). Five-year OS 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 non-HCT arm (n.s.). The secondary outcome RM-OS up to 5 years (i.e., the expected lifetime on a time horizon of 5 years) is 27.8 months (95%CI: 22.2-33.0) in the HCT and 28.6 months (95%CI: 21.7-35.3) in the non-HCT arm (p = 0.85; Figure S8B). Thus, the long-term RM-LFS benefit does not translate into a benefit in the secondary endpoint RM-OS – at least not within the study period. Of note, 19 of 34 (56%) non-HCT patients with an AML relapse received HCT in CR2 as part of second line treatment. OS of patients after relapse in the non-HCT arm according to HCT and non-HCT after relapse is given in Figure S9 and results of patients in the observation arm in Figure S10.

**Discussion**

HCT has become a commonly applied treatment modality in younger and middle-aged adults with AML, particularly for those patients with a comparatively high prognostic risk of recurrence of disease following chemotherapy.[27,29] The incidence of AML increases with age and older patients generally have an unfavorable outcome even in so called low or intermediate genetic risk, making them potential candidates for HCT[2,20]. The age-depended risk of transplant-related complications and the likely potential selection bias in older patients proceeding to HCT have created doubts about the comparative therapeutic value of HCT in older patients. Prospective randomized studies concerning the value of HCT treatment have proved difficult to conduct - particularly in elderly patients.

The present study with RM-LFS as primary endpoint represents the first randomized intention to treat cooperative effort of evaluating HCT in the setting of older patient in CR1 after intensive or low-intensive induction therapy and a matched donor. Our study confirms both the potent anti-leukemic effect as well the

NRM with HCT after NMA conditioning as compared with conventional consolidation therapy. Starting after 4 years, RM-LFS is significantly better with HCT compared to non-HCT consolidation outweighing the disadvantage of increased NRM. Previous studies in patients with hematopoietic donors have documented the potent anti-leukemic potential of HCT, but these were non-randomized [12,16,18]. By starting registration of the patients at CR1 immediately after induction and by randomization after subsequent first consolidation with a time limit of 5 months from diagnosis to randomization, this trial set out to avoid biases previously considered major issues in the evaluation of HCT in older patients. By choosing a uniform NMA, less toxic conditioning and short aplasia time without outcome differences between ages 60-64, 65-69 and ≥70 years as previously published and confirmed in our study (Figure S11), the selection of patients ineligible for HCT has been reduced as much as possible.[18]

RI (91.1% at 5 years) was extremely high in the non-HCT arm of elderly AML despite low, intermediate and high risk cytogenetic as published previously[2,20]. In contrast, RI after HCT was 37.8% in a range similar to the 50% after related, and 16% after unrelated HCT, described previously.[15] Furthermore, the study was performed over a period when subpopulation chimerism guided immune suppression, shown to decrease RI early after HCT, was not available to all participating centers.[30] Moreover, the NRM of 33.4% at 60 months seems similar to the 29.0% previously observed in phase II trials in this age group.[12,14,15] A high proportion of deaths (22.8% of deaths) was caused by bacterial or viral infections in this elderly patient population, which exceeded the proportion of deaths from GvHD (10.5%). Future HCT protocols including better infectious prophylaxis are expected to increase even more the outcome in this elderly patient population with excessively high RI of 91.1% with non-HCT consolidation.

The improved 5-year RM-LFS after HCT in comparison to non-HCT does not translate into a RM-OS benefit during the study period (Figure S8 and Table 3). The rescue possibility in the non-HCT arm after relapse by HCT impedes RM-OS comparisons. Of note, 19 out of the 34 (55.8%) relapsing non-HCT patients were transplanted in CR2.

The results of our study raise some additional points of interest. First, a considerable proportion of CR patients relapse within a few weeks after CR1 during consolidation and before randomization to HCT or non-HCT underscoring the need to generate more stable or deeper remissions with induction therapy. Unfortunately, we could not determine the MRD status pre-or post-HCT in patients in this study. In the meantime, new treatment strategies and techniques for determining MRD have become available, which allow for

more personalized management of additional therapeutic interventions following one or two induction chemotherapies. In addition, new remission induction approaches e.g., hypomethylating therapy in combination with venetoclax, may induce MRD-negativity prior to transplant with less toxicity. As extensively discussed before, the immunotherapeutic effect of HCT as a consolidation therapy is strong and extends across different subtypes of AML resulting in a reduction of relapse of at least a third of what can be observed in patients consolidated with chemotherapy, as shown again in the present study.[27,29] However, especially in older and medically less fit patients, NRM reduces the net effect on LFS and OS, necessitating the selection of patients for whom NRM can be predicted to be acceptable. Several predictive scores have been developed. For instance, the integrated EBMT/HCT-CI score by Versluis et al [28] and the HCT-CI score can be used to tailor the application of HCT and preclude excessive toxicities. However, the predictive value of such scores may be valued differently by physicians and patients and did not influence RI or OS (Figure S4 and data not shown) in our trial.

For 75.4% of patients in our study, an HLA-identical related or unrelated donor was identified within a few weeks of CR1 and during consolidation, allowing HCT to be scheduled within 5 months from diagnosis of the disease. The best time for a donor search is as early as possible and may already be started at CR1 or even at diagnosis, although depending on local institutional circumstances the time needed to find a donor and the possibility to cancel a donor search in patients not undergoing HCT will impact on the choice for an early donor search strategy. Increasing donor availability and shorter diagnosis-HCT time intervals are foreseen in the future due to the increased use of haploidentical donors in clinical practice worldwide.[31]

This trial has a few limitations. During the trial period transplant strategies evolved, but none of them have been proven to be superior to low-dose TBI in a prospective trial with unbiased patient inclusion. The use of this minimally toxic, low-dose TBI based, nonmyeloablative regimen conditioning with CyA/MMF immunosuppression has been developed in the dog model[32], translated to clinical phase II studies with long-term outcomes on more than thousand patients[13–15,18] and was now studied in a phase III study. While short-term results are available on heterogeneous patients populations with newer transplant strategies, long-term results are missing in elderly patients with post-Cy or newer immunosuppressive therapies[33].

While new drugs including venetoclax combinations have become available as consolidation and/or maintenance for non-HCT treatment since study start, most of these have yet to demonstrate improvement of long-term outcome in the broader AML population. E.g. maintenance with CC-486 in comparison to placebo prolonged median relapse free survival and 2 years survival, but long-term LFS and OS was unaf-

fected.[34] Combinations of apoptosis interacting drugs with HMA and targeted therapy, where possible, have high CR rates and longer median OS, but resistance caused by e.g. loss of p53 function, activating kinase mutations and alternative anti-apoptotic proteins are considered reasons for failing better long-term LFS and OS.[35]

The preparative regimen described here is currently used less frequently (8.5% of 6289 AML patients >60 years transplanted from 2020-2022) according to the EBMT registry in comparison to RIC (EBMT personal communication). The latter regimen requires significant expertise and MRD or subpopulation chimerism guided immunosuppression. However, it exerts potent anti-leukemic activity[13–15]. The NMA regimen has been used intentionally to avoid selection of elderly patients to HCT being associated with an extremely short duration of aplasia and a missing age effect in this elderly patients[18]. As a possible sign of selection, only 35% of patients transplanted in 2020-2022 according to the EBMT registry were older than 60 years of age, despite the highest incidence of the disease in this as compared to younger age group. In our trial, only one patient in CR1 after consolidation was considered unfit for HCT. The extent of selection for HCT using RIC cannot be reliably estimated, but is assumed to be substantial by looking at the HCT activity of elderly patients with AML. It might well be that RIC or even myeloablative conditioning (MAC) may reduce the RI in selected patients in comparison to NMA, but prospective randomized studies in similar patient populations are missing or have similar RI[36]. Preemptive or post-HCT MRD driven targeted therapy may improve results further. Unfortunately, no ancillary quality of life studies were performed in this trial.

Furthermore, our study was not intended to answer the question, if HCT in CR2 ultimately leads to similar results as HCT in CR1. As reported previously, patients with hematological relapse, and especially elderly patients, have a dismal outcome. Only 28.6% of patients >60 years achieve CR2 after relapse and LFS has been described to be only 13.8% at 5 years in this age group.[2]

Even if induction therapy of AML has changed (and will continuously change), the study provides a solid basis for further trials and an essential backbone for evidence-based AML therapy in elderly aiming at improving long-term LFS from diagnosis. Achievement of molecular CR1 after induction therapy remains the goal to decrease early relapses before consolidation and improve results of HCT consolidation. Since none of the available targeted therapies and combinations have shown to be superior in long-term outcome by inducing resistance, consolidation treatment for long-term LFS is urgently needed. Perceptions of main treatment goals/chances of cure (80%) from patients and of chances of cure (7%) from physicians are clearly discordant in elderly patients with AML.[37] The only treatment able to improve long-term LFS is HCT

as shown in our unbiased randomized ITT study. The current study provides the rationale to increase the use of HCT in elderly patients (currently performed only in a small proportion). Further advances in elderly AML can be reached only by improving the different steps of therapy: decrease relapse after CR1 by increasing molecular remissions and better timing of HCT, decrease relapse incidence after HCT or non-HCT by better maintenance, decrease NRM after HCT and increase long- (not only short) term outcome using the results of our study as baseline. The need to analyze the different steps within studies will be the main aim for the next years and the only way to improve long-term outcome of AML in a population of increasing life-expectancy today of >82 years (https://www.worldometers.info/demographics/life-expectancy/).

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**Table 1: Patient characteristics at randomization**

| variable | | Total n | Total availbale % of total | Total % tested positive | HCT n=83 | HCT % tested positive | non-HCT n=42 | non-HCT % tested positive | p-value |
|---|---|---|---|---|---|---|---|---|---|
| age (years) | median (IQR) | 125 | 100 | | 67.3 | (64.7-70.4) | 66.4 | (63.6-69.9) | 0.23 |
| gender | male | 86 | 68.8 | | 57 | 68.7 | 29 | 69 | 1 |
| | female | 39 | 31.2 | | 26 | 31.3 | 13 | 31 | |
| diagnosis | AML | 122 | 97.6 | | 81 | 97.6 | 41 | 97.6 | 1 |
| | RAEB | 3 | 2.4 | | 2 | 2.4 | 1 | 2.4 | |
| cytogenetic risk§ | low | 16 | 12.8 | | 11 | 13.3 | 5 | 11.9 | 0.62 |
| | intermediate | 73 | 58.4 | | 46 | 55.4 | 27 | 64.3 | |
| | High | 36 | 28.8 | | 26 | 31.3 | 10 | 23.8 | |
| molecular analysis | *BCR::ABL1* | 41 | 33 | 0.0 | 29 | 0.0 | 12 | 0.0 | n.a. |
| | *FLT3-ITD* | 111 | 89 | 19.8 | 75 | 21.3 | 36 | 16.7 | 0.75 |
| | *FLT3-TKD* | 31 | 25 | 0.0 | 20 | 0.0 | 11 | 0.0 | n.a |
| | *NPM1mut* | 109 | 87 | 33.9 | 74 | 28.4 | 35 | 45.7 | . 0.12 |
| | *ASXL1* | 25 | 20 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| | *IDH1* | 35 | 28 | 5.79 | 26 | 7.7 | 9 | 0.0 | 1 |
| | *IDH2* | 35 | 28 | 17.1 | 27 | 18.5 | 8 | 12.5 | 1 |
| | *RUNX1* | 25 | 20 | 16.0 | 18 | 16.7 | 7 | 14.3 | 1 |
| | *TP53* | 24 | 19 | 25.0 | 18 | 16.7 | 6 | 50.0 | 0.07 |
| donor type | related | 28 | 22.4 | | 19 | 22.9 | 9 | 21.4 | 1 |
| | unrelated | 97 | 77.6 | | 64 | 77.1 | 33 | 78.6 | |
| HCT-CI Comorbidity index | 0 | 53 | 44.9 | | 33 | 42.3 | 20 | 50 | 0.23 |
| | 1 | 44 | 37.3 | | 27 | 34.6 | 17 | 42.5 | |
| | 2 | 13 | 11.0 | | 10 | 12.8 | 3 | 7.5 | |
| | 3 | 6 | 5.1 | | 6 | 7.7 | 0 | 0 | |
| | 4 | 2 | 1.7 | | 2 | 2.6 | 0 | 0 | |
| | valid | 118 | 94.4 | | 78 | | 40 | | |
| Integrated NRM score* | 0-3 | 69 | 55.2 | | 38 | 45.8 | 31 | 73.8 | 0.01 |
| | 4+ | 56 | 44.8 | | 45 | 54.2 | 11 | 26.2 | |

Abbreviations: RAEB, refractory anemia with excess of blasts; § cytogenetic risk according to[20], # data of full molecular analyses are presented in Table S1; HCT, Hematopoetic Cell Trasplantation;* integrated Non Relapse Mortality (NRM) score[28]

**Table 2: Patient outcome**

| | | HCT (95%CI) | | non-HCT (95%CI) | | p-value |
|---|---|---|---|---|---|---|
| RM-LFS up to 5 years | months | 24.5 | (95%CI: 18.9-30.1) | 15.6 | (95%CI: 10.4-20.8) | p = 0.02 |
| RM-OS up to 5 years | months | 27.7 | (95%CI: 22.2-33.0) | 28.5 | (95%CI: 21.7-35.3) | p = 0.85 |
| LFS 5 years | % | 28.8 | (95%CI: 20.4-40.6) | 8.9 | (95%CI: 3.1-25.7) | p = 0.02* |
| OS 5 years | % | 31.3 | (95%CI: 22.6-43.2) | 27.1 | (95%CI: 15.9-46.4) | p = 0.16* |
| Cum RI 5 years | % | 37.8 | (95%CI: 27.2-48.4) | 91.1 | (95%CI: 80.7-100.0) | p < 0.0001 |
| Cum. NRM 5 years | % | 33.4 | (95%CI: 23.0-43.9) | 0 | n.a. | p < 0.0001# |

Abbreviations: HCT, Hematopoetic Cell Trasplantation; RM-LFS, restricted mean leukemia free survival; RM-OS, restricted mean overall survival; OS, overall survival; cum. RI, cumulative relapse incidence; cum NRM, cumultative non-relapse mortality; *derived from the Kaplan Meier rate estimates, # Fisher's exact test (0 in one arm); n.a. not available (0 events)

**Table 3: Restricted Mean-Leukemia Free Survival and Restricted Mean-Overall Survival for different time horizons**

| RM-LFS | HCT | HCT 95%CI | non-HCT- | non-HCT 95%CI | Difference RM-LFS | Difference 95%CI | p-value |
|---|---|---|---|---|---|---|---|
| 12 months | 7.80 | [ 6.8; 8.7 ] | 8.1 | [ 7.0; 9.2 ] | -0.3 | [ -1.8; 1.2 ] | 0.8 |
| 24 months | 12.5 | [ 10.4; 14.6 ] | 11.0 | [ 8.6; 13.3 ] | 1.5 | [ -1.7; 4.7 ] | 0.35 |
| 36 months | 16.8 | [ 13.5; 20.1 ] | 13.0 | [ 9.5; 16.4 ] | 3.9 | [ -0.9; 8.6 ] | 0.11 |
| 48 months | 20.8 | [ 16.3; 25.2 ] | 14.3 | [ 10.0; 18.6 ] | 6.4 | [ 0.2; 12.6 ] | 0.042 |
| 60 months | 24.5 | [ 18.9; 30.1 ] | 15.6 | [ 10.4; 20.8 ] | 8.9 | [ 1.3; 16.6 ] | 0.022 |
| 72 months | 27.6 | [ 21.0; 34.3 ] | 16.8 | [ 10.7; 23.0 ] | 10.8 | [ 1.7; 19.9 ] | 0.019 |
| **RM-OS** | **HCT** | **HCT 95%CI** | **non-HCT-** | **non-HCT 95%CI** | **Difference RM-OS** | **Difference 95%CI** | **p-value** |
| 12 months | 9.2 | [ 8.4; 10.0 ] | 10.9 | [ 10.2; 11.5 ] | -1.65 | [ -2.7; -0.6 ] | 0.002 |
| 24 months | 14.7 | [ 12.8; 16.7 ] | 17.3 | [ 15.2; 19.4 ] | -2.57 | [ -5.5; 0.3 ] | 0.078 |
| 36 months | 19.5 | [ 16.4; 22.7 ] | 21.7 | [ 18.1; 25.2 ] | -2.11 | [ -6.9; 2.6 ] | 0.38 |
| 48 months | 23.8 | [ 19.5; 28.0 ] | 25.2 | [ 20.3; 30.2 ] | -1.48 | [ -8.0; 5.1 ] | 0.66 |
| 60 months | 27.8 | [ 22.3; 33.2 ] | 28.6 | [ 22.2; 35.0 ] | -0.79 | [ -9.2; 7.6 ] | 0.85 |
| 72 months | 31.2 | [ 24.6; 37.7 ] | 31.1 | [ 23.3; 38.8 ] | 0.09 | [ -10.0; 10.2 ] | 0.98 |

Abbreviations: LFS, leukemia free survival; OS, overall survival; HCT, Hematopoetic Cell Trasplantation; RM-LFS, restricted mean leukemia free survival; RM-OS, restricted mean overall survival; OS, overall survival; CI, confidence interval

## Legends to the Figures

Figure 1: Flow chart

*reason for drop out: 34 patients (morbidity, withdrawal of informed consent, no donor available, or unknown reasons) 26 no longer in CR1 (relapse, non CR1, no hematological recovery) and 6 patients died,

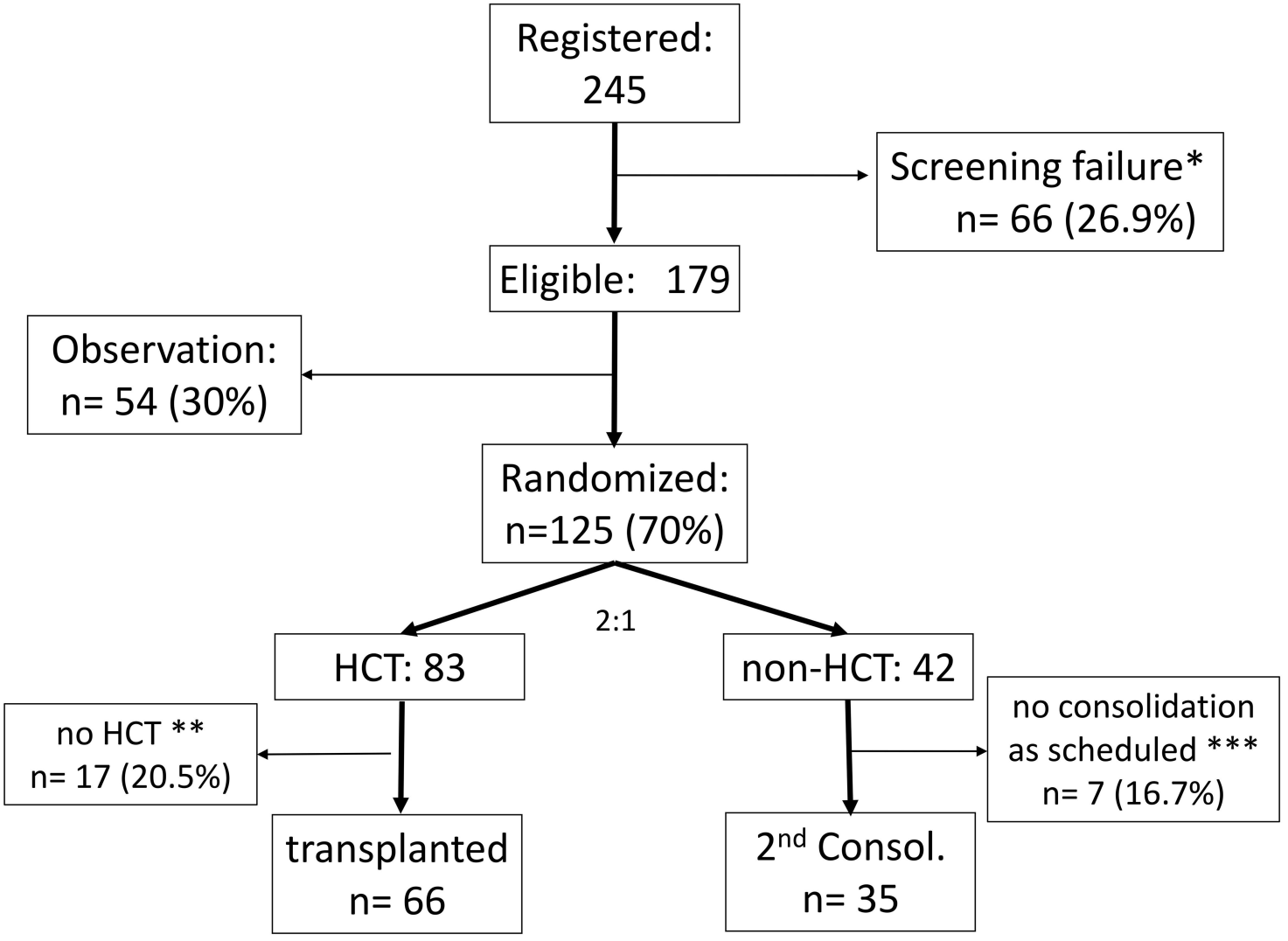
** Patients not receiving treatment according to randomization 20.5% (relapse n=7; morbidity n=4; withdrawal n=3; unavailable donor n=3)

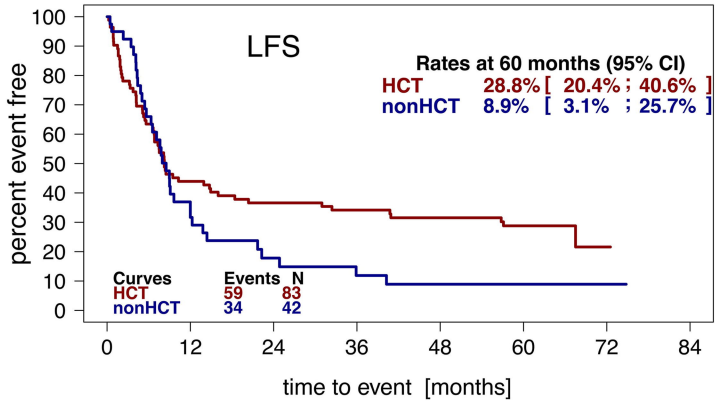
*** Patients not receiving treatment according to therapy as planned 16.7% (relapse n=2; morbidity n=2; withdrawal n=3).

Abbreviations: HCT, Hematopoietic Cell Transplantation; CT, chemotherapy; Consol, consolidation; CR, complete remission.

Figure 2: Outcome according to randomization to Hematopoietic Cell Transplantation (HCT) or non-HCT analyzed following the intention to treat principles. Numbers below LFS and OS are number of patients at risk (number of patients censored).

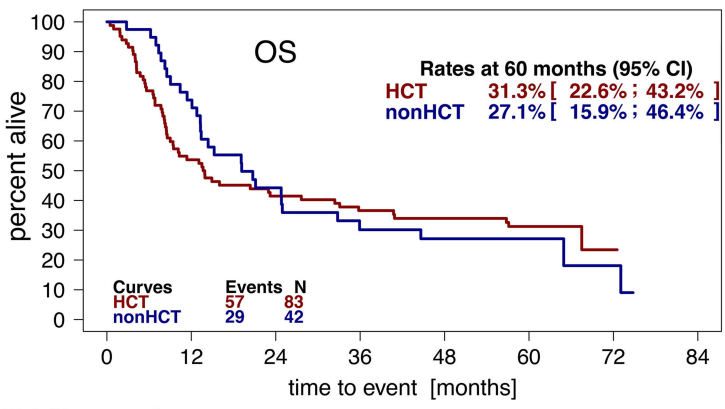
A) Leukemia-free survival (LFS), B) Overall survival (OS), C) Cumulative Relapse incidence (RI) and D) Non-relapse mortality (NRM)


Registered:
245
Screening failure*
n= 66 (26.9%)
Eligible: 179
Observation:
n= 54 (30%)
Randomized:
n=125 (70%)
2:1
HCT: 83
non-HCT: 42
no HCT **
n= 17 (20.5%)
no consolidation
as scheduled ***
n= 7 (16.7%)
transplanted
n= 66
2nd Consol.
n= 35



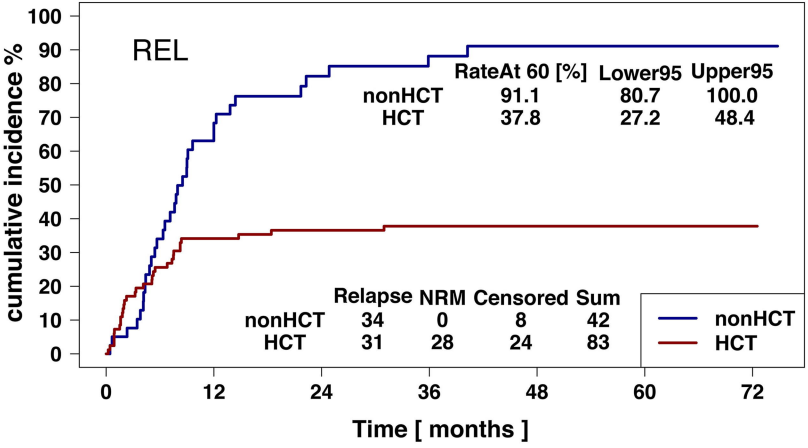

N at Risk (N censored)

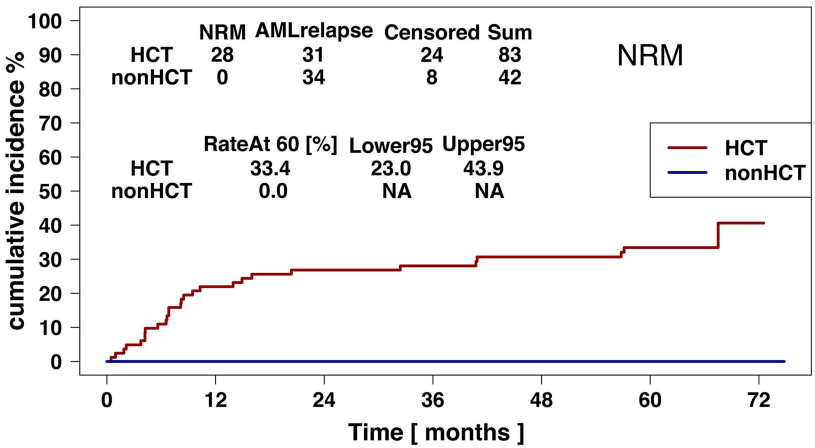
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HCT | 83(0) | 36(1) | 30(1) | 28(1) | 23(4) | 20(5) | 1(23) |
| nonHCT | 41(1) | 12(4) | 6(5) | 4(5) | 3(5) | 2(6) | 1(7) |




N at Risk (N censored)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HCT | 83(0) | 44(1) | 34(1) | 30(1) | 25(4) | 21(6) | 1(25) |
| nonHCT | 42(0) | 28(4) | 16(5) | 10(6) | 8(7) | 4(11) | 2(12) |



# Supplemental material

# Supplemental material to methods

Observation arm:

Patients with no-matched donor (n=26), patients with a mismatched donor (n=15) and patients with a matched donor refusing to be randomized or treated before randomization (n=10) were allocated to an observation group and treated at the discretion of the local investigator including HCT with mismatched donors (Figure S10).

Inclusion and exclusion criteria:

Inclusion criteria at registration were age ≥60 and ≤75 years, *de novo* or secondary AML or refractory anemia with excess blasts 5-20% in bone marrow (RAEB), ≤2 induction chemotherapies to reach CR1, Karnofsky Index >70%, and written informed consent. Patients with acute promyelocytic leukemia and Human Immunodeficiency Virus (HIV) positivity were ineligible. Inclusion criteria at randomization were previous registration in the trial, CR after first consolidation and availability of an HLA-identical related or 10/10 unrelated donor. Excluded were patients with more than one consolidation, an interval of >5 months after diagnosis, creatinine clearance <50 ml/min, cardiac ejection fraction <40%, severe pulmonary dysfunction or poorly controlled hypertension (Table S1).

Statistical Analysis

In the initial protocol, the analysis relied on the proportional hazard assumption by specifying a Cox regression adjusting for randomization strata. Assuming a 5-year LFS rate of 45% with HCT versus 25% with non-HCT and requiring 90% power with a two-sided significance level of 5%, the target sample size was 231 patients in order to observe 135 events with a 2:1 randomization. Two interim analyses after 1/3 and 2/3 of the expected events were scheduled using the O'Brien-Fleming sequential design. The time horizon was set at 5 years as initially planned. A conditional power analysis showed that with RM-LFS, reasonable power would be achieved already with a reduced target sample size of 150 randomized patients. The final analysis was performed using a nominal alpha = 5% significance level. The false positive error of the final analysis is practically not affected (Haybittle-Peto) since the first interim analysis was carried out at an alpha =0.0002 level. The changes were proposed to, and approved by, the DMC on occasion of the first planned interim analysis from 78 patients in 2014.

RM-LFS estimation and regression analyses for LFS and OS were performed using the R-package "pseudo".[21–26] As a supportive analysis, we present plots of the difference in RM-LFS as a function of

the time horizon in order to illustrate how the preference for the treatment options depends on the chosen time horizon.

# Legend to Figures

Figure S1: Study design

Figure S2: Accrual of patients to the study according to registration, assignment and randomization

Figure S3: A: Time from diagnosis to randomization for all patients (n=125)

B: Time from diagnosis to hematopoietic cell transplantation (HCT; n=66)

Figure S4: Cumulative incidence of Non Relapse mortality (NRM) according to an integrated risk score combining the most dominant parameter from the HCT-CI and the EBMT score (Versluis et al [25]) in the 66 patients with HCT

Figure S5: Cumulative incidence of acute GvHD

Figure S6: Cumulative incidence of chronic GvHD

Figure S7: Leukemia Free Survival (LFS) in the control group after relapse according to related or unrelated HCT

Figure S8: RM-LFS (A) and RM-OS (B) according to HCT vs. non-HCT. RM LFS quantifies the expected number of years alive in CR up to the time horizon with a given therapy; similarly, RM -OS gives the expected years alive at 5 years. The figure makes this phenomenon explicit depicting the difference in RM-LFS (A) and RM-OS (B) varying the time horizon. Due to early NRM, non-HCT is beneficial short term compared to HCT. For RM-LFS, HCT becomes beneficial after about 4 years.

Figure S9: Overall Survival (OS) in the non-HCT group according to HCT vs. non-HCT after relapse

Figure S10: Flow chart of the observation group

Figure S11: OS according to age groups in patients <65, 65-70 and 70+ years.

**Table S1: Eligibility criteria at registration and at randomization**

| a) at registration | | b) at randomization |
|---|---|---|
| | **inclusion criteria** | |
| • Age ≥60 and ≤75 years<br>• *De novo* or *sec.* AML or RAEB<br>• CR1 ≤2 induction chemotherapies<br>• Karnofsky Index >70%<br>• Written informed consent | | • Patient registered in the trial<br>• CR after first consolidation<br>• Matching related or unrelated donor (10/10) |
| | **exclusion criteria** | |
| • AML FAB M3<br>• HIV positivity | | • >1 consolidation cycle<br>• >5 months (>150 days) after diagnosis<br>• Creatinine clearance <50 ml/min<br>• Cardiac ejection fraction <40%<br>• Severe pulmonary dysfunction or $O_2$ support<br>• Poorly controlled hypertension |

## Table S2: Randomization by trial site

| Ntotal=245 | Randomised | % | Observation | % | Registered Only | % |
|---|---|---|---|---|---|---|
| UK Leipzig | 35 | 45.5 | 21 | 27.3 | 21 | 27.3 |
| UK Muenster | 21 | 47.7 | 17 | 38.6 | 6 | 13.6 |
| Erasmus MC Rotterdam | 14 | 50 | 1 | 3.6 | 13 | 46.4 |
| Hopitaux universitaires de Geneve | 12 | 85.7 | 2 | 14.3 | 0 | 0 |
| University Hospital Maastricht | 8 | 61.5 | 0 | 0 | 5 | 38.5 |
| VU University Medical Center Amsterdam | 6 | 46.2 | 2 | 15.4 | 5 | 38.5 |
| UK Dresden | 9 | 75 | 2 | 16.7 | 1 | 8.3 |
| Isala Klinieken, Locatie Sophia, Zwolle | 2 | 28.6 | 3 | 42.9 | 2 | 28.6 |
| UK Rostock | 4 | 57.1 | 0 | 0 | 3 | 42.9 |
| Klinikum Chemnitz gGmbH | 4 | 100 | 0 | 0 | 0 | 0 |
| UK Jena | 1 | 25 | 0 | 0 | 3 | 75 |
| UK Magdeburg | 1 | 25 | 1 | 25 | 2 | 50 |
| Academisch Ziekenhuis bij de Universiteit Amsterdam | 3 | 100 | 0 | 0 | 0 | 0 |
| Charite Berlin | 2 | 66.7 | 0 | 0 | 1 | 33.3 |
| University Hospital Basel | 1 | 33.3 | 2 | 66.7 | 0 | 0 |
| Klinikum E. v. Bergmann gGmbH, Potsdam | 2 | 100 | 0 | 0 | 0 | 0 |
| Centre Hospitalier Sud Amiens | 0 | 0 | 0 | 0 | 1 | 100 |
| CHU de Nantes | 0 | 0 | 0 | 0 | 1 | 100 |
| Kantonsspital Luzern | 0 | 0 | 1 | 100 | 0 | 0 |
| Med. UK Tuebingen | 0 | 0 | 1 | 100 | 0 | 0 |
| The Alfred Hospital, Melbourne Victoria | 0 | 0 | 0 | 0 | 1 | 100 |
| UK Aachen | 0 | 0 | 0 | 0 | 1 | 100 |
| University Medical Centre Utrecht | 0 | 0 | 1 | 100 | 0 | 0 |
| Nvalid | 125 | 51 | 54 | 22 | 66 | 26.9 |

# Table S3: Molecular alterations in randomized patients and according to treatment allocation

| | | TOTAL | | | HCT | | non-HCT | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | | n tested | % total | % positive | n=83 | % positive | n=42 | % positive | p-value |
| Molecular alterations | *BCR::ABL1* | 41 | 32.8 | 0.0 | 29 | 0.0 | 12 | 0.0 | n.a. |
| | *PML::RARalpha* | 66 | 52.8 | 0.0 | 45 | 0.0 | 21 | 0.0 | n.a. |
| | *AML1::ETO* | 82 | 65.6 | 2.4 | 55 | 1.8 | 27 | 3.7 | 1 |
| | *FLT3-ITD* | 111 | 88.8 | 19.8 | 75 | 21.3 | 36 | 16.7 | 0.747 |
| | *FLT3-TKD* | 31 | 24.8 | 0.0 | 20 | 0.0 | 11 | 0.0 | n.a. |
| | *NPM1 mutation* | 109 | 87.2 | 33.9 | 74 | 28.4 | 35 | 45.7 | 0.117 |
| | *MLL-PTD* | 36 | 28.8 | 8.3 | 25 | 8.0 | 11 | 9.1 | 1 |
| | *inv 16;CBF-beta::NYH11* | 59 | 47.2 | 3.4 | 40 | 5.0 | 19 | 0.0 | 1 |
| | *CEBPA mutation* | 80 | 64.0 | 2.5 | 55 | 1.8 | 25 | 4.0 | 0.53 |
| | *EVI* | 27 | 21.6 | 3.7 | 19 | 0.0 | 8 | 12.5 | 0.296 |
| | *JAK2* | 24 | 19.2 | 8.3 | 17 | 11.8 | 7 | 0.0 | 1 |
| | *WT1* | 27 | 21.6 | 33.3 | 18 | 27.8 | 9 | 44.4 | 0.423 |
| | *ABL1* | 16 | 12.8 | 0.0 | 11 | 0.0 | 5 | 0.0 | n.a. |
| | *ASXL1* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| | *ATRX* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| | *BCOR* | 25 | 20.0 | 8.0 | 18 | 5.6 | 7 | 14.3 | 0.49 |
| | *BCORL1* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | 1 |
| | *BRAF* | 16 | 12.8 | 0.0 | 11 | 0.0 | 5 | 0.0 | n.a. |
| | *CALR* | 25 | 20.0 | 4.0 | 18 | 0.0 | 7 | 14.3 | 0.28 |
| | *CBL* | 25 | 20.0 | 4.0 | 18 | 0.0 | 7 | 14.3 | 0.28 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *CBLB* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *CBLC* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *CDKN2A* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *CSF3R* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *CUX1* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *DNMT3A* | 26 | 20.8 | 34.6 | 19 | 31.6 | 7 | 42.9 | 0.661 |
| *ETV6/TEL* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *EZH2* | 25 | 20.0 | 12.0 | 18 | 5.6 | 7 | 28.6 | 0.18 |
| *FBXW7* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *FLT3* | 31 | 24.8 | 0.0 | 22 | 0.0 | 9 | 0.0 | n.a. |
| *GATA1* | 25 | 20.0 | 4.0 | 18 | 0.0 | 7 | 14.3 | 0.28 |
| *GATA2* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *GNAS* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *HRAS* | 27 | 21.6 | 0.0 | 19 | 0.0 | 8 | 0.0 | n.a. |
| *IDH1* | 35 | 28.0 | 5.7 | 26 | 7.7 | 9 | 0.0 | 1 |
| *IDH2* | 35 | 28.0 | 17.1 | 27 | 18.5 | 8 | 12.5 | 1 |
| *IKZF1* | 26 | 20.8 | 7.7 | 19 | 10.5 | 7 | 0.0 | 1 |
| *JAK3* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *KDM6A* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *KIT* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | n.a. |
| *KRAS* | 25 | 20.0 | 4.0 | 18 | 0.0 | 7 | 14.3 | 1 |
| *MLL* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *MPL* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *MYD88* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *NOTCH1* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | 1 |
| *NRAS* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *PDGFRA* | 25 | 20.0 | 8.0 | 18 | 5.6 | 7 | 14.3 | 0.49 |
| *PHF6* | 25 | 20.0 | 12.0 | 18 | 16.7 | 7 | 0.0 | 0.534 |
| *PTEN* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *PTPN11* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | 1 |
| *RAD21* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *RUNX1* | 25 | 20.0 | 16.0 | 18 | 16.7 | 7 | 14.3 | 1 |
| *SETBP1* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *SF3B1* | 25 | 20.0 | 4.0 | 18 | 0.0 | 7 | 14.3 | 0.28 |
| *SMC1A* | 25 | 20.0 | 0.0 | 18 | 0.0 | 7 | 0.0 | n.a. |
| *SMC3* | 27 | 21.6 | 0.0 | 19 | 0.0 | 8 | 0.0 | n.a. |
| *SRSF2* | 29 | 23.2 | 10.3 | 21 | 9.5 | 8 | 12.5 | 1 |
| *STAG2* | 27 | 21.6 | 0.0 | 20 | 0.0 | 7 | 0.0 | n.a. |
| *TET2* | 24 | 19.2 | 4.2 | 18 | 5.6 | 6 | 0.0 | 0.49 |
| *TP53* | 24 | 19.2 | 25.0 | 18 | 16.7 | 6 | 50.0 | 0.0664 |
| *U2AF1* | 25 | 20.0 | 4.0 | 18 | 5.6 | 7 | 0.0 | 1 |
| *ZRSR2* | 25 | 20.0 | 8.0 | 18 | 0.0 | 7 | 28.6 | 0.07 |

# Table S4A: Pretreatment [Induction(s) and 1st consolidation]

| Induction 1 | | | | Induction 2 | | | consolidation | | |
|---|---|---|---|---|---|---|---|---|---|
| **drug 1** | **drug 2** | **drug 3** | **n (%)** | **drug 1** | **drug 2** | **n (%)** | **drug 1** | **drug 2** | **n (%)** |
| cytarabine | Dauno | No drug/ Azacitidine/ Lena/Temsirolimus/Tosedostat | 99 (40.4) | none | | 173 (70.6) | cytarabine | | 93 (38.0) |
| cytarabine | Mito | | 73 (29.8) | cytarabine | Mito | 30 (12.2) | cytarabine | Mito ± PEG | 76 (31.0) |
| cytarabine | Ida | no drug/ATRA | 43 (17.5) | cytarabine | | 12 (4.9) | cytarabine | Amsacrine±Clofarabine | 30 (12.2) |
| Azacitidine | no | If no response day 14 cytarabine/Mito | 21 (8.6) | cytarabine | Dauno ± Azacitidine | 11 (4.5) | cytarabine | | 20 (8.2) |
| cytarabine | | | 7 (2.8) | cytarabine | ± Lena | 5 (2.0) | cytarabine | Dauno ± Tosedostat or Azacitidine | 8 (3.3) |
| cytarabine | Thio | Amsacrine | 2 (0.8) | cytarabine | Ida | 5 (2.0) | cytarabine | Ida | 5 (2.0) |
| | | | | cytarabine | Amsacrin | 4 (1.6) | cytarabine | Lena | 4 (1.6) |
| | | | | cytarabine | | 4 (1.6) | cytarabine | Eto | 4 (1.6) |
| | | | | cytarabine | Tosedostat | 1 (0.4) | cytarabine | Tosedostat | 3 (1.2) |
| | | | | | | | cytarabine | Cladribine+Midost | 1 (0.4) |
| | | | | | | | Busulfan | Cyclo | 1 (0.4) |
| Total | | | 245 (100) | | | 245 (100) | | | 245 (100) |

Abbreviations: ATRA, all-trans-retinoic acid; Cyclo, cyclophosphamide; Dauno, Daunorubicin; Eto, etoposide; Ida, idarubicin; Lena, Lenalidomide; Midost, midostaurin; Mito, Mitoxantrone; Thio, thioptepa; PEG, pegfilgrastim

# Table S4B: Consolidation therapy of the non-HCT arm

| **Therapy** | **n (%)** |
|---|---|
| High dose Cytarabine ± Mitoxantrone | 20 (57.1) |
| Busulfan+Cyclophosphamide followed by autologous HCT | 3 (8.6) |
| Etoposid and Mitoxantrone | 3 (8.6) |
| Azacytidine | 1 (2.9) |
| Not documented | 8 (22.9) |
| **Total** | **35 (100)** |

# Table S5: Multivariate analysis of Restricted Mean LFS up to 5 years

**Linear model on RM-LFS up to 5 years adjusting for cytogenetic risk and donor type**

| | mean RM-LFS in months | 95% CI lower | 95% CI upper | P Value |
|---|---|---|---|---|
| (intercept) | 27.41 | 10.73 | 44.09 | 0.0013 |
| HCT arm | 11.05 | 2.68 | 19.41 | 0.0096 |
| intermediate cytogenetic risk | -11.09 | -26.44 | 4.26 | 0.157 |
| high cytogenetic risk | -19.16 | -35.12 | -3.20 | 0.0186 |
| donor unrelated | 0.85 | -9.56 | 11.26 | 0.873 |

**Table S6: Number of patients in continuous CR, relapse and NRM according to NPM1 mutation**

| Total | HCT NPM1 mut neg | | HCT NPM1 mut pos. | | non-HCT NPM1 mut neg. | | Non-HCT NPM1 mut pos. | |
|---|---|---|---|---|---|---|---|---|
| n= 125 | n | % | n | % | n | % | n | % |
| CCR1 | 15 | 28.3 | 8 | 38.1 | 4 | 21.1 | 4 | 25 |
| Relapse | 22 | 41.5 | 6 | 28.6 | 15 | 78.9 | 12 | 75 |
| NRM | 16 | 30.2 | 7 | 33.3 | 0 | 0 | 0 | 0 |

Abbreviations: CCR, continuous complete remission; NRM, non-relapse mortality

# Table S7: Causes of death in all patients and according to treatment allocation

| | | Total | | HCT | | Non-HCT | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| Relapse | | 58 | 67.4 | 29 (7) | 50.9 (12.3) | 29 | 100.0 |
| Infection | bacterial | 11 | 12.8 | 11 | 19.3 | 0 | |
| | viral | 2 | 2.3 | 2 | 3.5 | 0 | |
| GvHD (acute/chronic) | | 6 | 7.0 | 6 | 10.5 | 0 | |
| Hemorrhage | | 4 | 4.7 | 4 | 7.0 | 0 | |
| Others | | 3 | 3.5 | 3 | 5.3 | 0 | |
| Secondary neoplasm | | 1 | 1.2 | 1 | 1.8 | 0 | |
| Graft failure | | 1 | 1.2 | 1 | 1.8 | 0 | |
| Total | | 86 | 100.0 | 57 | 100.0 | 29 | 100.0 |

**Figure S1**

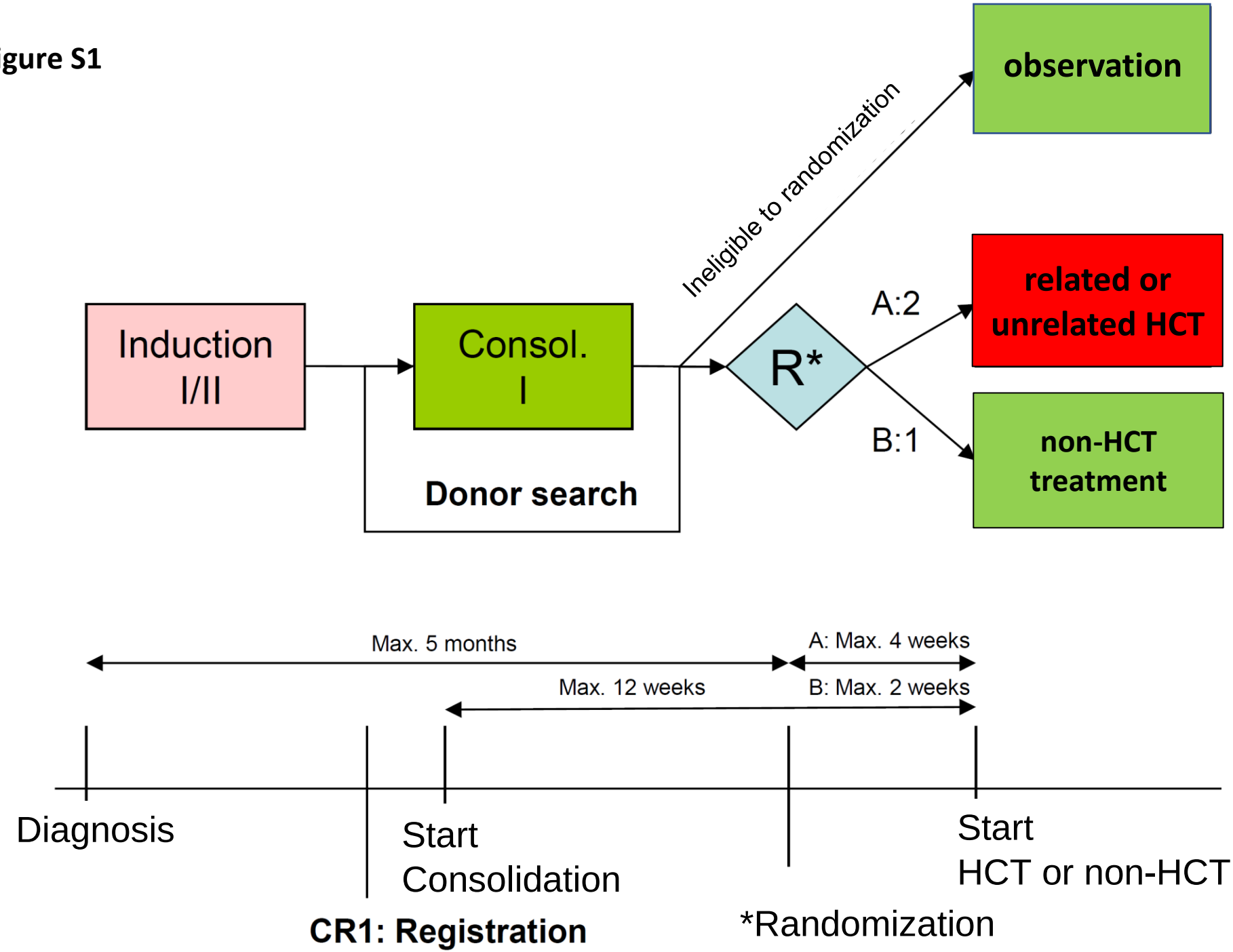

observation
Ineligible to randomization
related or unrelated HCT
A:2
Induction I/II
Consol. I
R*
B:1
non-HCT treatment
Donor search
Max. 5 months
A: Max. 4 weeks
Max. 12 weeks
B: Max. 2 weeks
Diagnosis
Start Consolidation
Start HCT or non-HCT
CR1: Registration
*Randomization

**Figure S2**

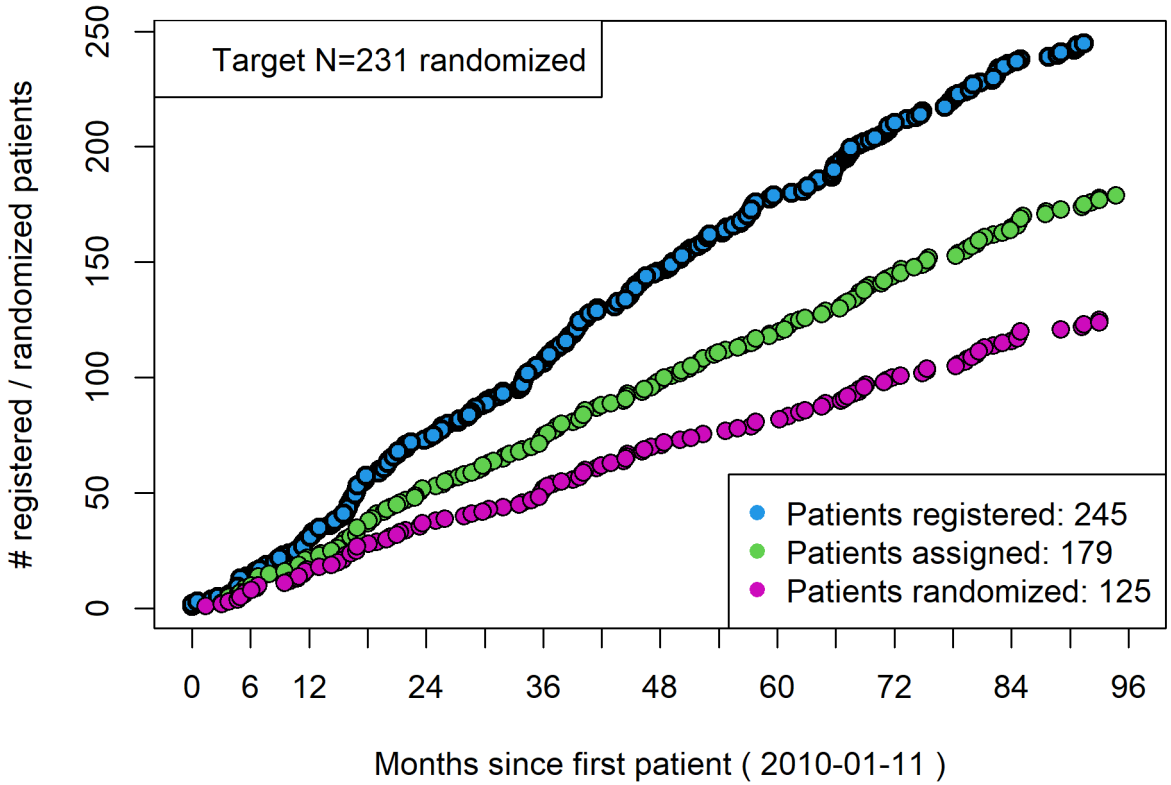

Target N=231 randomized
Patients registered: 245
Patients assigned: 179
Patients randomized: 125
# registered / randomized patients
0
50
100
150
200
250
0
6
12
24
36
48
60
72
84
96
Months since first patient ( 2010-01-11 )

**Figure S3 A**

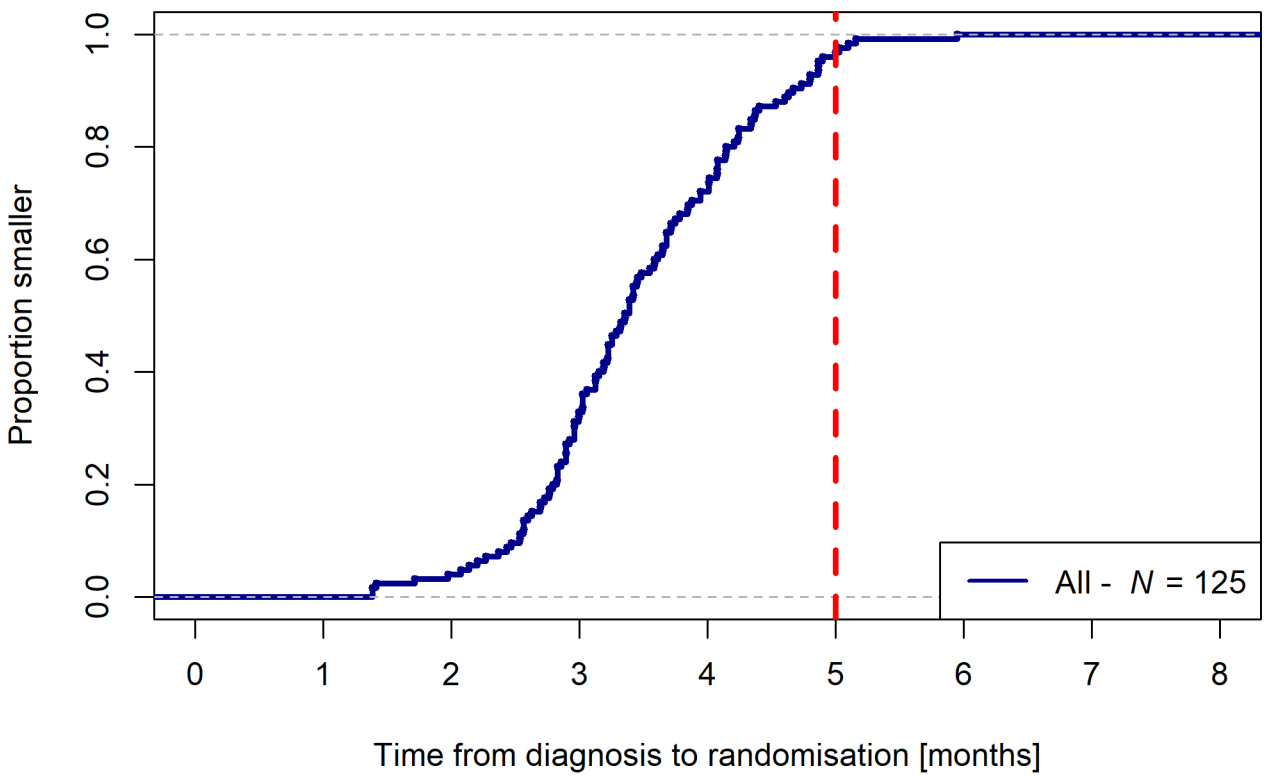

Proportion smaller
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
Time from diagnosis to randomisation [months]
All - N = 125

**Figure S3 B**

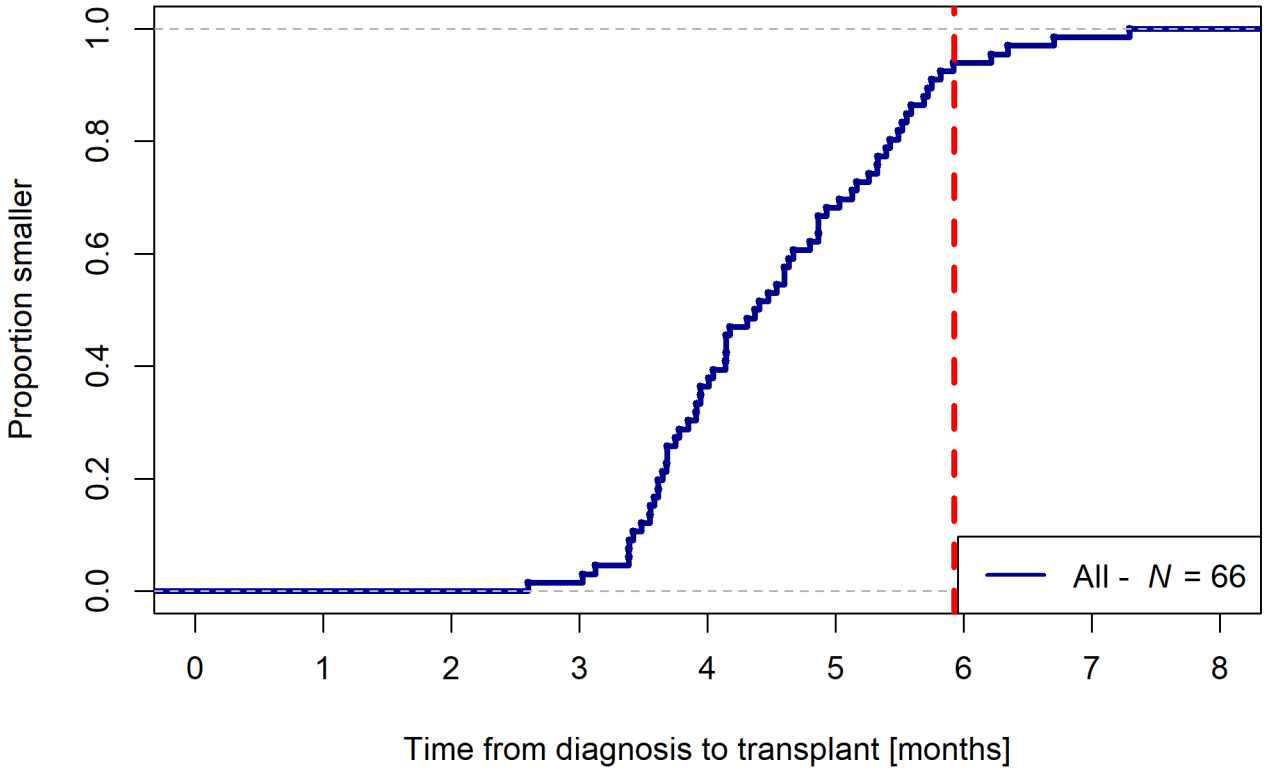

Proportion smaller
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
Time from diagnosis to transplant [months]
All - N = 66

**Figure S4**

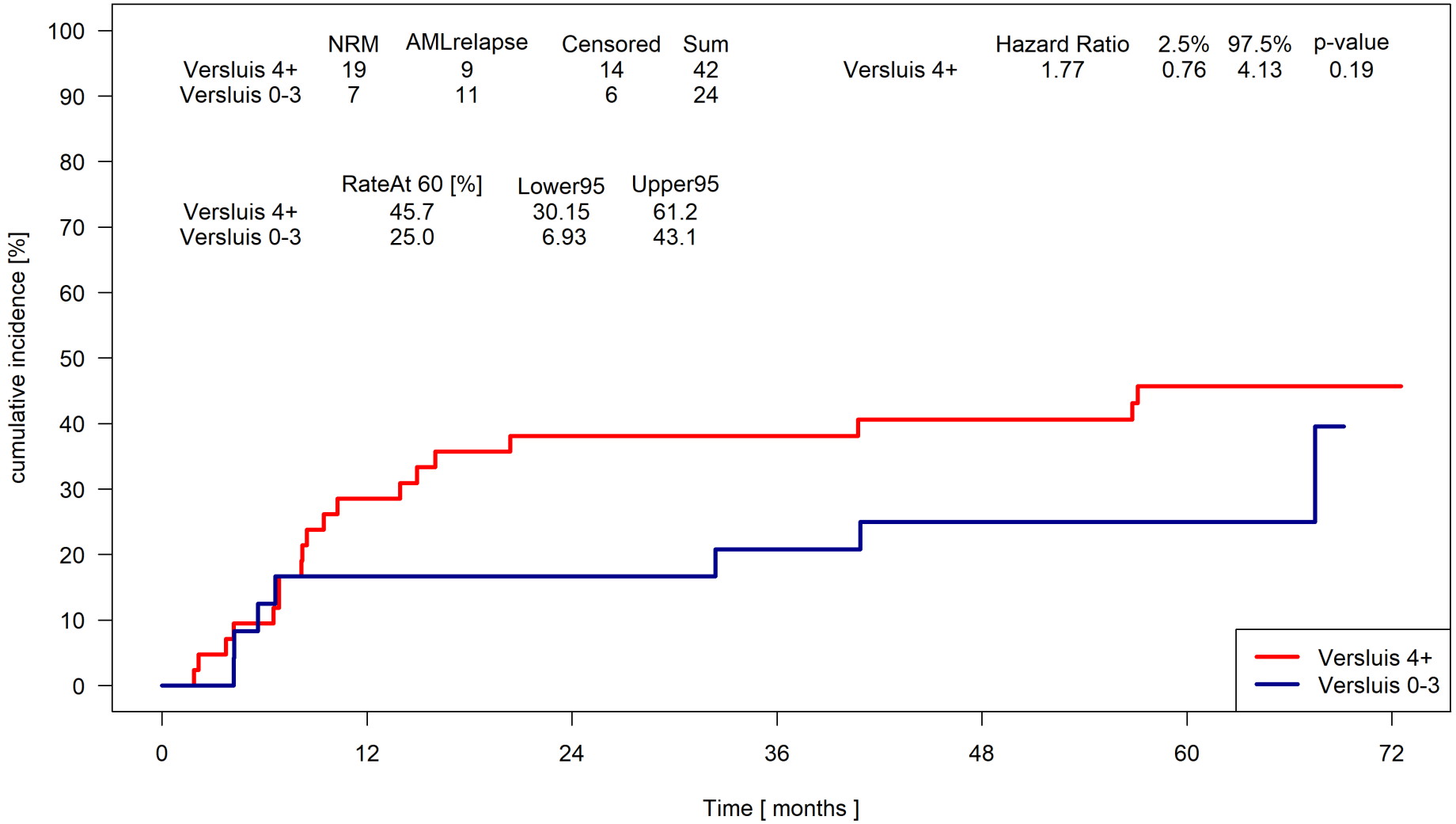

NRM AMLrelapse Censored Sum
Versluis 4+ 19 9 14 42
Versluis 0-3 7 11 6 24
Hazard Ratio 2.5% 97.5% p-value
Versluis 4+ 1.77 0.76 4.13 0.19
RateAt 60 [%] Lower95 Upper95
Versluis 4+ 45.7 30.15 61.2
Versluis 0-3 25.0 6.93 43.1
cumulative incidence [%]
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
Time [ months ]
Versluis 4+
Versluis 0-3

**Figure S5**

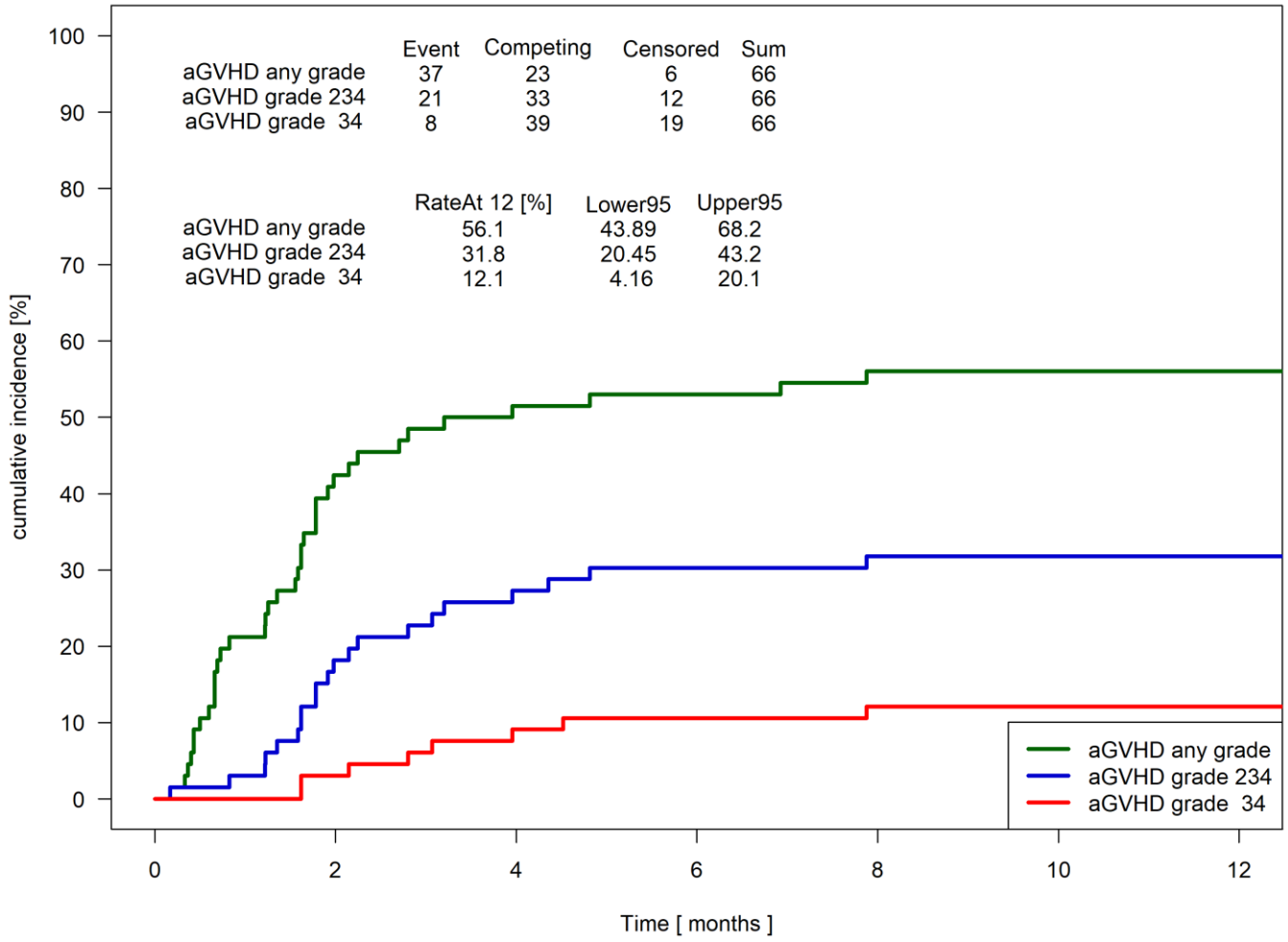

Event Competing Censored Sum
aGVHD any grade 37 23 6 66
aGVHD grade 234 21 33 12 66
aGVHD grade 34 8 39 19 66
RateAt 12 [%] Lower95 Upper95
aGVHD any grade 56.1 43.89 68.2
aGVHD grade 234 31.8 20.45 43.2
aGVHD grade 34 12.1 4.16 20.1
cumulative incidence [%]
Time [ months ]
aGVHD any grade
aGVHD grade 234
aGVHD grade 34

**Figure S6**

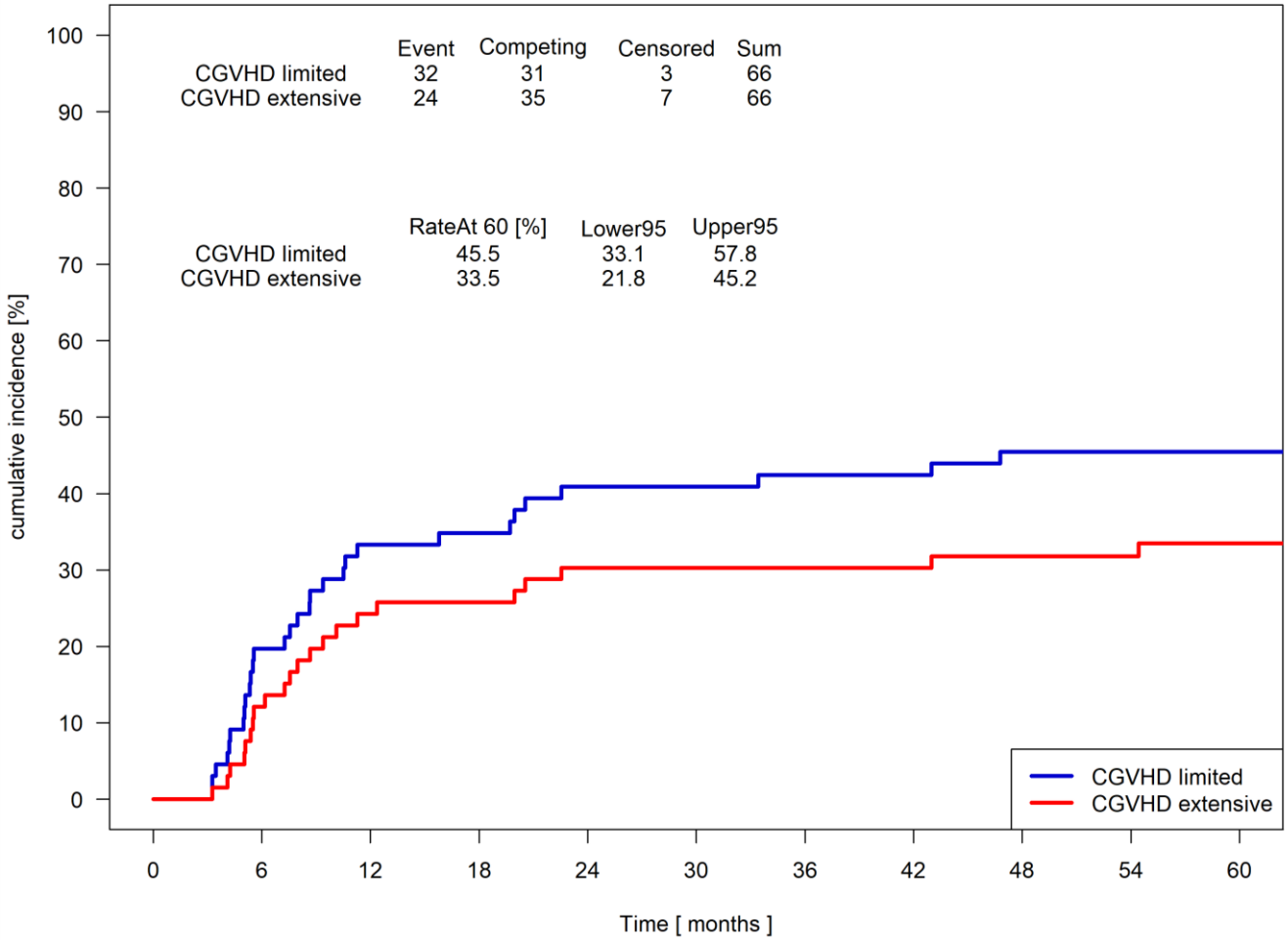
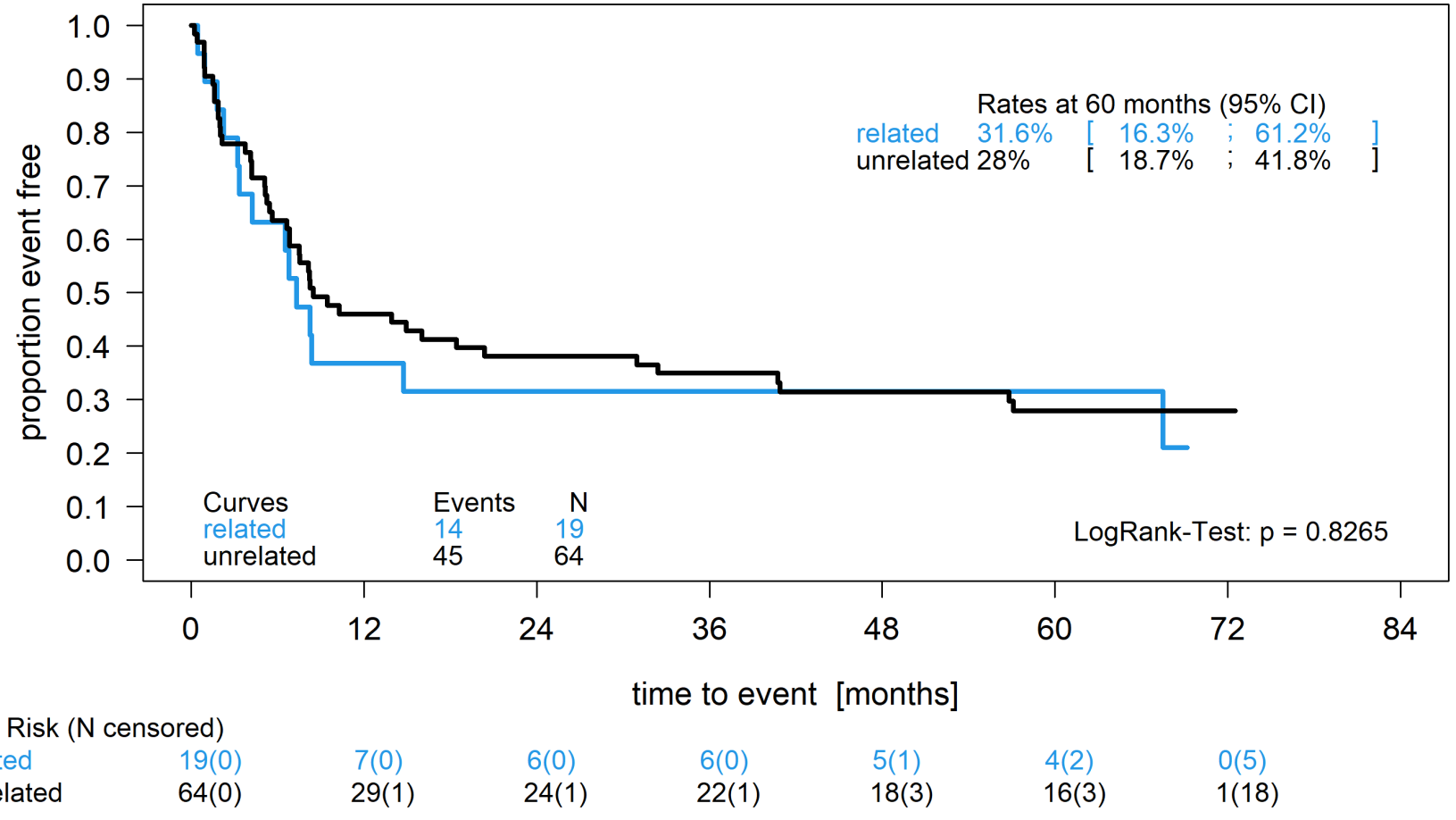

Event Competing Censored Sum
CGVHD limited 32 31 3 66
CGVHD extensive 24 35 7 66
RateAt 60 [%] Lower95 Upper95
CGVHD limited 45.5 33.1 57.8
CGVHD extensive 33.5 21.8 45.2
cumulative incidence [%]
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
Time [ months ]
CGVHD limited
CGVHD extensive

**Figure S7**




| N at Risk (N censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| related | 19(0) | 7(0) | 6(0) | 6(0) | 5(1) | 4(2) | 0(5) |
| unrelated | 64(0) | 29(1) | 24(1) | 22(1) | 18(3) | 16(3) | 1(18) |

**Figure S8 A**

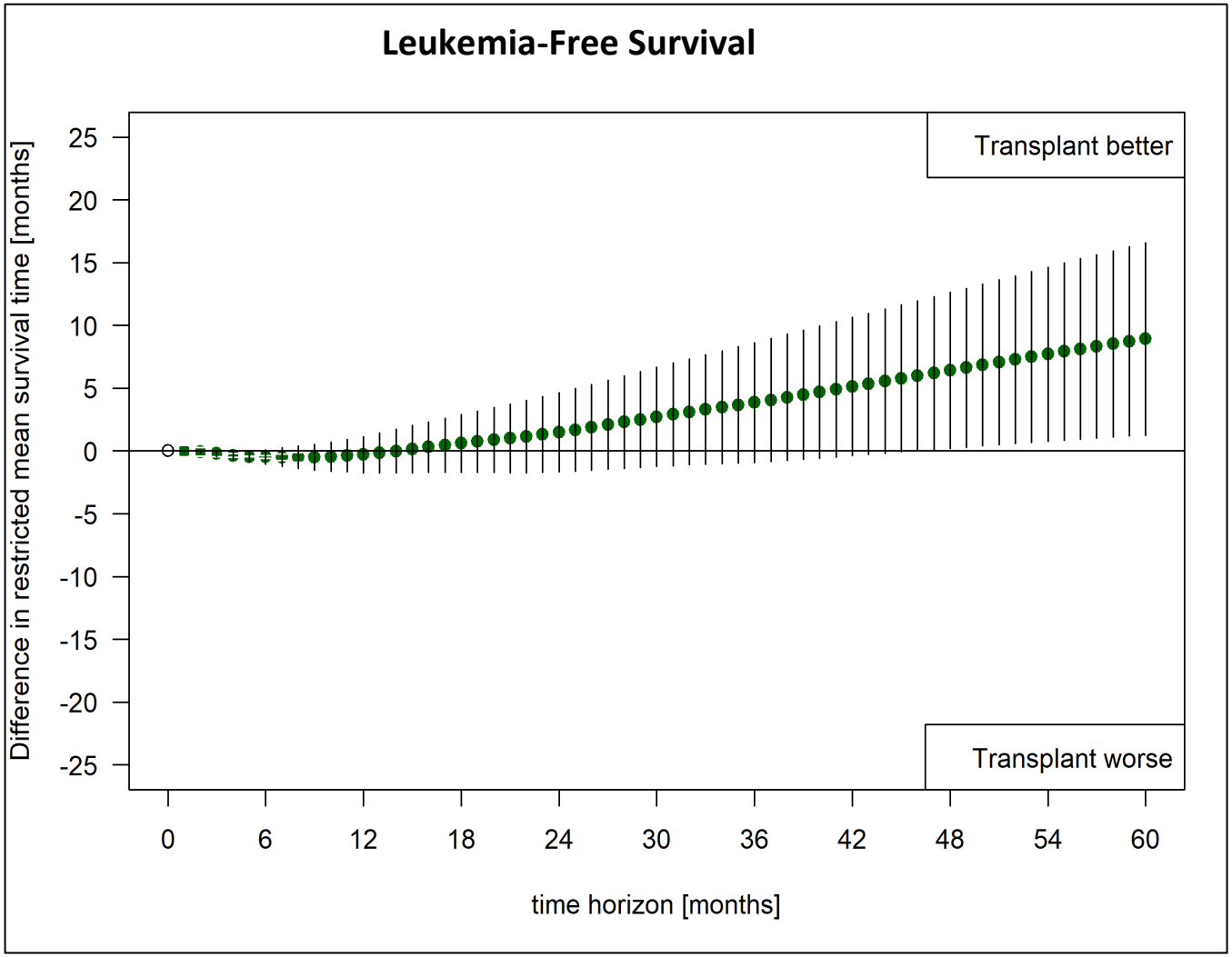

Leukemia-Free Survival
Transplant better
Transplant worse
Difference in restricted mean survival time [months]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
6
12
18
24
30
36
42
48
54
60
time horizon [months]

**Figure S8 B**

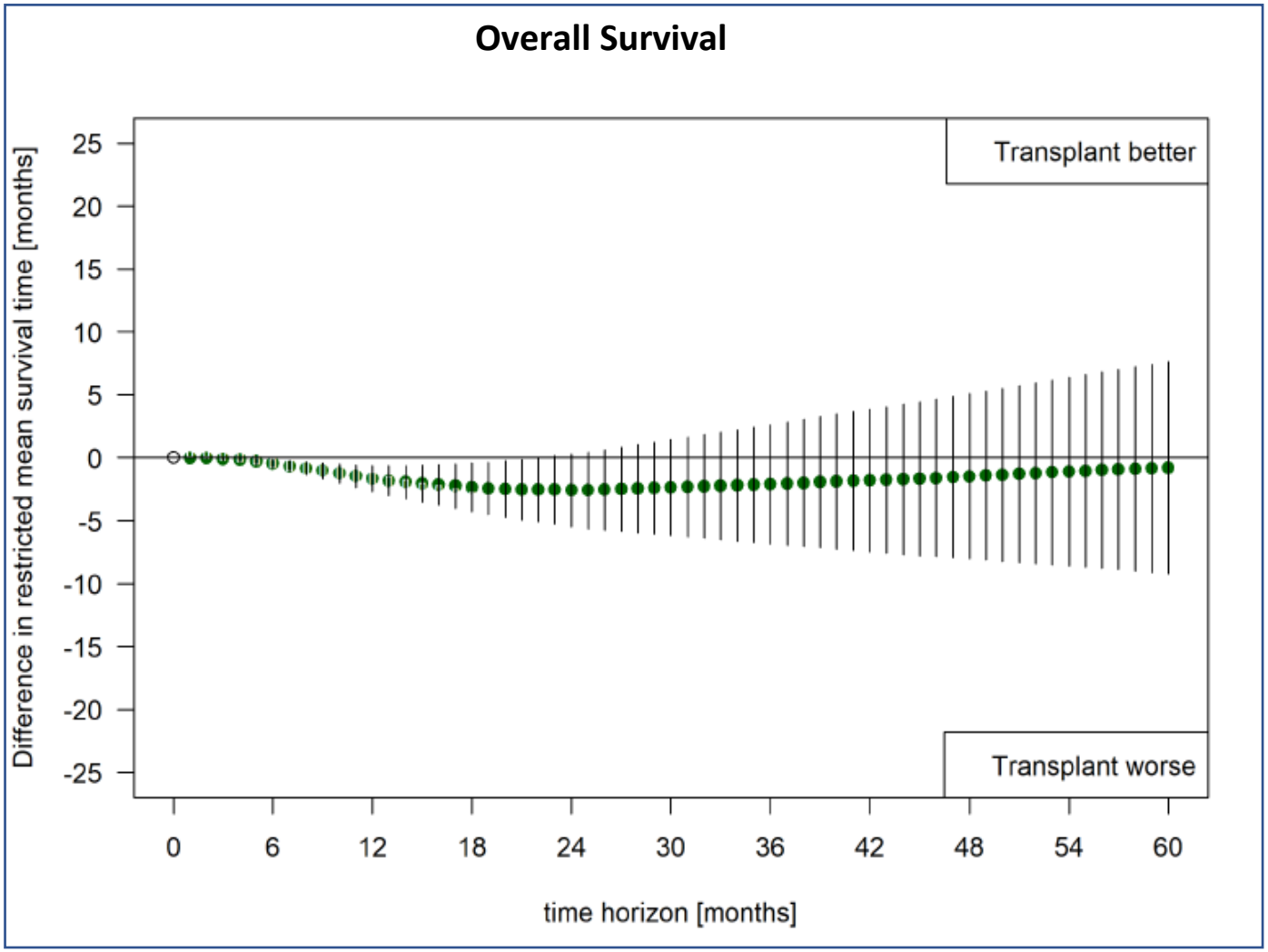

Overall Survival
Transplant better
Transplant worse
Difference in restricted mean survival time [months]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
6
12
18
24
30
36
42
48
54
60
time horizon [months]

**Figure S9**

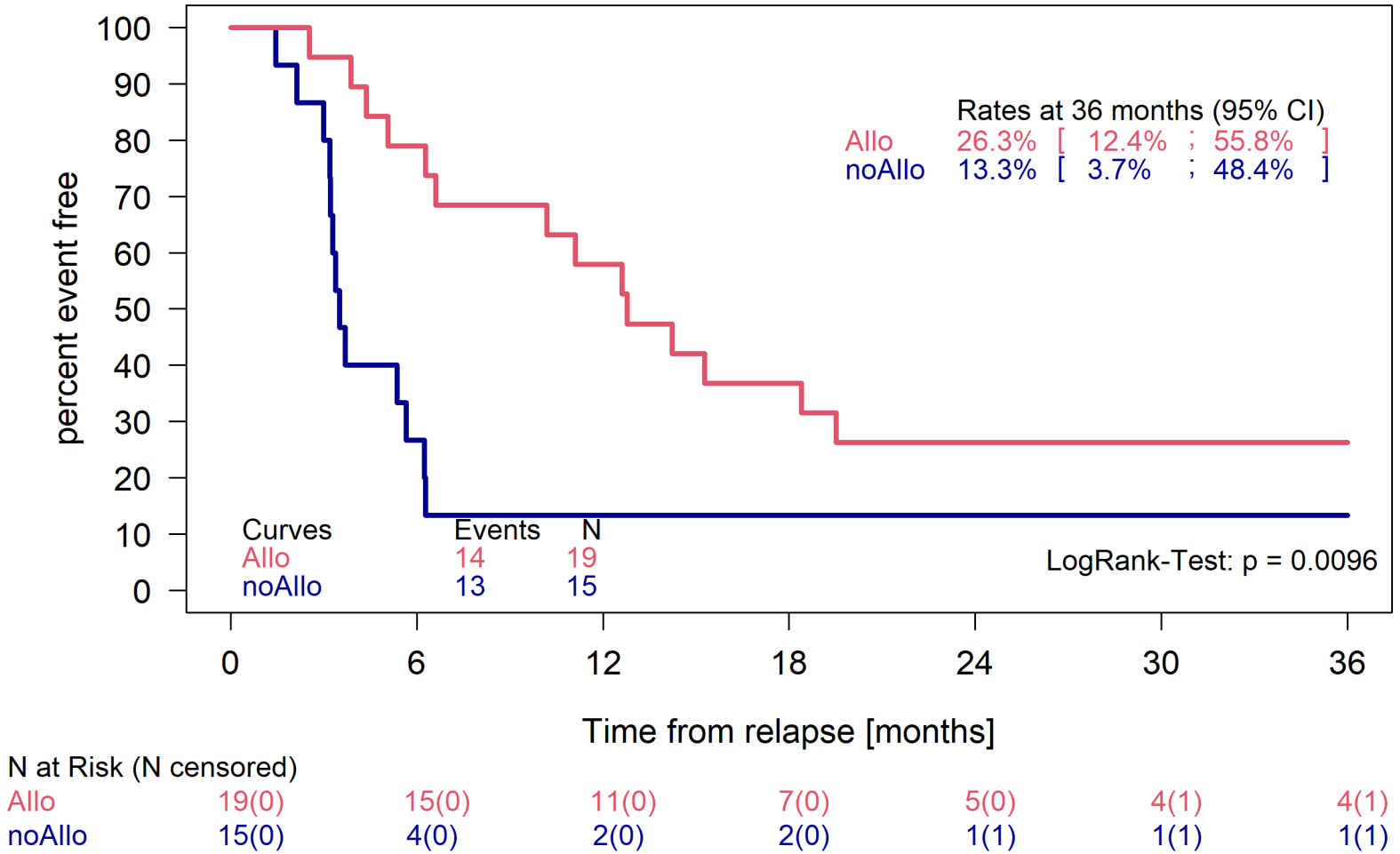

100
90
80
70
60
50
40
30
20
10
0
percent event free
Rates at 36 months (95% CI)
Allo 26.3% [ 12.4% ; 55.8% ]
noAllo 13.3% [ 3.7% ; 48.4% ]
Curves Events N
Allo 14 19
noAllo 13 15
LogRank-Test: p = 0.0096
0
6
12
18
24
30
36
Time from relapse [months]
N at Risk (N censored)
Allo 19(0) 15(0) 11(0) 7(0) 5(0) 4(1) 4(1)
noAllo 15(0) 4(0) 2(0) 2(0) 1(1) 1(1) 1(1)

**Figure S10**

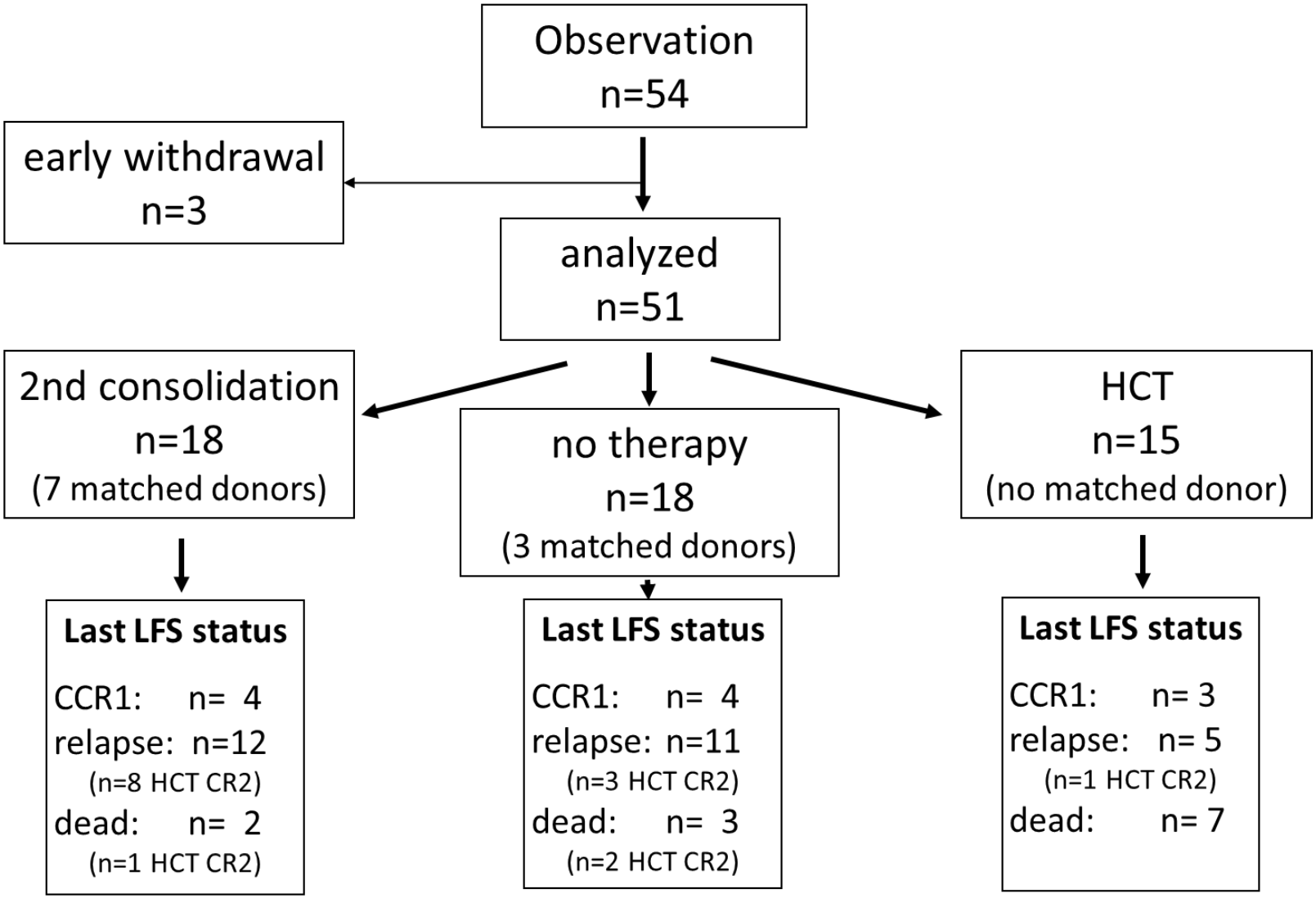
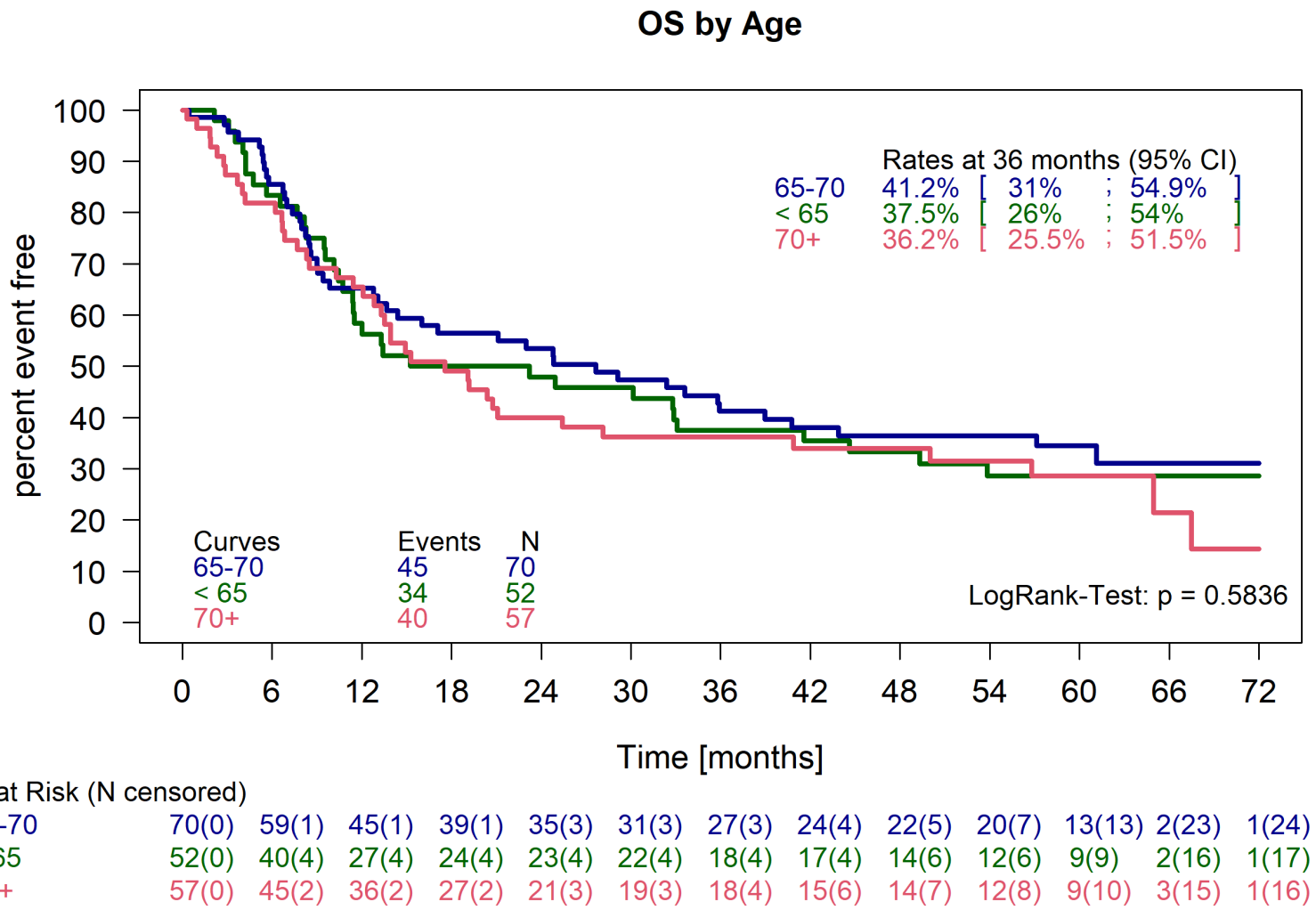

Observation
n=54
early withdrawal
n=3
analyzed
n=51
2nd consolidation
n=18
(7 matched donors)
no therapy
n=18
(3 matched donors)
HCT
n=15
(no matched donor)
Last LFS status
CCR1: n= 4
relapse: n=12
(n=8 HCT CR2)
dead: n= 2
(n=1 HCT CR2)
Last LFS status
CCR1: n= 4
relapse: n=11
(n=3 HCT CR2)
dead: n= 3
(n=2 HCT CR2)
Last LFS status
CCR1: n= 3
relapse: n= 5
(n=1 HCT CR2)
dead: n= 7

**Figure S11**




N at Risk (N censored)

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 65-70 | 70(0) | 59(1) | 45(1) | 39(1) | 35(3) | 31(3) | 27(3) | 24(4) | 22(5) | 20(7) | 13(13) | 2(23) | 1(24) |
| < 65 | 52(0) | 40(4) | 27(4) | 24(4) | 23(4) | 22(4) | 18(4) | 17(4) | 14(6) | 12(6) | 9(9) | 2(16) | 1(17) |
| 70+ | 57(0) | 45(2) | 36(2) | 27(2) | 21(3) | 19(3) | 18(4) | 15(6) | 14(7) | 12(8) | 9(10) | 3(15) | 1(16) |