

Measurable residual disease-guided therapy in intermediate-risk acute myeloid leukemia patients is a valuable strategy in reducing allogeneic transplantation without negatively affecting survival

Treatment of patients with acute myeloid leukemia (AML) fit to receive intensive treatment and under 65 years of age consists of one or two cycles of high-dose induction (“3+7”) chemotherapy (C1 or C2) followed by different options of post-remission treatment.¹ These options include allogeneic stem cell transplantation (allo-SCT), continuation with chemotherapy or high-dose chemotherapy with autologous-SCT (auto-SCT).² Choosing the right consolidation treatment is a trade-off between anti-leukemic effect and treatment safety. Relapse chances are lowest after allo-SCT, but this treatment modality is also associated with considerable therapy-related morbidity (e.g., graft-versus-host disease), reduced quality of life, and higher procedure-related mortality.^{3,4} Therefore, for patients with a relatively favorable outcome (i.e., core-binding factor AML), allo-SCT is often avoided as first-line consolidation treatment. In contrast, for patients with an adverse-risk disease (if deemed feasible) this additional anti-leukemic effect is needed, making allo-SCT the preferred post-remission treatment option. For patients with intermediate-risk AML, the optimal post-remission therapy is still a subject of debate.⁵ Measurable residual disease (MRD) assessment, by multiparameter flow cytometry (MFC) and/or by *NPM1* gene mutation reverse transcriptase polymerase chain reaction (RT-PCR), has been proposed to guide this decision due to the strong prognostic value and the ability to predict relapse when applied in complete remission (CR) (or CR with incomplete hematologic recovery [CRi], according to the 2017 European LeukemiaNet [ELN] classification) after C2.^{1,6} Therefore, the presence of MRD at this time point may warrant an allo-SCT as additional intensive therapy.² In contrast, patients in CRi without MRD before transplant have a relatively low risk of relapse and therefore allo-SCT may be omitted.⁷ According to the protocol of the HOVON-SAKK132 trial (HO132: registered as NTR4376; available from the Netherlands Trial Register at <https://trialssearch.who.int/>), the choice of post-remission therapy in intermediate-risk patients was guided by MRD status defined by MFC (>0.1%) and mutant *NPM1* (>10⁻⁴). Patients with MRD were recommended to receive allo-SCT while patients without MRD were recommended to proceed with less intensive non-allo treatment (auto-SCT or a third cycle of chemotherapy).¹ Notably, the previously reported analysis on the HO132 trial showed no difference in relapse-free survival for the ELN-2017 intermediate-risk category,

which may suggest the positive effect of MRD guidance.⁸ In order to better understand the influence of MRD guidance, we present a more detailed analysis of the results of MRD-guided post-remission therapy for intermediate-risk AML or high-risk myelodysplastic syndrome (MDS) patients in relation to treatment outcome in the HO132 trial, including a per protocol analysis. In addition, since the HO132 was guided by MRD status, we compared this MRD-guided cohort to an unguided cohort using a propensity score match (PSM) analysis. This unguided matched control group was derived from previous HOVON-SAKK trials that had no MRD-guided post-remission therapy.

A total of 153 ELN intermediate-risk patients in the HO132 trial (also including patients enrolled in the run-in phase) were in CRi and had a MRD result after C2 as assessed by either leukemia-associated immunophenotype detection with MFC and/or by RT-PCR for mutated *NPM1*, according to earlier published guidelines.^{2,9} Of these 153 patients, 110 (72%) were MRD-negative (by both techniques), of which 44/110 (40%) received, as advised per protocol, non-allo-SCT consolidation therapy and 48/110 (44%) patients received an allo-SCT. The other 18 patients (16%) received no consolidation therapy, mainly due to an early relapse. Reasons for deviating from the advised protocol treatment were not systematically collected, but MRD-negative patients who received allo-SCT had significantly more complex karyotype (45.8% vs. 4.5%) and were more often in first CR after C2 instead of C1 (33.3% vs. 4.5%), compared to MRD-negative non-allo consolidated patients. Protocol adherence was better for MRD-positive patients, with 36/43 (84%) receiving the per protocol recommended allo-SCT. Survival differences were analyzed using Kaplan-Meier curves for event-free survival (EFS) and overall survival (OS), with Cox regression accounting for clustering. There was no significant difference in EFS, defined as the time between MRD-assessment after C2 in CRi and relapse or death, between the patients with and without MRD (hazards ratio [HR]: 1.24; 95% CI: 0.75-2.00; *P*=0.42) (Figure 1A), with an EFS after 36 months of 47% compared to 54%, respectively. OS (defined as the time between MRD-assessment in CRi and death or censoring) (HR: 1.50; 95% CI: 0.85-2.64; *P*=0.16) (Figure 1B) seems to be slightly worse for MRD-positive patients (5-year OS 54% compared to 65% for MRD-negative), although not statistically significant. Both EFS and OS were in line with

recently published HOVON-SAKK trials.^{8,11} For MRD-negative patients, we also compared the patients who, contrary to trial protocol, received allo-SCT with patients who received non-allo-SCT treatment according to protocol. Between these two groups, there were no apparent significant differences in EFS (HR: 0.69; 95% CI: 0.37-1.29; $P=0.24$) (Figure 1C)

nor in OS (HR: 1.24; 95% CI: 0.59-2.63; $P=0.57$) (Figure 1D). However, the sequence of events did differ between MRD-negative patients treated with allo-SCT *versus* non-allo-SCT. A total of 15/48 (31%) of allo-SCT treated patients relapsed within three years after CR, of whom most (93%, 14/15) died within ten months after relapse. Although in the non-allo-SCT

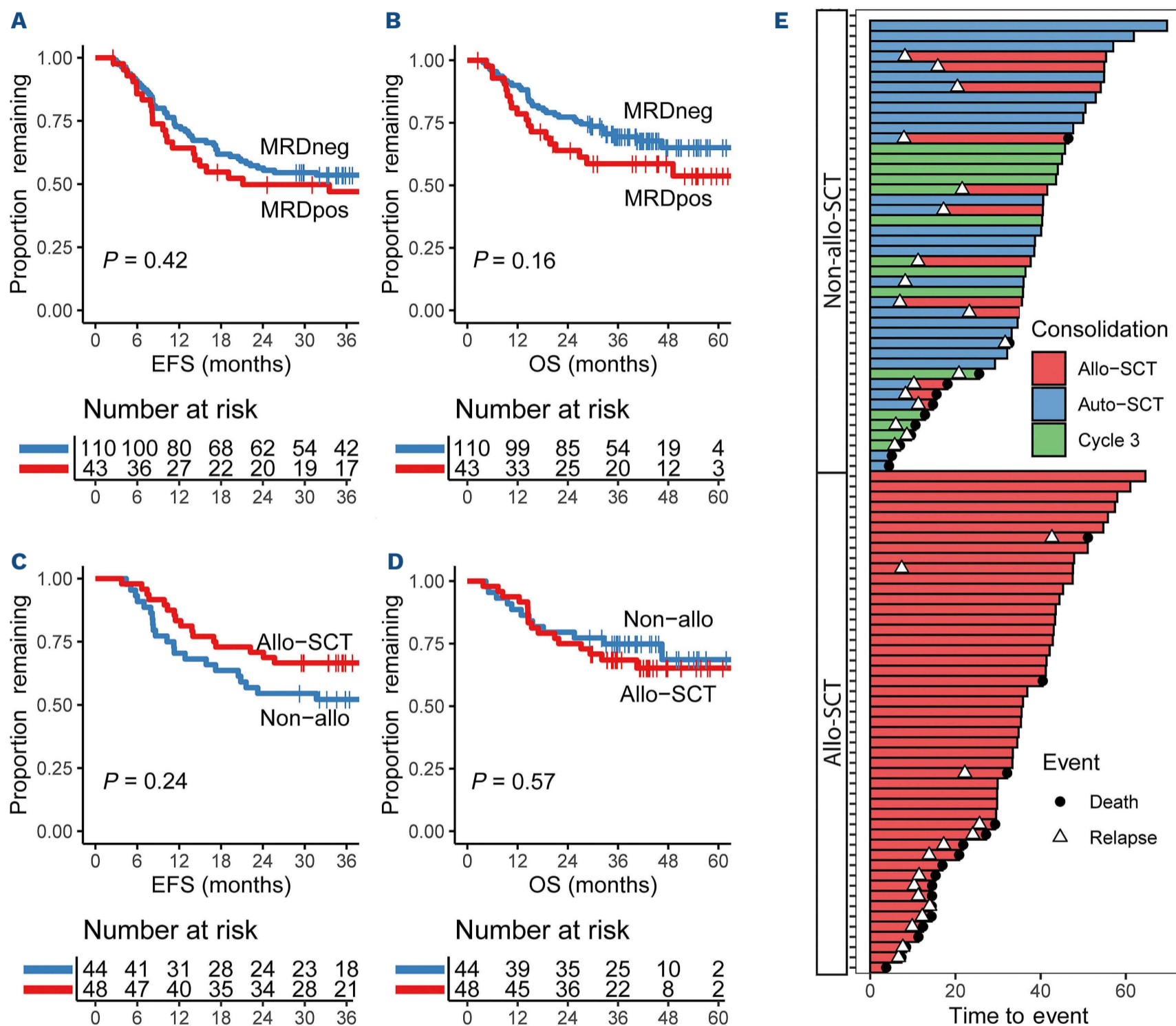
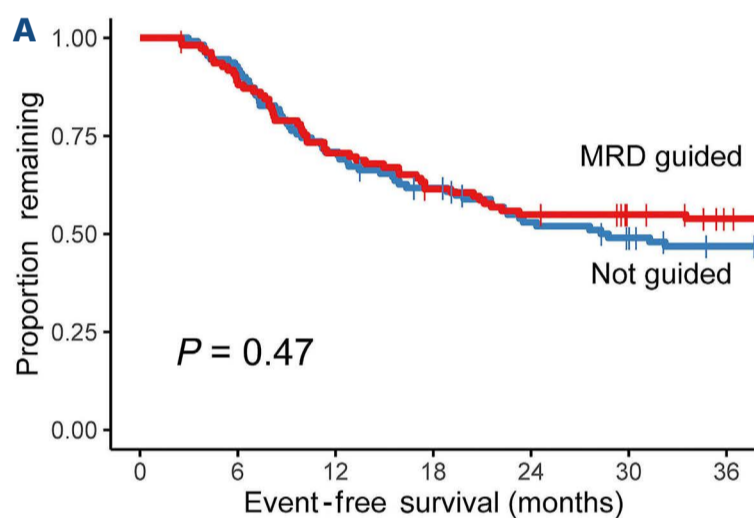


Figure 1. Survival of European LeukemiaNet (ELN) intermediate-risk patients in the measurable residual disease (MRD)-guided HO132 trial and subgroup analyses for MRD-negative patients after two cycles of induction chemotherapy. (A) In the HO132 trial, a total of 153 patients with an MRD result were ELN intermediate-risk, of which 110 (72%) were (MRDneg) after two cycles of chemotherapy. There was no significant difference in event-free survival (EFS) assessed using Cox regression between MRDneg and MRDpos patients (HR: 1.24; 95% CI: 0.75-2.00; $P=0.42$). (B) Neither was there any significant difference in overall survival (OS) between MRDneg and MRDpos patients (HR: 1.50; 95% CI: 0.85-2.64; $P=0.16$). (C) A subgroup analysis of the intermediate-risk MRDneg patients in the HO132 trial showed no difference in EFS between 44 patients who received the recommended non-allo (cycle 3 or auto-SCT) consolidation treatment compared to 48 patients who received an allo-SCT (HR: 0.69; 95% CI: 0.37-1.29; $P=0.24$). (D) The same subgroup also showed no difference in OS between patients treated with non-allo and allo-SCT (HR: 1.24; 95% CI: 0.59-2.63; $P=0.57$). (E) Swimmer plot of MRDneg patients in the HO132 (MRD-guided) study ordered by first post-remission therapy (y-axis) and OS (x-axis). The non-allo-stem cell transplant (SCT) group consists of 30 patients who received an auto-SCT and 14 patients who received a third cycle of chemotherapy. The majority (67%, 12/18 patients) of the relapsed patients (symbolized by a triangle) who initially received a non-allo consolidation therapy were able to undergo a delayed allo-SCT after successful salvage therapy (red beam). (The HO132 trial is registered as NTR4376; available from the Netherlands Trial Register at <https://trialsearch.who.int/>)

group 18/44 (41%) relapsed, 12 patients could be successfully salvaged with a (delayed) allo-SCT, which was followed by a long leukemia-free follow-up for 10/18 (55%) patients (Figure 1E). Importantly, for MRD-negative patients, 32 allo-SCT could be averted and 12 postponed without negatively affecting EFS and OS compared to the patients treated with allo-SCT. Therefore, based on these results from the HO132 trial, non-allo-SCT treatment options seem to be justified for intermediate-risk MRD-negative patients.

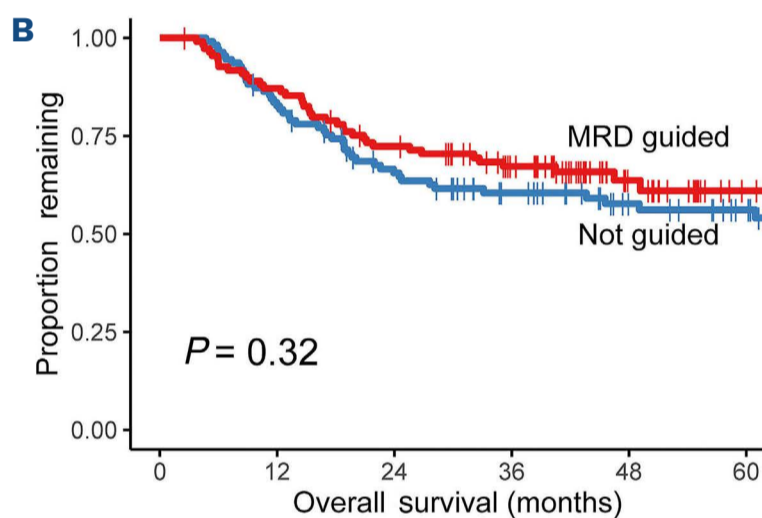
Although benefits of MRD-guided therapy would preferably be evaluated in a randomized controlled trial (RCT), we do not consider this realistic due to the extensive use of MRD in daily practice and the current evidence for the prognostic value of MRD. In addition, no such AML trials are currently reported to be ongoing or planned. Hence, we simulated the analysis by comparing survival of the MRD-guided intermediate-risk patients from the HO132 trial (conducted from 2014

to 2017) to an MRD-unguided cohort from HOVON-SAKK phase II/III trials (HO42A: NTR230; HO81: NTR904; HO92: NTR1446; HO102: NTR2187; all available from the Netherlands Trial Register at <https://trialsearch.who.int/>), conducted from 2006 to 2013.^{7,10-12} The principle of measuring MRD and gating strategy remained the same across the studies and followed a strict protocol.⁹ Via PSM,¹³ the intermediate-risk patients derived from the unguided studies in CR with MRD measurement after C2 (n=150) were matched to the HO132 MRD-guided patients using six baseline variables that are associated with survival: age, white blood cell count at diagnosis, WHO classification, karyotype, *NPM1* status, and *FLT3-ITD* status (*Online Supplementary Figure S1*). The MRD-guided and unguided studies included in our analyses were randomized for an investigational treatment, but no significant differences in EFS or OS were observed between the standard and the investigational arms for included patients



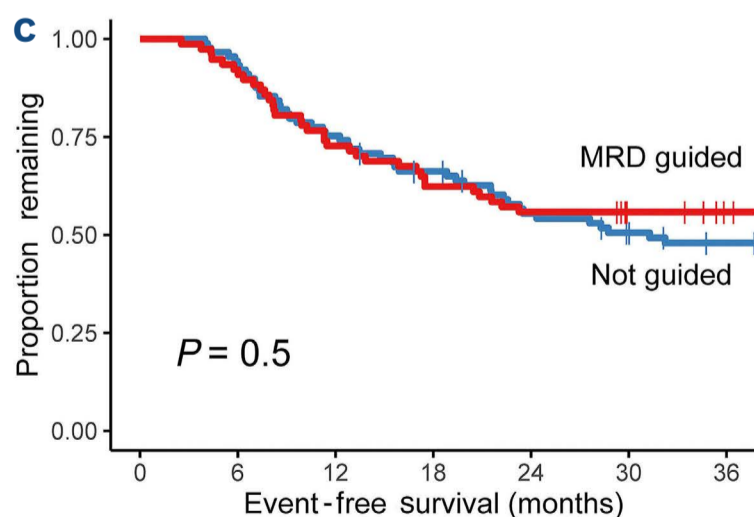
Number at risk

—	110	101	78	66	54	48	42
—	110	97	77	66	59	53	46
	0	6	12	18	24	30	36



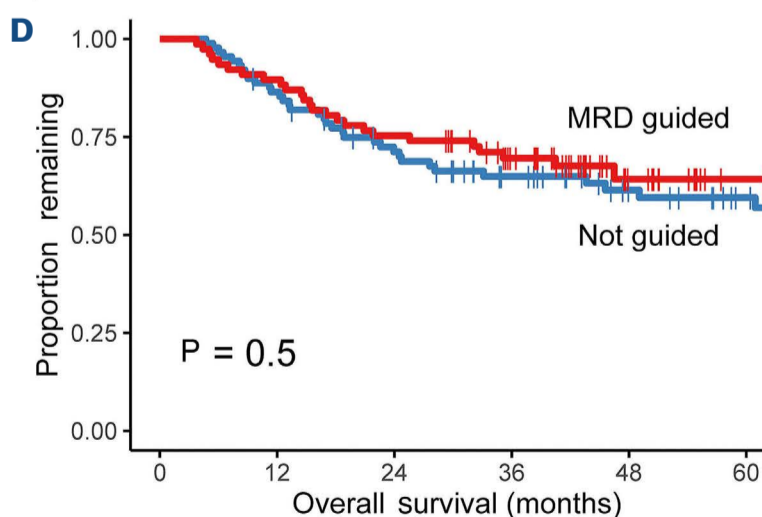
Number at risk

—	110	90	66	52	37	29
—	110	95	77	57	24	6
	0	12	24	36	48	60



Number at risk

—	89	83	67	57	46	40	35
—	77	71	56	48	43	38	33
	0	6	12	18	24	30	36



Number at risk

—	89	76	58	45	32	24
—	77	69	58	41	15	3
	0	12	24	36	48	60

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Figure 2. Survival by propensity score match analysis between measurable residual disease (MRD)-unguided and MRD-guided groups, and subgroup analysis of only MRD-negative patients. (A) Event-free survival (EFS) after 36 months was 47% for the MRD-unguided group and 54% for the MRD-guided group (Hazard Ratio [HR]: 0.87; 95% confidence interval [CI]: 0.60-1.26; $P=0.47$). (B) Overall survival (OS) after 60 months was 56% in the MRD-unguided group and 61% in the MRD-guided group (HR: 0.80; 95% CI: 0.52-1.24; $P=0.32$). (C) EFS for MRD-negative patients after 36 months was 48% in the unguided group compared to 56% in the MRD-guided group (HR: 0.86; 95% CI: 0.56-1.33; $P=0.50$). (D) OS after 60 months was 60% in the unguided group, compared to 64% in the MRD-guided group (HR: 0.84; 95% CI: 0.50-1.40; $P=0.50$).

(*Online Supplementary Figure S2*); hence, investigational treatment was omitted in the matching. We used the ‘nearest neighbor’ matching technique with a caliper (maximum distance between cases) of 0.25, because this rendered the lowest standardized mean difference of 0.09.¹⁴ This resulted in 110 matches with similar patient characteristics. All clinical features between the MRD-guided and matched control group were comparable, except for more karyotype abnormalities in the MRD-guided cohort (*Online Supplementary Table S1*). EFS after 36 months was comparable between the MRD-guided group (54%) and the historical control cohort (47%) (HR: 0.87; 95% CI: 0.60-1.26; $P=0.47$) (Figure 2A). In addition, the same comparable results were found for OS with a 61% survival rate for MRD-guided and 56% for the unguided cohort after 60 months (HR: 0.80; 95% CI: 0.52-1.24; $P=0.32$) (Figure 2B). Between the two cohorts, preferred consolidation treatment had only changed for MRD-negative patients. In former HOVON-SAKK trials, all intermediate-risk patients had been advised to receive an allo-SCT, which changed to only for the MRD-positive patients in the HO132 trial. Therefore, a separate subgroup analysis was carried out for only MRD-negative patients, which showed that there was no significant difference in EFS after three years (HR: 0.86; 95% CI: 0.56-1.33; $P=0.50$) or OS after five years (HR: 0.84; 95% CI: 0.50-1.40; $P=0.50$) between unguided and guided MRD-negative patients (Figure 2C, D). These results again suggest that MRD-guidance for consolidation selection in intermediate-risk patients allows allo-SCT treatment to be safely circumvented without having a negative impact on EFS or OS, which is in accordance with previous data provided by the GIMEMA AML1310 trial.¹⁵

We wish to add that the PSM method is a valuable alternative for RCT to compare two groups, although it is less preferred because of possible unequal distributions of unknown confounding factors. In addition, due to matching with historical data, the time frame in which patients were treated differed, which may have influenced survival due to changes in patient care, such as supportive care. Here, these effects seem relatively limited since OS did not deviate between patients included from different studies (*Online Supplementary Figure S2*). Unfortunately, for both cohorts, the exact reasons for choosing a specific consolidation treatment are not known. The conclusions of the retrospective PSM-based comparison with historical non-guided data are based on non-statistical significant data with a broad confidence interval. Nevertheless, these conclusions are substantiated by the results from the in-depth subgroup

analysis of the MRD-guided patients in the HO132 trial, which also support the value of MRD-negativity for selecting a less intensive consolidation treatment than allo-SCT for intermediate-risk patients. Future improvements to MRD assays can potentially further increase appropriate MRD-guided post remission therapy.

Authors

Jesse M. Tettero,^{1,2} Lok Lam Ngai,^{1,2} Costa Bachas,^{1,2} Dimitri A. Breems,³ Thomas Fischer,⁴ Bjorn T. Gjertsen,⁵ Patrycja Gradowska,⁶ Laimonas Griskevicius,⁷ Jeroen J.W.M. Janssen,^{1,2} Gunnar Juliusson,⁸ Johan Maertens,⁹ Markus G. Manz,^{10,11} Thomas Pabst,^{11,12} Jakob Passweg,^{11,13} Kimmo Porkka,¹⁴ Peter J.M. Valk,¹⁵ Bob Löwenberg,¹⁵ Gert J. Ossenkoppele^{1,2} and Jacqueline Cloos^{1,2}

¹Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands; ²Imaging and Biomarkers, Cancer Center Amsterdam, Amsterdam, The Netherlands; ³Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium; ⁴Otto von Guericke University Hospital Magdeburg, Magdeburg, Germany; ⁵Haukeland University Hospital, Bergen, Norway; ⁶Dutch-Belgian Hemato-Oncology Cooperative Group Data Center-Erasmus MC Cancer Institute, Rotterdam, The Netherlands; ⁷Vilnius University Hospital Santaros Klinikos and Vilnius University, Vilnius, Lithuania; ⁸Skanes University Hospital, Lund, Sweden; ⁹University Hospital Gasthuisberg, Leuven, Belgium; ¹⁰University Hospital, Zurich, Switzerland; ¹¹Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland; ¹²Department of Medical Oncology, Inselspital; University Hospital, Bern, Switzerland; ¹³University Hospital, Basel, Switzerland; ¹⁴Helsinki University Hospital Cancer Center, Helsinki, Finland and ¹⁵Erasmus University Medical Center (MC) and Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence:

J. CLOOS - j.cloos@amsterdamumc.nl

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Disclosures

BG serves as a consultant for BerGenBio, Pfizer Inc., and Novartis, and holds stock options in Alden Cancer Therapy and KinN Therapeutics. JJ serves as a consultant for Bristol-Myers Squibb, Novartis, Pfizer Inc., has received research funding from Bristol-Myers Squibb, Novartis, Incyte Biosciences Benelux BV, Uppsala County Council, Glycomimetics, Avillion and Ellipses Pharma, is a Speaker Bureau member for Incyte Biosciences Benelux BV, Roche and Celgene, and holds a membership on an entity's Board of Directors for Celgene. MM serves as a consultant for CDR-Life Inc., holds stock options in CDR-Life Inc., and has a patent licensed to the University of Zurich. BL holds a membership on an entity's Board of Directors for AbbVie, Astellas, Catamaran Bio Inc., Bristol-Myers Squibb, Celgene, and F. Hoffmann La Roche, serves as a consultant for Clear Creek Bio, and has received honoraria from Clear Creek Bio. GO serves as a consultant for Novartis, Pfizer Inc., Celgene, Janssen, AGIOS, Amgen, Gilead, Astellas, Roche, Jazz Pharmaceuticals and Merus, has received honoraria from Novartis, Celgene, AGIOS, Gilead and Astellas, has received research funding from Novartis, and holds a membership on an entity's Board of Directors for Roche. JC serves as a consultant for Novartis, and has received research funding from Takeda, DC-one, Genentech, Janssen, Novartis and Merus.

Contributions

JT, LN, CB, GO and JC contributed to the conception and design of the study. DB, TF, BG, LG, JJ, GJ, JM, MM, TP, JP, KP, BL and GO collected the data. JT and LN organized the database. JT performed the statistical analysis. PG provided statistical consultation. JT wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript, and read and approved the final version for publication.

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Data-sharing statement

The datasets used and/or analyzed during the study are available from the HOVON/SAKK AML Group upon reasonable request to the corresponding author.

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