Clinical value of the measurable residual disease status within the ELN2017 risk groups in AML patients undergoing allogeneic stem cell transplantation

To the Editor:

Over recent years, the clinical value of measurable residual disease (MRD) status in acute myeloid leukemia (AML) for informed treatment decisions became increasingly evident. Even though several aspects with respect to MRD assessment in AML - such as the most adequate target, method, tissue, and time-point of assessment - remain to be defined, the clinical value of MRD status determination is widely accepted. In 2017, the European LeukemiaNet (ELN) defined “complete remission (CR) without MRD” (CRiMRD) as a response endpoint in AML to acknowledge the general prognostic impact of the MRD status. Today MRD assessment is complementing baseline AML patient risk factors such as age, karyotype, and some gene mutations (including FLT3-ITD and mutations affecting NPM1, CEBPA, TP53, ASXL1, or RUNX1) to determine prognosis and help to inform treatment decisions.

In AML patients, allogeneic hematopoietic stem cell transplantation (HSCT) remains the consolidation therapy with the highest chance of long-term remission. For various targets and methods it has been shown that a positive MRD status prior to HSCT is a strong prognostic marker for relapse and shorter survival. Even though some HSCT-related factors, as conditioning intensity or donor source, impact outcomes of these patients, a positive MRD status in general associates with an increased relapse probability, compared to patients transplanted without detectable MRD. However, an aspect that has gained little attention so far is the relation of MRD assessment with the genetic context, including the genuine relapse risk of the considered population. The clinical value of MRD assessment - the ability to identify those patients at higher risk of relapse after HSCT - may depend on this context.

To explore the impact of the MRD status within the context of a different baseline relapse risk we identified 176 AML patients who received a HSCT in CR, or CR with incomplete peripheral recovery (CIR) between 2002 and 2018 at our center. All patients had information on ELN2017 risk classification as well as MRD status (based on NPM1 mutation, BAALC, MN1, and WT1 expression, as previously described) up to 28 days prior to HSCT available. A positive MRD status was defined by positivity of any of the considered MRD markers using the previously published cut-offs. Mutations in CEBPA, FLT3, and NPM1 were determined and for patients with material available (n = 112) the mutation status of 54 genes included in the TruSight Myeloid Sequencing Panel (Illumina) were evaluated at diagnosis as previously described.

The median age at HSCT was 63 (range 23–77) years. Prior to HSCT, all but one patient - that received azacitidine alone - received intensive chemotherapy cycles. Donors were HLA matched related (15%), matched unrelated (64%) or had at least one antigen mismatch (21%). The majority of patients (n = 160; 91%) received non-myeloablative peripheral blood HSCT with 3 × 30 mg/m² fludarabine and 2 Gy (one patient received 3 Gy) total body irradiation. Further details are shown in the supplemental methods and Table S1, Appendix S1. Median follow up after HSCT was 3.4 years.

In the entire cohort, 56 patients (32%) relapsed following HSCT. With respect to the three ELN2017 risk groups favorable, intermediate, and adverse the relapse rates were 23%, 24%, and 50%, respectively (Figure 1A), reflecting the escalating AML aggressiveness within the three ELN2017 risk groups. In line with previous reports, the MRD status was a significant factor associated with relapse: while 49% (n = 33) of AML patients transplanted with a positive MRD status relapsed, significantly less MRD negative patients relapsed (21%, n = 23; p < .01). The impact of a positive MRD status prior to HSCT on the cumulative incidence of relapse (CIR) was dependent on the ELN2017 risk group (Figure 1B-E): while MRD positivity prior to HSCT was a significant factor for relapse in the ELN2017 favorable intermediate group (HR = 3.4, range 1.1–10) to the ELN2017 adverse group (HR = 3.2, range 0.9–5.5; Appendix S1, Figure S1A). Similarly, the c-statistics decreased from 0.80 in the ELN2017 favorable group to 0.66 in the ELN2017 intermediate group, to just 0.55 in the ELN2017 adverse group (Appendix S1, Figure S1B). The relapse rates for patients with a positive MRD status at HSCT were relatively consistent over the three ELN2017 groups (ELN2017 favorable: 50%, ELN2017 intermediate: 40%, ELN2017 adverse: 30%).
adverse: 57%). In contrast, the relapse rates for patients transplanted without detectable MRD prior to HSCT were different for the three ELN2017 groups increasing from ELN2017 favorable (5.1%) to ELN2017 intermediate (15%) to ELN2017 adverse (46%), leading to a significantly lower specificity of MRD detection in the ELN2017 adverse group (0.54) compared to the ELN2017 favorable (0.95, $p < .01$) or ELN2017 intermediate group (0.85; $p < .01$). These data show that while the chance to experience relapse is high for patients transplanted with a positive MRD status irrespective of the assigned ELN2017 risk group, an AML patient transplanted with a negative MRD status is relatively safe not to relapse, only if assigned to the ELN2017 favorable or ELN2017 intermediate group. In contrast, MRD-negative ELN2017 adverse patients have a much higher risk of experiencing relapse. These findings are supported by the data of a recent manuscript analyzing the utility of flow-based MRD prior to HSCT in patients with or without a monosomal karyotype (MKT) – an entity assigned to the ELN2017 adverse group. Here, MRD-negative patients harboring a MKT had a relapse risk as high as 46%. In this manuscript the risk stratification by MRD status in patients without a MKT (3-years CIR 20% for MRD-negative patients vs. 64% for MRD-positive patients) was improved compared to the high risk population of patients with a MKT (3-years CIR 46% for MRD-negative patients vs. 72% for MRD-positive patients).

Thus, the ability of MRD assessment to identify those patients at higher risk of relapse after HSCT seems to be reduced in adverse risk patients, due to a higher “background” risk of relapse, likely because of a more aggressive genuine AML phenotype.

Since the NPM1 mutation burden at HSCT is relevant only in the ELN2017 favorable and intermediate group and has a strong impact in these groups we performed the analyses excluding this MRD marker. This reduced the number of patients that could be analyzed, but yielded similar results (see Appendix S1, Figures S1, S2).

Finally, we also observed a time aspect regarding relapse within the ELN2017 groups. For MRD-positive patients at HSCT the time from HSCT to relapse was relatively short and not significantly different across the three ELN2017 risk groups (median for the favorable ELN2017 group 0.57 years; intermediate ELN2017 group 1.3 years; adverse ELN2017 group 0.24 years; Appendix S1, Figure S3). However, for MRD-negative patients, the time from HSCT to relapse differed with a median of 3.6 years in the ELN2017 favorable, of 2.1 years in the ELN2017 intermediate and of 0.5 years in the ELN2017 adverse group (ELN2017 favorable vs. ELN2017 adverse: $p < .01$; intermediate vs. adverse $p = .05$; Appendix S1, Figure S3). Thus, relapse in AML patients transplanted with positive MRD is a relatively early event after HSCT, irrespective of the ELN2017 risk group. In contrast, for patients transplanted with no detectable MRD, relapse dynamics were different and dependent on the ELN2017 risk group, with the ELN2017 adverse group experiencing relapses much earlier.
In summary, ELN2017 adverse group patients transplanted without detectable MRD still had a high risk of early relapse after HSCT, reducing the ability to identify a patient subpopulation at high risk of relapse and subsequently the clinical value of MRD assessment in this ELN2017 group. Of note, when we compared MRD-negative patients that relapsed to those that did not relapse in the ELN2017 adverse group, except for a higher white blood count at diagnosis, we did not observe any clinical or biological differences; especially the frequencies of ASXL1, RUNX1, and TP53 mutations were not significantly different (Appendix S1, Table S3).

It remains to be determined whether our observations remain true also when other MRD methods are used. However, some flow-based MRD studies that reported outcome within distinct AML risk groups, also described relapse incidences as high as 50% in MRD-negative MRD studies that reported outcome within distinct AML risk groups, also described relapse incidences as high as 50% in MRD-negative methods. The employment of more sensitive assays (eg., ddPCR-based, or error-corrected NGS-based) that target specific genetic aberrations may reduce the population of relapsing patients transplanted within the group of patients with “no detectable MRD” and, thus, may improve the low specificity of MRD assessment in the ELN2017 adverse group. However, the high “background” relapse rate in patient populations with very aggressive AML phenotypes, such as in the ELN2017 adverse group, will probably remain.

Taken together, our data show that the clinical value of MRD assessment also depends on the genetic context, which should be taken into account when considering treatment or surveillance aspects following HSCT.

ACKNOWLEDGMENTS
The authors thank Laura Kloss for her help in NPM1 mutation assessment, Christel Müller, Daniela Bretschneider, Evelin Hennig, Sabine Leiblein, Martina Pleß, Ulrike Bergmann, Janet Bogardt, Annette Jilo, and Dagmar Cron for their help in determining cytogenetic and morphologic analyses, and Christine Günther, Scarlett Schwabe, Ines Kovacs, and Kathrin Wildenberger for their help in sample processing. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FUNDING INFORMATION
Deutsche Gesellschaft für Innere MedizinClinician Scientist Program (MJ); José Carreras Leukänie-Stiftung04R/2016 (SSch). PS15/05 (JG); Zusammen gegen den Krebs e.V.(SSch)

AUTHOR CONTRIBUTIONS
Madlen Jentzsch and Sebastian Schwind contributed to the design and analysis of this study and the writing of the manuscript, and all authors agreed on the final version. Madlen Jentzsch, Juliane Grimm, Marius Bill, Dominic Brauer, Donata Backhaus, Rosmarie Pointner, Karoline Goldmann, and Julia Schulz carried out the laboratory-based research; Madlen Jentzsch and Sebastian Schwind performed statistical analyses; and Uwe Platzbecker, Dietger Niederwieser and Sebastian Schwind provided administrative support.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

Madlen Jentzsch ; Juliane Grimm, Marius Bill, Dominic Brauer, Donata Backhaus, Rosmarie Pointner, Karoline Goldmann, Julia Schulz, Dietger Niederwieser, Uwe Platzbecker, Sebastian Schwind

Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Leipzig, Germany

Correspondence
Sebastian Schwind, Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Liebigstraße 22, Haus 7, Leipzig 04103, Germany.

Email: sebastian.schwind@medizin.uni-leipzig.de

ORCID
Madlen Jentzsch https://orcid.org/0000-0002-2270-0804
Sebastian Schwind https://orcid.org/0000-0002-1315-2332

REFERENCES
1. Döhner 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. https://doi.org/10.1182/blood-2016-08-733196.424.
2. Morsink LM, Othus M, Bezerra ED, et al. Impact of pretransplant measurable residual disease on the outcome of allogeneic hematopoietic cell transplantation in adult monosomal karyotype AML. Leukemia. 2020;34(6):1577-1587. https://doi.org/10.1038/s41375-020-0717-0.
3. Norkin M, Katragadda L, Zou F, et al. Minimal residual disease by either flow cytometry or cytogenetics prior to an allogeneic hematopoietic stem cell transplant is associated with poor outcome in acute myeloid leukemia. Blood Cancer J. 2017;7(12):1-7. https://doi.org/10.1038/s41375-018-0007-x.
4. Jentzsch M, Grimm J, Bill M et al. Prognostic relevance of remission and measurable residual disease status in AML patients prior to reduced intensity or non-myeloablative allogeneic stem cell transplantation. Blood Cancer J. 2018;93(9):1142-1152.
5. Grimm J, Bill M, Jentzsch M, et al. Clinical impact of clonal hematopoiesis in acute myeloid leukemia patients receiving allogeneic transplantation. Bone Marrow Transplant. 2019;54(8):1189-1197. https://doi.org/10.1038/s41409-018-0413-0.
6. Terwijn M, Van Putten WLJ, 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. https://doi.org/10.1200/JCO.2012.45.9628.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.