Clinical implications of SRSF2 mutations in AML patients undergoing allogeneic stem cell transplantation

Juliane Grimm | Madlen Jentzsch | Marius Bill | Donata Backhaus | Dominic Brauer | Johannes Küpper | Julia Schulz | Georg-Nikolaus Franke | Vladan Vucinic | Dietger Niederwieser | Uwe Platzbecker | Sebastian Schwind

Medical Clinic and Policlinic 1, Hematology, Cellular Therapy, and Hemostaseology, University of Leipzig Medical Center, Leipzig, Germany

Correspondence
Sebastian Schwind, Medical Clinic and Policlinic 1, Hematology, Cellular Therapy, and Hemostaseology, University of Leipzig Medical Center, Liebigstrasse 22; Haus 7, 04103 Leipzig, Germany.
Email: sebastian.schwind@medizin.uni-leipzig.de

Funding information
Deutsche Gesellschaft für Innere Medizin, Grant/Award Number: Clinician Scientist Program; Ein Herz für Kinder e.V.; José Carreras Leukämie-Stiftung, Grant/Award Numbers: 04R/2016, PS15/05; Verein Zusammen gegen den Krebs

Abstract
The SRSF2 mutations are frequently found in acute myeloid leukemia (AML) and mostly affect the P95 residue. Mutations in this splicing factor mediate abnormal splicing associated with exon skipping events, including EZH2 as a crucial target. While SRSF2 mutations are enriched in secondary AML and associated with worse outcomes following chemotherapy consolidation, very little is known about the associated biological and clinical implications in AML patients consolidated with allogeneic hematopoietic stem cell transplantation (HSCT). Here we retrospectively analyzed 263 adult AML patients who received an allogeneic HSCT regarding the biological and clinical implications of the SRSF2 mutation status at diagnosis and in morphologic remission at HSCT. We found 12.5% of the patients to be SRSF2 mutated at diagnosis. Mutated patients had increased EZH2 missplicing events with P95H likely driving this pathobiology most effectively. However, the amount of EZH2 missplicing events, as a functional surrogate marker did not associate with relevant biological or clinical characteristics. We observed a persistence of mutations in remission before HSCT in the majority (93%) of SRSF2 mutated AML patients. Importantly, the variant allele frequency (VAF) levels of SRSF2 mutations in remission at HSCT did not correlate with outcomes following HSCT consolidation, limiting the applicability of SRSF2 mutations as a marker for residual AML disease. Following allogeneic HSCT SRSF2 mutated AML patients experienced a 2-year overall survival of 77%, indicating that SRSF2 mutated AML patients may benefit from HSCT consolidation.

1 | INTRODUCTION

Mutations in the SRSF2 gene can be found in various myeloid disease entities, including myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and acute myeloid leukemia (AML). In these entities the biological context and specific co-mutation patterns at diagnosis may help differentiating disease entities of myeloid neoplasms and help to improve risk stratification. Almost all SRSF2 mutations are heterozygous and mostly affect the proline 95 (P95) residue. Note, SRSF2 is a splicing factor and SRSF2 gene mutations cause abnormal splicing associated with exon skipping events. And, EZH2 is a common target of splicing alterations associated with SRSF2 and may at least in part mediate the mutated SRSF2

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. American Journal of Hematology published by Wiley Periodicals LLC.
biology. The SRSF2 mutation-dependent splicing of EZH2 triggers nonsense-mediated decay by the inclusion of a toxic exon, which, in turn, results in impaired hematopoietic differentiation. Restoration of normally spliced EZH2 mRNA partially rescues the defective hematopoiesis in SRSF2 mutated cells and may provide a therapeutic avenue that until today has not been clinically exploited.

In AML, SRSF2 mutations occur dependent on the age range of the analyzed set in 13% to up to 25% in older patients and a positive mutation status generally associates with older age, male sex, and lower white blood count (WBC). The mutations are also frequent in MDS and CMML, often indicate an antecedent hematologic disorder when found in AML patients, and may persist in remission. Thus, in AML, mutations in SRSF2 are enriched in secondary AML and some studies even described these mutations as specific for secondary AML. Consequently, SRSF2 mutations are usually associated with worse outcomes following chemotherapy consolidation. With respect to secondary AML, patients are older and more likely have an adverse European LeukemiaNet 2017 (ELN2017) risk. However, outcomes between de novo and secondary AML patients may not be different in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) when ELN2017 risk is considered, and not all secondary AML patients have a dismal prognosis when undergoing allogeneic HSCT. Allogeneic HSCT is a feasible and often curative consolidation option for secondary AML patients and remains the consolidation therapy with the highest chance of sustained remission for most younger and older individuals.

To this day only one smaller study with 14 SRSF2 or U2AF1 mutated patients suggested a potential benefit from HSCT consolidation comparing the results to a chemotherapy treated cohort. To gain better insights into the biological and clinical implications of SRSF2 mutations in the context of an allogeneic HSCT, we retrospectively analyzed the biological and clinical impact of mutated SRSF2 at AML diagnosis on EZH2 missplicing, as well as at HSCT in a larger set of AML patients receiving consolidating allogeneic HSCT.

2 METHODS

2.1 Patients and treatment

We retrospectively analyzed 263 adult AML patients at a median age at diagnosis of 61.1 years (range 19.2–75.8 years) who received an allogeneic HSCT at the University of Leipzig Medical Center between May, 2000 and August, 2020. For all enrolled patients diagnostic bone marrow (BM) samples were available.

For outcome evaluation the analyses were restricted to AML patients who received a HSCT in complete remission (CR; CR1, n = 152; CR2, n = 37) or CR with incomplete peripheral recovery (CRi, n = 44) and survived at least 30 days following HSCT. To increase the homogeneity in the set we also excluded non-P95 mutated patients from outcome analyses (n = 233, with 25 [10.7%] SRSF2-P95 mutated patients; see Figure S1).

All but one patient received age-dependent intensive chemotherapy protocols (under or over 60 years); one patient was treated with azacytidine only. One hundred eighty-two patients received a non-myeloablative (NMA) conditioning protocol and 51 patients a reduced intensity conditioning (RIC, n = 7) or a myeloablative conditioning (MAC, n = 44). The SRSF2 mutated patients received NMA conditioning in 22 cases, RIC in two cases and MAC in one case. For more details on the conditioning protocols, reasons for choosing a certain protocol and graft-versus-host disease (GvHD) prophylaxis please see the supplemental data. Median follow up after HSCT for patients alive was 4.9 years. Written informed consent for participation in these studies was obtained in accordance with the Declaration of Helsinki.

2.2 Assessment of SRSF2 mutation status at diagnosis and pre-HSCT

For SRSF2 mutation analyses at diagnosis, we amplified and directly sequenced genomic or complementary DNA depending on the material available for each patient. For primer sequences and PCR conditions please refer to the supplemental data (Table S1). For patients with adequate material available (n = 106) the SRSF2 mutation status was assessed and verified by next generation sequencing (NGS) as previously described. Consequently, for these patients the BM variant allele frequency (VAF) of SRSF2 and co-mutations at diagnosis were available.

For SRSF2 mutated patients with adequate material available (n = 15: P95H n = 8; P95L n = 5; P95R n = 2), the SRSF2 P95 mutation status at HSCT was analyzed by specific ddPCR assays in peripheral blood (PB; n = 12) or BM (n = 3) at measurable residual disease (MRD) level as previously described (also see Figure S1).

2.3 Determination of EZH2 toxic exon usage

For 138 patients (17 with SRSF2 mutations) diagnostic BM material for EZH2 missplicing analysis was available. For details concerning the primers and PCR conditions please see the supplemental data.

2.4 Cytogenetics, flow cytometry, and additional molecular markers

Cytogenetic analyses were performed centrally in our institution using standard banding techniques. In cases where no metaphases could be obtained, fluorescence in-situ hybridization (FISH) was used to screen for recurrent abnormalities (i.e., del5/5q, del7/7q, trisomy 8, inv(3), abn11q23, t(8;21), and inv(16)). At diagnosis, the presence of internal
tandem duplication in the FLT3 gene (FLT3-ITD), mutations in the FLT3 tyrosine kinase domain (FLT3-TKD) and in the NPM1 and CEBPA genes were determined as previously described.\textsuperscript{13} A panel of AML associated genes was analyzed using next generation sequencing platform MiSeq (Illumina) for 106 patients with available material at diagnosis.\textsuperscript{9} Patients were grouped according to the ELN2017 classification in three risk groups.\textsuperscript{14,19}

For patients with material available, an institutional’s standard panel was used for determination of immunophenotype, including CD34+/CD38- cell population as previously described.\textsuperscript{20} Analysis for MRD markers in CR/CRi at HSCT - NPM1 mutation burden, BAALC, and MN1 expression - were evaluated as previously described.\textsuperscript{21-23}

### 2.5 Definition of clinical endpoints and statistical analyses

For event-free survival (EFS) and overall survival (OS), survival estimates were calculated using the Kaplan–Meier method and groups were compared with the log-rank test. Cumulative incidence of relapse (CIR) was calculated considering the competing risk non-relapse mortality (NRM) using the Fine and Gray model.\textsuperscript{24} Associations with baseline clinical, demographic, and molecular characteristics were compared using the Kruskal-Wallis test and Fisher’s exact test for continuous and categorical variables, respectively. Statistical analyses were performed using the R statistical software platform (version 4.0.3).\textsuperscript{25} For further details see the supplemental data.

### 3 RESULTS

#### 3.1 Diagnostic SRSF2 mutations

In the entire analyzed cohort of 263 (12.5%) AML patients harbored a SRSF2 mutation. Resulting protein aberrations were P95H (n = 17), P95L (n = 8), P95R (n = 2), P95S (n = 1), P95_R102del (n = 1), and non-P95 mutations (n = 4; i.e., R86W, G93D, P96R, and S119N). The median VAF at diagnosis was 37.2%, with the highest VAFs in P95H, P95L, and P95R mutated patients (supplemental data; Figure S2).

Clinical and biological characteristics associated with SRSF2 mutations are shown in Table 1.

In general, SRSF2 mutations associated with older age, male sex, and secondary origin of the disease (Table 1). The most frequent co-mutations were in ASXL1 37%, IDH2 37%, TET2 28%, RUNX1 26%, and NRAS 24% (Figure 1(A)). Of these, all but NRAS had comparable median VAFs at diagnosis (Figure 1(B)). Noteworthy, all co-mutated IDH2 mutations were R140Q substitutions. Regarding immunophenotypical characteristics we observed a higher CD117 expression in SRSF2 mutated patients (supplemental data; Table S2; Figure S3).

With respect to the ELN2017 risk classification we observed a relatively equal distribution (Figure 1(C)) with seven patients (23%) being defined as favorable-risk, 13 patients (43%) as intermediate-risk, and 10 patients (33%) as adverse-risk (p = 0.28). Similarly, with respect to the SRSF2 mutation type, while there was an increasing incidence of P95L mutations from ELN2017 favorable-risk to intermediate-risk to adverse-risk, no significant enrichment was observed (Figure 1(C)).

#### 3.2 Outcomes associated with diagnostic SRSF2 mutation status

In AML patients consolidated with HSCT, the SRSF2 P95 mutation status did not significantly impact CIR (p = 0.68, Figure 2(A)), EFS (p = 0.40, Figure 2(B)), or OS (p = 0.10, Figure 2(C)). Thus, following HSCT SRSF2 P95 mutations do not seem to associate with a particularly worse outcome in AML patients.

With the caveat of low patient numbers, grouped by the ELN2017 risk classification, SRSF2 P95 mutated patients had significantly higher relapse rates in the adverse-risk group (CIR: p < 0.01; EFS: p = 0.20; OS p = 0.50) compared to the favorable-risk and intermediate-risk, respectively, but did not seem to add additional prognostic information to the ELN2017 risk classification (supplemental data; Figure S4).

#### 3.3 SRSF2 mutations and EZH2 toxic exon use

The EZH2 toxic exon use was more frequent in SRSF2 mutated patients (Figure S5(A), p = 0.01). There was a trend for an increased EZH2 toxic exon use in SRSF2 mutation with a P95H substitution (Figure S5(B)). Considering the diagnostic mutation burden the different SRSF2 mutation types clustered together (supplemental data; Figure S6), indicating a potential differential effect of the SRSF2 mutation type on missplicing events. Here the P95H substitution had the highest EZH2 toxic exon use when the diagnostic VAF was considered (supplemental data). However, the analyzed number of patients was low. Noteworthy, there was no clear association of co-mutations or relapse with EZH2 toxic exon use (Figure S5(C)) in SRSF2 mutated patients.

#### 3.4 Detection of SRSF2 mutations at HSCT

To determine the impact of detectable SRSF2 mutations at the time-point of HSCT – including a possible use as MRD marker – we applied previously described sensitive ddPCR assays.\textsuperscript{18}

There were 15 SRSF2 mutated patients with material to determine the VAF pre-HSCT available (P95H n = 8; P95L n = 5; P95R n = 2). All but one (93%) had a detectable SRSF2 mutation burden at HSCT in CR/CRi with a median VAF of 12.6% (range: 0.07% - 43.0%). VAFs at HSCT did not differ according to the SRSF2 mutation type.
There was no correlation between the VAF at diagnosis and at HSCT (supplemental data; Figure S7). Furthermore, there was no association of the SRSF2 VAF at HSCT with the ELN2017 risk classification or the EZH2 toxic exon use (data not shown). Also the detected SRSF2 VAF at HSCT - using a median cut - did not impact the prognosis of the AML patients (Figure 3(C), (D) and (E)).

### TABLE 1  Characteristics associated with SRSF2 mutation status

| Characteristics   | SRSF2 wild type n = 230 | SRSF2 mutated n = 33 | p       |
|-------------------|-------------------------|----------------------|---------|
| Age at diagnosis  |                         |                      | <0.001  |
| median (range)    | 60.1 (19.2–75.8)        | 62.7 (50.1–73.7)     |         |
| Sex, n (%)        |                         |                      | 0.04    |
| female            | 122 (53)                | 11 (33)              |         |
| Hb, g/dL          |                         |                      | 0.56    |
| median (range)    | 9.0 (4.3–15.7)          | 8.9 (5.8–14.1)       |         |
| Platelets, 10⁹/L  |                         |                      | 0.56    |
| median (range)    | 65 (2–488)              | 56.5 (1–357)         |         |
| WBC, 10⁹/L        |                         |                      | 0.13    |
| median (range)    | 7.4 (0.5–385)           | 2.9 (0.7–117)        |         |
| Blasts BM, %      |                         |                      | 0.81    |
| median (range)    | 54 (0–95)               | 55 (16–92)           |         |
| Blasts PB, %      |                         |                      | 0.42    |
| median (range)    | 22.5 (0–98)             | 21 (0–80)            |         |
| ELN2017, n (%)    |                         |                      | 0.63    |
| favorable         | 60 (28)                 | 7 (23)               |         |
| intermediate      | 74 (34)                 | 13 (43)              |         |
| adverse           | 83 (38)                 | 10 (33)              |         |
| AML origin, n (%) |                         |                      | 0.02    |
| de novo           | 163 (71)                | 16 (48)              |         |
| Complex KT, n (%) |                         |                      | 0.09    |
| present           | 32 (15)                 | 1 (3.1)              |         |
| Monosomal KT, n (%) |                      |                      | 0.14    |
| present           | 28 (13)                 | 1 (3.1)              |         |
| NPM1, n (%)       |                         |                      | 0.83    |
| mutated           | 56 (24)                 | 7 (21)               |         |
| FLT3-ITD, n (%)   |                         |                      | 0.23    |
| present           | 44 (19)                 | 3 (9.1)              |         |
| CEBPA, n (%)      |                         |                      | 0.15    |
| mutated           | 23 (11)                 | 7 (21)               |         |
| ASXL1, n (%)      |                         |                      | 0.01    |
| mutated           | 11 (11)                 | 7 (37)               |         |
| RUNX1, n (%)      |                         |                      | 0.19    |
| mutated           | 14 (14)                 | 5 (26)               |         |
| TP53, n (%)       |                         |                      | 0.22    |
| mutated           | 13 (13)                 | 0 (0)                |         |
| DNMT3A, n (%)     |                         |                      | 0.55    |
| mutated           | 27 (28)                 | 3 (18)               |         |
| IDH1, n (%)       |                         |                      | 0.99    |
| mutated           | 14 (14)                 | 2 (11)               |         |
| IDH2, n (%)       |                         |                      | 0.01    |
| mutated           | 11 (11)                 | 7 (37)               |         |

Abbreviations: BM, bone marrow; ELN, European LeukemiaNet; Hb, hemoglobin; KT, karyotype; PB, peripheral blood; WBC, white blood count; ITD, internal tandem duplication.

(Figure 3(A) and (B)).
Noteworthy, also in multivariable analyses neither the \textit{SRSF2} mutation status at diagnosis nor the \textit{SRSF2} mutation burden at HSCT significantly impacted CIR, EFS, or OS (see supplemental data; Table S4).

4 | DISCUSSION

Mutations in \textit{SRSF2} are frequently found in many myeloid neoplasms, including AML.\textsuperscript{5–8} In the analyzed set 12.5\% of patients harbored an \textit{SRSF2} mutation mostly affecting the P95 residue. In line with previously published data, \textit{SRSF2} mutations associated with older age, male sex, as well as mutations in \textit{ASXL1} and \textit{IDH2}. Noteworthy, with respect to the immunophenotype we noted a higher CD117 surface expression (supplemental data; Table S2), with a possible clinical application for these patients in the future, eg, for CAR T-cell approaches.\textsuperscript{26}

Mutations in the splicing factor \textit{SRSF2} contribute to pathobiology by inducing abnormal splicing that associates with exon skipping events.\textsuperscript{3,4} In MDS \textit{EZH2} is a common target of this mechanism leading to nonsense-mediated decay by the inclusion of a toxic exon.\textsuperscript{3,4} Here we validated the association of mutated \textit{SRSF2} with \textit{EZH2} toxic exon use in AML. Interestingly, the quantitative effects in these missplicing events may depend on the \textit{SRSF2} P95 mutation type, with \textit{SRSF2}
P95H likely being most effective (see also supplemental data). However, no specific biological characteristics or co-mutation pattern were observed with the P95H substitution (Table S3). In general, the amount of \(\text{EZH2}\) missplicing did not associate with other biological or clinical features in \(\text{SRSF2}\) mutated patients.

With respect to outcome of AML patients following consolidation by HSCT, \(\text{SRSF2}\) mutation status at diagnosis did not negatively impact outcomes. Even though, the analyzed outcome set did not influence other biological or clinical features in \(\text{SRSF2}\) mutated patients.

With respect to outcome of AML patients following consolidation by HSCT, \(\text{SRSF2}\) mutation status at diagnosis did not negatively impact outcomes. Even though, the analyzed outcome set did not influence other biological or clinical features in \(\text{SRSF2}\) mutated patients.

In our cohort no significant enrichment of \(\text{SRSF2}\) mutations in any of the ELN2017 risk groups was observed, even though the \(\text{SRSF2}\) P95L mutation frequency increased from ELN2017 favorable to intermediate to adverse risk. The \(\text{SRSF2}\) mutations have been linked to secondary AML and – in line with this observation – also in our cohort 52% of the \(\text{SRSF2}\) mutated patients had secondary disease origin. Usually, secondary AML associates with worse outcome and worse ELN2017 risk.5 But when consolidated by HSCT not all secondary AML patients have a dismal prognosis,10 an observation that was also seconded by the rather favorable outcome of \(\text{SRSF2}\) mutated patients when consolidated by HSCT observed in this analysis.

At HSCT in remission the diagnostic \(\text{SRSF2}\) mutations were still detectable at various levels in all but one (93%) of the patients. With 12.6% (range: 0.07% - 43.0%) the median VAF at HSCT in remission was relatively high, indicating that classical intensive induction therapies are rarely able to eliminate these mutations in AML. There was no significant correlation between diagnostic VAFs and VAFs at HSCT (Pearson's product-moment correlation: 0.50). The level of the VAF at HSCT did not associate with any biological or clinical characteristic. Certainly, knowledge about the clinical meaning of persisting \(\text{SRSF2}\) mutation levels in AML remission at HSCT is of importance, since longitudinal, mutation-based residual disease detection is increasingly used in clinical routine. Here, the level of VAF detection at HSCT did not affect outcomes following HSCT consolidation in this AML cohort.

However, likely most comparable would be the widely accepted negative impact of a positive \(\text{NPM1}\) mutation MRD at HSCT. Only one of the \(\text{SRSF2}\) mutated patients with a measurable \(\text{SRSF2}\) mutation burden at HSCT was also \(\text{NPM1}\) mutated and remained \(\text{NPM1}\) mutation MRD positive at HSCT. This patient relapsed early. Comparing the EFS curves of \(\text{NPM1}\) mutated patients - in the here analyzed
set – those with a positive NPM1 mutation MRD had significantly worse outcomes compared to NPM1 MRD negative patients at HSCT. Noteworthy, those patients with detectable SRSF2 mutations at HSCT had comparable outcomes to those with negative NPM1 mutation MRD at HSCT, indicating a different impact of the presents of both mutations at HSCT (supplemental data and Figure S8). Similar to mutations in DNMT3A, TET2, or ASXL1 (DTA), mutations in SRSF2 in AML may rather have a role as an indicator for clonal hematopoiesis than being a factor directly driving AML disease or relapse.9,27,28

In conclusion, we show that in AML SRSF2 mutations lead to an increased EZH2 missplicing, with P95H driving this pathobiology most effectively. The presence of SRSF2 mutations at diagnosis associates with secondary disease origin. However, these patients do not have a dismal prognosis when consolidated with HSCT. Importantly, SRSF2 mutations persisted in most SRSF2 mutated AML patients in remission prior to HSCT following intensive induction therapy and their detection did not impact outcomes after HSCT. Thus, SRSF2 mutations do not present a useful MRD marker in AML and, therefore, the sole detection of a SRSF2 mutation in remission before HSCT should not trigger therapeutic interventions.

ACKNOWLEDGMENTS

The authors thank Amanda C. Winters and Daniel A. Pollyea from the University of Colorado, USA for providing us with the SRSF2 P95 MRD droPCR assay and conditions. This work was supported by the Deutsche José-Carreras-Stiftung (#04R/2016 S.Sch. and #PS15/05 J.G.), Deutsche Gesellschaft für innere Medizin (M.J.), Verein zusammen gegen den Krebs e.V. (S.Sch.), and Ein Herz für Kinder e.V. The authors thank Janet Bogardt, Annette Jilo, Dagmar Cron, Ines Kovacs, Kathrin Wildenberger, Scarlett Schwabe, Christine Günther, Daniela Bretschneider, Evelin Hennig, and Christel Müller for their assistance.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Juliane Grimm, 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. Juliane Grimm, Madlen Jentzsch, Marius Bill, Donata Backhaus, Dominic Brauer, Johannes Küpper, and Julia Schulz carried out the laboratory-based research; JG, MJ, and SSch performed statistical analyses; and Georg-Nikolaus Franke, Vladan Vucinic, Dietger Niederwieser, Uwe Platzbecker, and Sebastian Schwind provided administrative support.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORCID

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

REFERENCES

1. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221. https://doi.org/10.1056/NEJMoia1516192
2. Todisco G, Creignou M, Galli A, et al. Co-mutation pattern, clonal hierarchy, and clone size concur to determine disease phenotype of SRSF2 P95-mutated neoplasms. Leukemia. 2021;35(8):2371-2381. https://doi.org/10.1038/s41375-020-01106-z
3. Shiozawa Y, Malcovati L, Galli A, et al. Aberrant splicing and defective mRNA production induced by somatic spliceosome mutations in myelodysplasia. Nat Commun. 2018;9(1):3649. https://doi.org/10.1038/s41467-018-06063-x
4. Kim E, Ilagan JO, Liang Y, et al. SRSF2 mutations contribute to Myelodysplasia by mutant-specific effects on exon recognition. Cancer Cell. 2015;27(5):617-630. https://doi.org/10.1016/j.ccell.2015.04.006
5. Gardin C, Pautas C, Fournier E, et al. Added prognostic value of secondary AML-like gene mutations in ELN intermediate-risk older AML: ALFA-1200 study results. Blood Adv. 2020;4(9):1942-1949. https://doi.org/10.1182/bloodadvances.2019001349
6. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-1376.
7. Bamopoulos SA, Batcha AMN, Jurinovic V, et al. Clinical presentation and differential splicing of SRSF2, U2AF1 and SF3B1 mutations in patients with acute myeloid leukemia. Leukemia. 2020;34(10):2621-2634. https://doi.org/10.1038/s41375-020-0839-4
8. Prassek VV, Rothenberg-Thurley M, Sauerland MC, et al. Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. Haematologica. 2018;103(11):1853-1861. https://doi.org/10.3324/haematol.2018.191536
9. 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
10. Jentzsch M, Grimm J, Bill M, et al. ELN risk stratification and outcomes in secondary and therapy-related AML patients consolidated with allogeneic stem cell transplantation. Bone Marrow Transplant. 2021;56(4):936-945. https://doi.org/10.1038/s41409-020-01129-1
11. Michels FV, Atanafu EG, Gupta V, et al. Comparable outcomes post allogeneic hematopoietic cell transplant for patients with de novo or secondary acute myeloid leukemia in first remission. Bone Marrow Transplant. 2015;50(7):907-913. https://doi.org/10.1038/bmt.2015.59
12. Schmaelter AK, Labopin M, Socié G, et al. Inferior outcome of allogeneic stem cell transplantation for secondary acute myeloid leukemia in first complete remission as compared to de novo acute myeloid leukemia. Blood Cancer J. 2020;10(3):10-26. https://doi.org/10.1038/s41408-020-0296-3
13. Gupta V, Tallman MS, Weisdorf DJ. Allogeneic hematopoietic cell transplantation for adults with acute myeloid leukemia: myths, controversies, and unknowns. Blood. 2011;117(8):2307-2318. https://doi.org/10.1182/blood-2010-10-265 603
14. 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
15. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood. 2001;97(11):3390-3400. https://doi.org/10.1182/blood.V97.11.3390
16. Muffy L, Pasquin IC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130(9):1156-1164.
17. Hamilton BK, Visconte V, Jia X, et al. Impact of allogeneic hematopoietic cell transplant in patients with myeloid neoplasms carrying spliceosomal mutations. Am J Hematol. 2016;91(4):406-409. https://doi.org/10.1002/ajh.24306

18. Winters AC, Gutman JA, Purev E, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. Blood Adv. 2019;3(20):2911-2919. https://doi.org/10.1182/bloodadvances.2019000243

19. Grimm J, Jentzsch M, Bill M, et al. Prognostic impact of the ELN2017 risk classification in patients with AML receiving allogeneic transplantation. Blood Adv. 2020;4(16):3864-3874. https://doi.org/10.1182/bloodadvances.2020001904

20. Jentzsch M, Bill M, Nicolet D, et al. Prognostic impact of the CD34+/CD38− cell burden in patients with acute myeloid leukemia receiving allogeneic stem cell transplantation. Am J Hematol. 2017;92(4):388-396. https://doi.org/10.1002/ajh.24663

21. Bill M, Grimm J, Jentzsch M, et al. Digital droplet PCR-based absolute quantification of pre-transplant NPM1 mutation burden predicts relapse in acute myeloid leukemia patients. Ann Hematol. 2018;97(10):1757-1765.

22. Jentzsch M, Bill M, Grimm J, et al. Prognostic impact of blood MN1 copy numbers before allogeneic stem cell transplantation in patients with acute myeloid leukemia. HemaSphere. 2019;3(1):e167. https://doi.org/10.1097/hsp.0000000000000167

23. Jentzsch M, Bill M, Grimm J, et al. High BAALC copy numbers in peripheral blood prior to allogeneic transplantation predict early relapse in acute myeloid leukemia patients. Oncotarget. 2017;8(50):87944-87954. https://doi.org/10.18632/oncotarget.21322

24. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141-1154.

25. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria. 2017. http://www.R-project.org.

26. Myburgh R, Kiefer JD, Russkamp NF, et al. Anti-human CD117 CAR T-cells efficiently eliminate healthy and malignant CD117-expressing hematopoietic cells. Leukemia. 2020;34(10):2688-2703. https://doi.org/10.1038/s41375-020-0818-9

27. McKerrell T, Park N, Moreno T, et al. Leukemia-associated somatic mutations drive distinct patterns of age-related clonal Hemopoiesis. Cell Rep. 2015;10(8):1239-1245. https://doi.org/10.1016/j.celrep.2015.02.005

28. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477-2487. https://doi.org/10.1056/nejmoa1409405

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

How to cite this article: Grimm J, Jentzsch M, Bill M, et al. Clinical implications of SRSF2 mutations in AML patients undergoing allogeneic stem cell transplantation. Am J Hematol. 2021;96(10):1287-1294. https://doi.org/10.1002/ajh.26298