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

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

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Running title: Value of MRD-guidance in intermediate-risk AML

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Creek Bio; and 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; 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.

Treatment of patients with acute myeloid leukemia (AML) fit to receive intensive treatment and below 65 years old, 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 subject of debate.[5] Measurable residual disease (MRD) assessment (by multiparameter flow cytometry (MFC) and/or by *NPM1* gene mutations 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 ELN-2017 classification) after C2.[1, 6] Therefore, the presence of MRD at this time point may warrant an allo-SCT as additional intensive therapy.[2] Contrarily, patients in CR(i) 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), 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 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 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 CR(i) and had a MRD result after C2 as assessed by either the leukemia-associated immunophenotypes detection with MFC and/or by RT-PCR for mutated *NPM1*, according to earlier published guidelines.[2, 9] Of the 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. Still 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. EFS, defined as the time between MRD-assessment after C2 in CR(i) and relapse or death, was not significantly different 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. For OS (defined as the time between MRD-assessment in CR(i) and death or censoring) (HR, 1.50; 95% CI, 0.85-2.64; p= 0.16; **Figure 1B**) it seems to be slightly worse for MRD-positive patients (five-year OS 54% compared to 65% for MRD-negative), although not statistically significant. Both EFS and OS were in line with recent published HOVON-SAKK-trials. 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 conform 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 look different for MRD-negative patients treated with allo-SCT vs non-allo-SCT. Total of 15/48 (31%) of allo-SCT treated patients relapsed within three years after CR, of whom most (93%, 14/15) died within 10 months after relapse. Although in the non-all-SCT group 18/44 (41%) relapsed, 12 patients could successfully be salvaged with an (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 effecting 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 ongoing or planned. Hence, we simulated the analysis by comparing survival of the MRD-guided intermediate-risk patients from the HO132-trial (performed from 2014-2017) to an MRD-unguided cohort from HOVON-SAKK phase 2/3 trials (HO42A, HO81, HO92 and HO102), performed from 2006-2013.[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 (age, white blood cell count at diagnosis, WHO-classification, karyotype, *NPM1* status and *FLT3*-ITD status) that are associated with survival **(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 standard and investigational arms for included patients (**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 **(Supplemental 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 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 were advised to receive an allo-SCT, which changed to only for the MRD-positive patients in the HO132-trial. Therefore, a subgroup analysis was done for MRD-negative patients separately, which showed that EFS after three years (HR, 0.86; 95% CI, 0.56-1.33; *p*= 0.50) and OS after five years (HR, 0.84; 95% CI, 0.50-1.40; *p*= 0.50) were not significantly different 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 for safely circumventing allo-SCT treatment 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 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 (**Supplemental Figure S2**). For both cohorts, exact reasons for choosing a specific consolidation treatment are unfortunately unknown. 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.

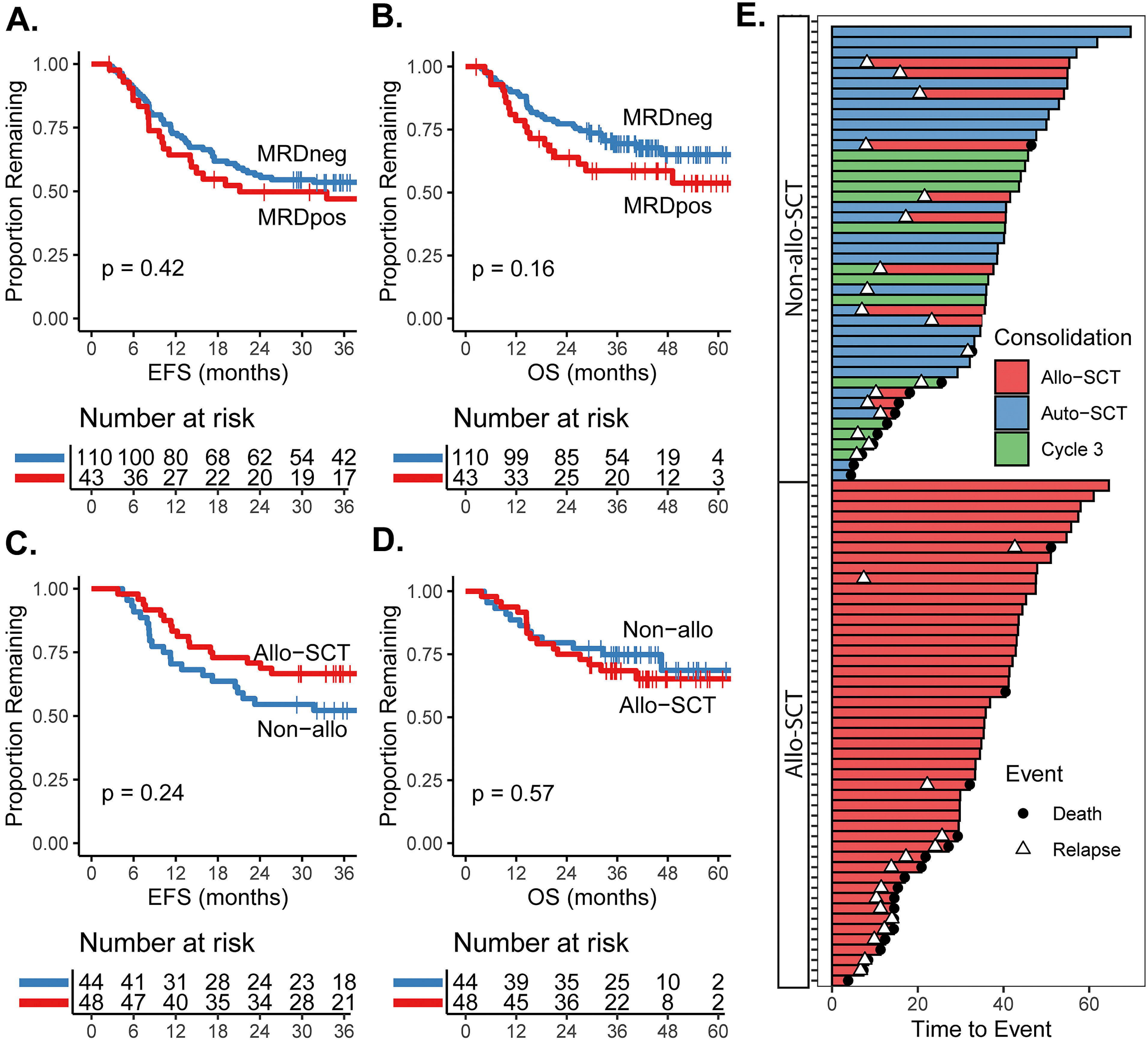
References

1. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
2. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 Update Measurable Residual Disease in Acute Myeloid Leukemia: European LeukemiaNet Working Party Consensus Document. Blood. 2021;138(26):2753-2767.
3. Versluis J, Kalin B, Zeijlemaker W, et al. Graft-Versus-Leukemia Effect of Allogeneic Stem-Cell Transplantation and Minimal Residual Disease in Patients With Acute Myeloid Leukemia in First Complete Remission. JCO Precis Oncol. 2017;1:1-13.
4. Andersson I, Ahlberg K, Stockelberg D, Persson LO. Patients' perception of health-related quality of life during the first year after autologous and allogeneic stem cell transplantation. Eur J Cancer Care (Engl). 2011;20(3):368-379.
5. Ganzel C, Rowe JM. Revisiting autologous transplantation in acute myeloid leukemia. Curr Opin Hematol. 2018;25(2):95-102.
6. Short NJ, Zhou S, Fu C, et al. Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia: A Systematic Review and Meta-analysis. JAMA Oncol. 2020;6(12):1890-1899.
7. Terwijn M, van Putten WL, Kelder A, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol. 2013;31(31):3889-3897.
8. Löwenberg B, Pabst T, Maertens J, et al. Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial. Blood Adv. 2021;5(4):1110-1121.
9. Cloos J, Harris JR, Janssen JJWM, et al. Comprehensive Protocol to Sample and Process Bone Marrow for Measuring Measurable Residual Disease and Leukemic Stem Cells in Acute Myeloid Leukemia. J Vis Exp. 2018;(133):56386.
10. Ossenkoppele GJ, Stussi G, Maertens J, et al. Addition of bevacizumab to chemotherapy in acute myeloid leukemia at older age: a randomized phase 2 trial of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the Swiss Group for Clinical Cancer Research (SAKK). Blood. 2012;120(24):4706-4711.
11. Löwenberg B, Pabst T, Maertens J, et al. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. Blood. 2017;129(12):1636-1645.
12. Randomized study to assess the added value of Laromustine in combination with standard remission-induction chemotherapy in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or myelodysplasia (MDS) (RAEB with IPSS >= 1.5). 2013 [cited 14 January 2022]; Available from: https://www.trialregister.nl/trial/1386
13. Cenzer I, Boscardin WJ, Berger K. Performance of matching methods in studies of rare diseases: a simulation study. Intractable Rare Dis Res. 2020;9(2):79-88.
14. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. Am J Epidemiol. 2014;179(2):226-235.
15. Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. Blood. 2019;134(12):935-945.

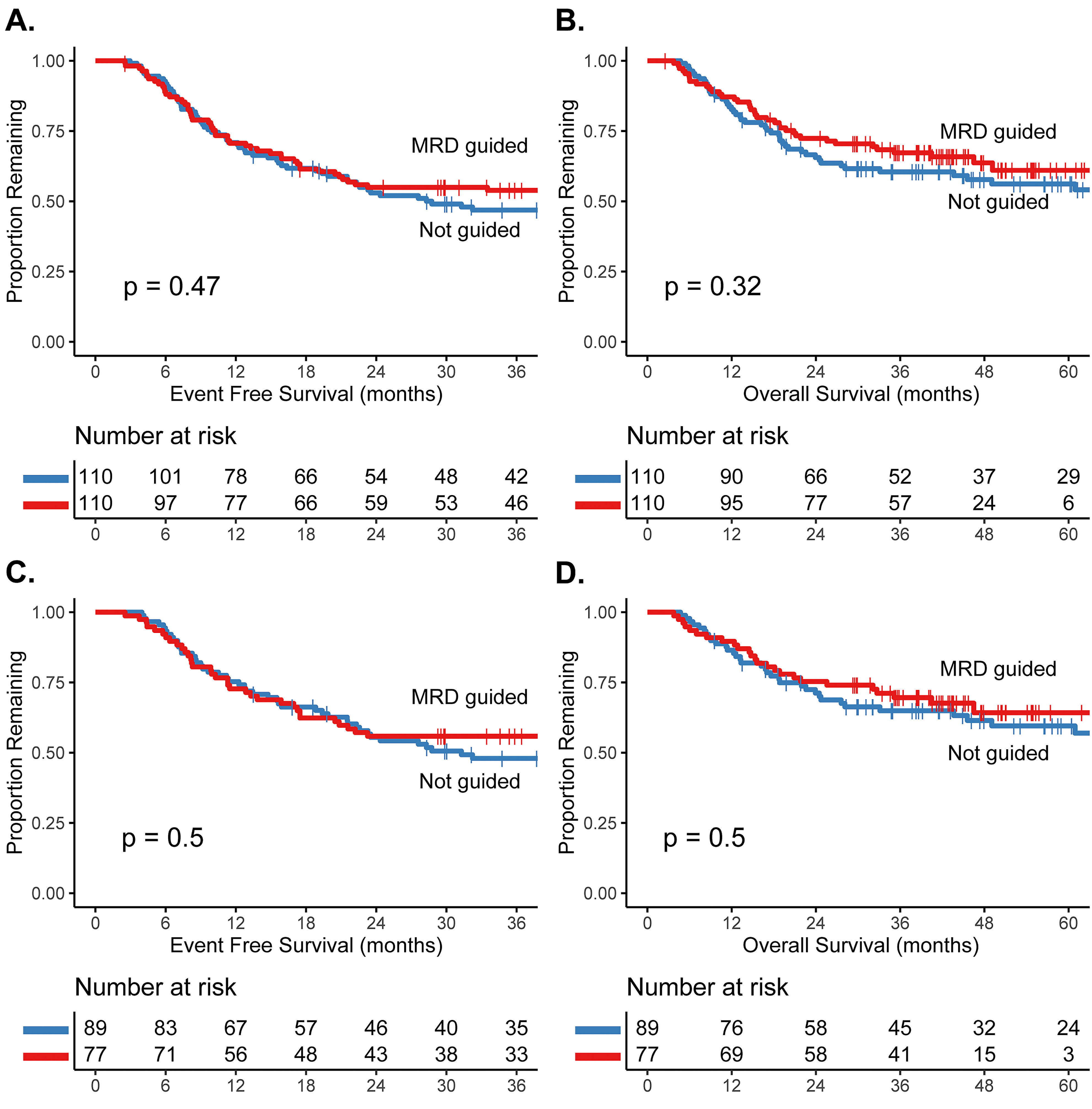
Figure Legends

Figure 1. Survival of ELN intermediate-risk patients in the HO132-trial (MRD-guided 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 a MRD result were ELN intermediate-risk, of which 110 (72%) were MRD-negative after two cycles of chemotherapy. Event-free survival (EFS) assessed using Cox regression was not significantly different between MRD-negative and positive patients (HR:1.24; 95% CI, 0.75-2.00; *p*=0.42). **(B)** Also overall survival (OS) was not significantly different between MRD-negative and positive patients (HR, 1.50; 95% CI, 0.85-2.64; *p*= 0.16). **(C)** A subgroup analysis of the intermediate-risk MRD-negative 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)** A swimmer plot of MRD-negative patients in the HO132 (MRD-guided) study ordered by first post-remission therapy (y-axis) and overall survival (x-axis). The non-allo-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).

Figure 2. Survival by PSM analysis between 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 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).



A.
Proportion Remaining
EFS (months)
MRDneg
MRDpos
p = 0.42
Number at risk
110 100 80 68 62 54 42
43 36 27 22 20 19 17
B.
OS (months)
MRDneg
MRDpos
p = 0.16
Number at risk
110 99 85 54 19 4
43 33 25 20 12 3
C.
Allo−SCT
Non−allo
p = 0.24
Number at risk
44 41 31 28 24 23 18
48 47 40 35 34 28 21
D.
Non−allo
Allo−SCT
p = 0.57
Number at risk
44 39 35 25 10 2
48 45 36 22 8 2
E.
Non-allo-SCT
Allo-SCT
Consolidation
Allo−SCT
Auto−SCT
Cycle 3
Event
Death
Relapse
Time to Event


A.
B.
C.
D.
Proportion Remaining
1.00
0.75
0.50
0.25
0.00
MRD guided
Not guided
p = 0.47
p = 0.32
p = 0.5
p = 0.5
Event Free Survival (months)
Overall Survival (months)
0 6 12 18 24 30 36
0 12 24 36 48 60
Number at risk
A: 110 101 78 66 54 48 42
A: 110 97 77 66 59 53 46
B: 110 90 66 52 37 29
B: 110 95 77 57 24 6
C: 89 83 67 57 46 40 35
C: 77 71 56 48 43 38 33
D: 89 76 58 45 32 24
D: 77 69 58 41 15 3

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		No. of patients evaluated	MRD-unguided group (%)	MRD-guided group (%)	*P*-value
Total			110 (100)	110 (100)	
Trial code	HO42a		40 (36)	0 (0)	
	HO81		7 (6)	0 (0)	
	HO92		5 (5)	0 (0)	
	HO102		58 (53)	0 (0)	
	HO132		0 (0)	110 (100)	
Male sex			53 (48)	56 (51)	0.686
Age (years)	≤45		30 (27)	42 (38)	0.223
	46-60		59 (54)	51 (46)	
	>60		21 (19)	17 (16)	
WHO/ECOG performance status	0		60 (55)	61 (56)	0.990
	1		46 (42)	45 (41)	
	2		4 (4)	4 (4)	
Diagnostic subgroup	AML		101 (92)	103 (94)	0.604
	High-risk RAEB		9 (8)	7 (6)	
AML type	De novo		94 (86)	100 (91)	0.247
	sAML		13 (12)	6 (6)	
	tAML		3 (3)	4 (4)	
WBC, x 10^9 /L	≤20		74 (67)	71 (65)	0.129
	20-100		33 (30)	29 (26)	
	>100		3 (3)	10 (9)	
Cytogenetics	CN-X-Y	215	94 (89)	76 (70)	0.003*
	CA rest		11 (10)	30 (28)	
	Monosomal karyotype[#]		1 (1)	3 (3)	
Sub classification of normal karyotype (NK)	NPM1-neg FLT3-ITD-neg	170	38 (40)	31 (41)	0.471
	NPM1-neg FLT3-ITD-pos		13 (14)	5 (7)	
	NPM1-pos FLT3-ITD-pos		35 (37)	32 (42)	
	NPM1/FLT3-ITD-unknown		8 (9)	8 (11)	
Gene mutations	NPM1-pos	200	37 (34)	36 (33)	0.895
	FLT3-ITD-pos	198	50 (46)	42 (38)	0.544
	NPM1-neg FLT3-ITD-neg	198	50 (46)	56 (51)	0.293
	NPM1-neg FLT3-ITD-pos		14 (13)	6 (6)	
	NPM1-pos FLT3-ITD-pos		36 (33)	36 (33)	
	IDH1-pos	183	11 (13)	11 (11)	0.722
	IDH2-pos	184	17 (20)	16 (16)	0.544
MRD status after cycle II	Neg		89 (81)	77 (70)	0.060
	Pos		21 (19)	33 (30)	
Consolidation therapy received	Cycle 3		18 (16)	13 (12)	0.772
	Auto-SCT		21 (19)	24 (22)	
	Allo-SCT		57 (52)	60 (55)	
	None		14 (13)	13 (12)	

Table S1: Characteristics of MRD-guided and MRD-unguided group. Not shown is ASXL1, CEPBA, RUNX1, TP53, t(8;21) and inv(16) because all patients were negative. [#]All patients with a monosomal karyotype had a t(9;11)(p21.3;q23.3) simultaneously present, which takes precedence over rare, concurrent adverse-risk gene mutations, making these patients intermediate risk according to the ELN-2017 classification. CA, abnormal cytogenetics; CN, normal cytogenetics; ECOG, Eastern Cooperative Oncology Group; neg, negative; pos, positive; sAML, secondary AML (after myelodysplastic syndrome and antecedent hematologic disease); tAML, therapy-related AML (in case of previous chemotherapy or radiotherapy); WHO, World Health Organization. Statistical differences are assessed using Pearson Chi-Square test or Fisher's Exact Test in categorical variables, and the Mann-Whitney U test was used to analyze continuous variables.

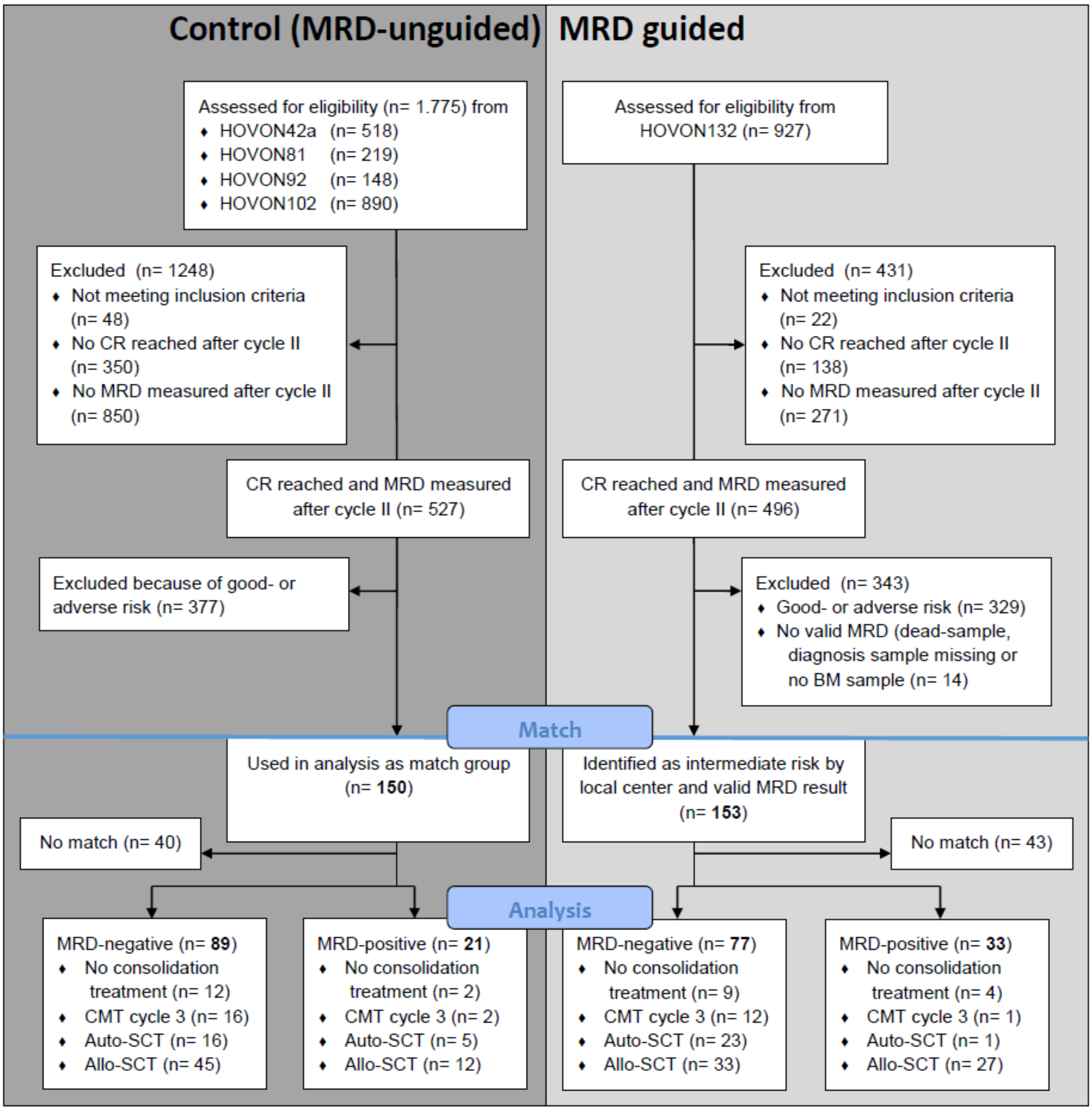

Figure S1. Consort diagram. Four studies were used for the matched MRD-unguided group (left side) and one study for the MRD guided group (right side). After matching, 110 patients remained in both groups.

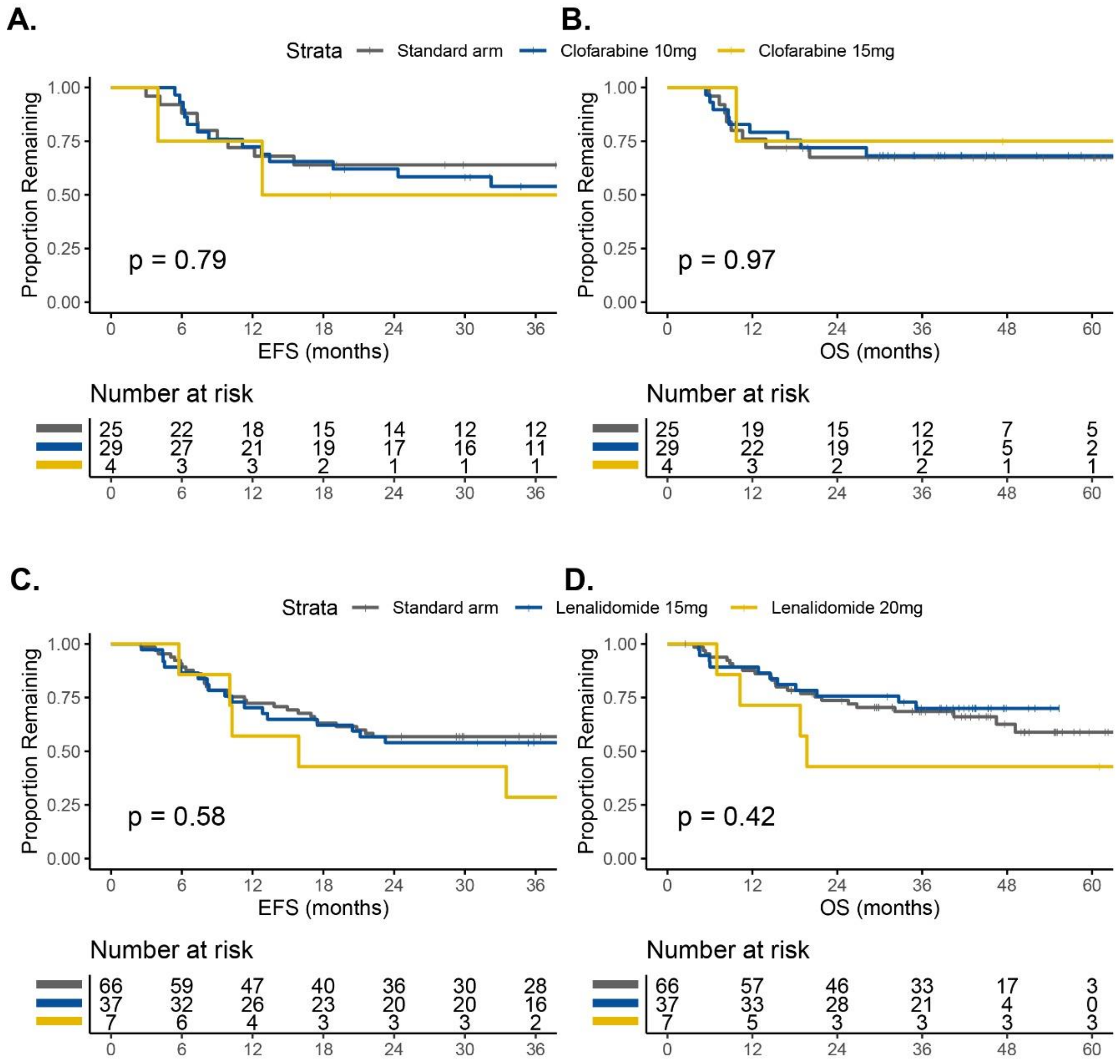

Figure S2: Event-free survival (EFS) and overall survival (OS) stratified by experimental agent randomization in the HO102 (top) and the HO132 study (bottom). The EFS and OS from the HO81 and HO92 studies were also not significantly different, but are not shown since only 7 and 5 patients are included, respectively. **(A)** EFS for patients included from the HO102 trial, stratified by randomization. **(B)** OS for patients included from the HO102 trial, stratified by randomization. **(C)** EFS for patients included from the HO132 trial, stratified by randomization. **(D)** OS for patients from HO132 trial, stratified by treatment arm.