Risk Stratification in Older Intensively Treated Patients With AML

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ABSTRACT

PURPOSE AML is a genetically heterogeneous disease, particularly in older patients. In patients older than 60 years, survival rates are variable after the most important curative approach, intensive chemotherapy followed by allogeneic hematopoietic cell transplantation (allo-HCT). Thus, there is an urgent need in clinical practice for a prognostic model to identify older patients with AML who benefit from curative treatment.

METHODS We studied 1,910 intensively treated patients older than 60 years with AML and high-risk myelodysplastic syndrome (HR-MDS) from two cohorts (NCRI-AML18 and HOVON-SAKK). The median patient age was 67 years. Using a random survival forest, clinical, molecular, and cytogenetic variables were evaluated in an AML development cohort (n = 1,204) for association with overall survival (OS). Relative weights of selected variables determined the prognostic model, which was validated in AML (n = 491) and HR-MDS cohorts (n = 215).

RESULTS The complete cohort had a high frequency of poor-risk features, including 2022 European LeukemiaNet adverse-risk (57.3%), mutated *TP53* (14.4%), and myelodysplasia-related genetic features (65.1%). Nine variables were used to construct four groups with highly distinct 4-year OS in the (1) AML development, (2) AML validation, and (3) HR-MDS test cohorts ([1] favorable: 54% ± 4%, intermediate: 38% ± 2%, poor: 21% ± 2%, very poor: 4% ± 1%; [2] 54% ± 9%, 43% ± 4%, 27% ± 4%, 4% ± 3%; and [3] 54% ± 10%, 33% ± 6%, 14% ± 5%, 0% ± 3%, respectively). This new AML60+ classification improves current prognostic classifications. Importantly, patients within the AML60+ intermediate- and very poor-risk group significantly benefited from allo-HCT, whereas the poor-risk patients showed an indication, albeit nonsignificant, for improved outcome after allo-HCT.

CONCLUSION The new AML60+ classification provides prognostic information for intensively treated patients 60 years and older with AML and HR-MDS and identifies patients who benefit from intensive chemotherapy and allo-HCT.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

AML is a malignant disorder of the bone marrow frequently diagnosed in the elderly population, with two thirds of patients older than 60 years.[1] Overall, the outcome of patients older than 60 years with AML remains poor compared with younger patients, despite treatment advances, with decreased morphological complete remission (CR) rates, shorter duration of CR, and poorer overall survival (OS).[2-7] This is likely to be related to genetic and epigenetic disease-specific features, resulting in therapy resistance together with patient-specific comorbidities leading to decreased tolerance of treatment toxicity. For fitter older patients, the most important curative treatment is intensive chemotherapy, often followed by consolidation with allogeneic hematopoietic cell transplantation (allo-HCT).[8] Allo-HCT is

CONTEXT

Key Objective

To develop a novel risk stratification system for patients 60 years and older with AML who are eligible for intensive induction chemotherapy.

Knowledge Generated

The new AML60+ classification identifies four groups in patients 60 years and older with AML and high-risk myelodysplastic syndrome (HR-MDS) and provides information on outcomes after intensive induction chemotherapy. For consolidation treatment, AML60+ intermediate- and very poor-risk patients had significantly improved overall survival (OS) after allogeneic hematopoietic cell transplantation (allo-HCT) in remission, whereas an indication for improved OS after allo-HCT was found for the poor-risk subgroup.

Relevance *(S. Lentzsch)*

The AML60+ classification introduces a prognostic score tailored for intensively treated AML and HR-MDS patients aged 60 and above. This score not only offers simple application in clinical practice but also delivers crucial insights into post allo-HCT survival, enabling clinicians to better weigh the benefits of allo-HCT against potential none relapsed mortality assessed by specific risk scores.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

frequently used as a curative therapeutic modality in patients up to age 75 years because of increased availability of toxicity-reducing strategies (eg, reduced intensity conditioning, unrelated and haploidentical donor availability, and improved graft-*v*-host disease prophylaxis approaches including post-transplant cyclophosphamide). Two key questions in the field are how can we best identify older patients with AML who optimally benefit from intensive chemotherapy alone and which intensively treated older patients will optimally benefit from receiving allo-HCT as consolidation therapy. Despite the importance of these questions and the older age preponderance of patients with AML, prognostic models have been based on younger patients leading to uncertainty as to which older patients are optimally treated with intensive chemotherapy, with or without allo-HCT.[8]

In most adults, the development of AML occurs through a stepwise acquisition of somatic genetic and epigenetic changes which are present in the majority (>95%) of patients with AML.[9,10] Coinciding with the discovery of the genetic mutational landscape of AML, genetic aberrations were shown to distinguish AML patient subtypes with distinct prognostic features, increasingly necessitating tailored treatment approaches. Arguably, the current most widely used genetic prognostic tool is the 2022 European LeukemiaNet (ELN2022) AML risk classification. This model, on the basis of genetic and clinical outcome data, stratifies adults of younger and middle age (<60 years) into favorable, intermediate, or adverse response groups when treated intensively.[8] This, and the advent of genetically targeted therapies, has meant that genetic analysis at diagnosis is pivotal in management and determining prognosis of patients with AML.[11] However, as there are age-dependent differences in the frequencies of genetic changes in AML and in toxicity profiles to intensive therapy, there is a need for prognostic risk classification for older, intensively treated patients with AML. Recently, a risk model for older patients with AML was developed, but this did not address which patients would optimally benefit from allo-HCT, leaving an important gap in the field relevant for clinical decision making.[12]

To address this gap, to our knowledge, we studied the largest cohort of older patients with AML compiled to date who had been intensively treated on prospective clinical trials, where comprehensive genetic and mature clinical outcome data were available for the majority of patients. We applied a machine learning approach to develop a novel risk stratification system, with better performance than current risk classifications. Using this stratification system, we evaluated which older patients with AML may optimally benefit from intensive chemotherapy and allo-HCT.

METHODS

Clinical Cohorts

The cohort included 1,910 intensively treated patients, 60 years and older, with newly diagnosed AML and high-risk myelodysplastic syndrome (HR-MDS) with International Prognostic Scoring System (IPSS) ≥1.5, revised IPSS >4.5, or excess blasts of ≥10% (Fig 1; Table 1). United Kingdom patients were enrolled in the NCRI-AML18 trial (Data Supplement, Fig S1A, online only; n = 976).[4] European patients were enrolled in one of four consecutive HOVON-SAKK randomized phase II

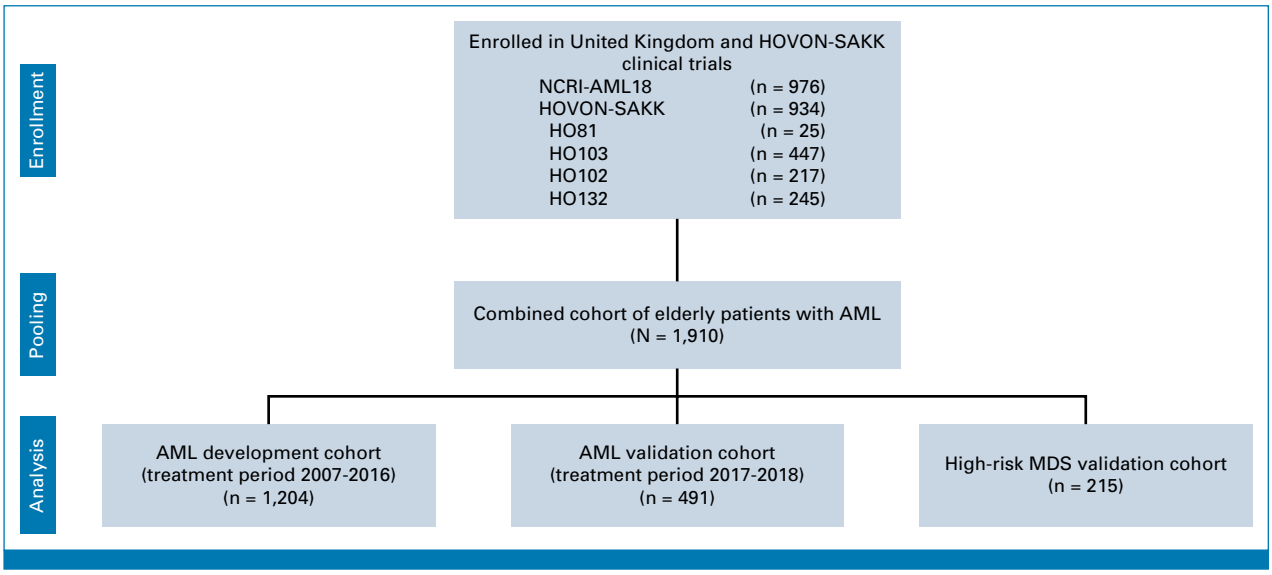

FIG 1. CONSORT diagram. MDS, myelodysplastic syndrome.

(HO81, HO103) or phase III trials (HO102, HO132; Data Supplement, Figs S1B-S1E; n = 934).[2,3,13,14] Extensive, and detailed, clinical trial data, including patient-related variables, disease-related variables, treatment given, and comprehensive treatment outcomes, were available for all patients. Allo-HCT was performed according to study protocols (details are given in the Data Supplement, Methods). All trial participants provided written informed consent in accordance with the Declaration of Helsinki.

Genetic Analysis

High–molecular weight genomic DNA was isolated from bone marrow or peripheral blood samples. Gene resequencing was performed on diagnostic samples using either a 97-gene panel (Oxford for NCRI-AML18) or 54-gene panel (Erasmus MC, Rotterdam for HOVON-SAKK) containing the most frequently mutated genes in myeloid malignancies. Details of cytogenetic analysis, next-generation sequencing, and complementary molecular analyses are provided in the Data Supplement (Methods, Tables S5 and S6).

Model Development

As the clinical and genetic data of the NCRI-AML18 and HOVON-SAKK AML cohorts were broadly similar (Data Supplement, Table S1 and Fig S2), we combined the two data sets to maximize the power of the analysis. The model was developed in a cohort of patients with AML recruited between 2007 and 2016 (AML development cohort, n = 1,204, 63.0%) and evaluated in a subsequently treated cohort of patients with AML, enrolled between 2017 and 2018 (AML validation cohort, n = 491, 25.7%), and a HR-MDS cohort (n = 215, 11.2%; Data Supplement, Table S2), consistent with TRIPOD recommendations for external validation.[16] The following variables were considered for prediction of OS (Data Supplement, Table S3): age, sex, WBC count, gene mutations, and cytogenetic abnormalities. Model development consisted of three sequential stages including (1) variable selection using the hierarchy from a random survival forest, which variables were (2) introduced stepwise into a multivariable cox regression analysis and (3) points were assigned for each predictor according to the hazard ratio (HR) of the final Cox model. Further details are available in the Data Supplement (Methods).

RESULTS

Patient Characteristics

The median age of patients in this cohort of 1,910 intensively treated patients with AML was 67 years (range, 60-84; Table 1), which was higher in the NCRI-AML18 cohort compared with the HOVON-SAKK cohort (68 *v* 65 years; $P < .001$, respectively; Data Supplement, Table S1). The majority of patients with AML were classified as adverse risk according to the ELN2022 classification in both cohorts (57.0% and 57.7%, respectively; $P = .652$). CR or CR with incomplete count recovery (CRi) after induction treatment was achieved by 74.9% of patients in the NCRI-AML18 cohort compared with 76.4% in the HOVON-SAKK cohort. Allo-HCT in first CR/CRi was performed in 31.9% of patients, with a lower transplant frequency in the NCRI-AML18 cohort compared with the HOVON-SAKK cohort (27.4% *v* 36.5%; $P < .001$). The median follow-up of patients alive was 46.1 months (range, 0.2-74.3) for the NCRI-AML18 cohort and 54.9 months (range, 1.6-117) for the HOVON-SAKK cohort. OS did not differ significantly between the NCRI-AML18 and the HOVON-SAKK cohorts (28% ± 2% [SE] *v* 31% ± 2% at 4-years $P = .644$; Data Supplement, Fig S3).

TABLE 1. Baseline Characteristics

Characteristic	Total (N = 1,910)
Age, years	
Median (range)	67 (60-84)
>65 years, No. (%)	1,143 (59.8)
Sex, No. (%)	
Male	1,160 (60.7)
Female	750 (39.3)
WHO performance status, No. (%)	
0	918 (48.1)
1	844 (44.2)
2	132 (6.9)
3	1 (0.1)
Missing	15 (0.8)
WBC, ×10e9/L	
Median (range)	5.0 (0.0-417)
>20, No. (%)	484 (25.3)
Disease type, No. (%)	
De novo	1,437 (75.2)
sAML	172 (9.0)
tAML	86 (4.5)
High-risk MDS	215 (11.3)
ELN2017 classification, No. (%)	
Favorable	524 (27.4)
Intermediate	472 (24.7)
Adverse	914 (47.9)
ELN2022 classification, No. (%)	
Favorable	382 (20.0)
Intermediate	433 (22.7)
Adverse	1,095 (57.3)
Best response after induction, No. (%)	
CR	1,276 (66.8)
CRi	168 (8.8)
PR	73 (3.8)
Refractory	188 (9.8)
Induction death	126 (6.6)
Missing/NA	79 (4.1)
Allogeneic HCT in first CR, No. (%)	
Yes	460 (31.9)
No	984 (68.1)

Abbreviations: CR, complete remission; CRi, CR with incomplete count recovery; ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; NA, not available; PR, partial response; sAML, secondary AML; tAML, therapy-related AML.

Mutations and Genetic Analyses

The overall distribution of somatic gene mutations was similar between the NCRI-AML18 and HOVON-SAKK cohorts, with the frequency of mutations in any one gene not varying by more than 5% across the two cohorts (Data Supplement, Fig S2). The most commonly mutated genes across the two cohorts were *DNMT3A* (28% *v* 28%; $P = .799$), *NPM1* (28% *v* 25%; $P = .131$), *TET2* (26% *v* 21%; $P = .011$), *SRSF2* (24% *v* 19%; $P = .015$), *ASXL1* (23% *v* 18%; $P = .020$), and *TP53* (13% *v* 16%; $P = .019$). Complex and monosomal karyotypes[8] were the most frequent cytogenetic alterations in both cohorts (15% *v* 18%; $P = .042$; and 12% *v* 15%; $P = .019$). The highly similar baseline clinical and genetic characteristics of the older patients with AML enrolled in the NCRI-AML18 and HOVON-SAKK AML cohorts justified combining both data sets (Fig 2; Data Supplement, Table S1).

In this combined older AML/HR-MDS cohort, the frequency of patients with mutations either in genes (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *or ZRSR2*) or cytogenetic changes (complex karyotype, −5/del(5q), −7/del(7q), abn(12p)/−12, or −17/abn(17p)/del(17p))[8,17,18] associated with AML with myelodysplasia-related changes was 65.1%, much higher than the 9.0% of patients with clinical secondary AML. OS at 4 years in the combined cohort for patients with clinical secondary AML was estimated at 20% ± 3% which was 27% ± 1% for patients with AML with myelodysplasia-related genetic features. These outcomes were inferior to patients with clinical or genetic de novo AML (31% ± 1% and 42% ± 2%, respectively; Data Supplement, Fig S4). The poorest prognosis was associated with *TP53*-mutant AML (4% ± 1%).

Patient Outcomes

We initially tested the prognostic value of published risk classifications[8,12,19,20] for this older intensively treated AML patient cohort (Data Supplement, Fig S5). Although the ELN2017 and ELN2022 classifications were devised using data from younger patients, these classifications segregate older patients with AML into distinct favorable-, intermediate- and adverse-risk groups (Data Supplement, Figs S5A and S5B). The OS at 4 years using ELN2017 and ELN2022 was estimated to be 49% ± 2% and 53% ± 2% for favorable-risk patients, 30% ± 2% and 31% ± 2% for intermediate-risk patients, and 17% ± 2% and 18% ± 1% for adverse-risk patients, respectively. Similarly, another classification based primarily on younger patients with AML yielded similar 4-year OS outcomes for favorable-risk (50% ± 2%), intermediate-risk (32% ± 2%), and adverse-risk (18% ± 1%; Data Supplement, Fig S5C) patients.[20] By contrast, a stratification specific for older intensively treated patients identifies a particularly poor-risk no-go group with a 4-year OS of 3% ± 1% (Data Supplement, Fig S5D).[12] The predictive performance of these models for OS, as measured by the C-index, where the higher the value, the better the discrimination of the model, was 0.655 ± 0.013 (ELN2017), 0.646 ± 0.013 (ELN2022), 0.654 ± 0.013 (Tazi[20]), and 0.608 ± 0.012 (Acute Leukemia French Association [ALFA][12]). This provides a baseline evaluation for a prognostic risk classification system applied to this cohort.

Development of a Clinically Useful Unbiased Model for Risk Stratification

Patients in the AML development cohort were younger compared with the AML validation cohort (66 *v* 68 years;

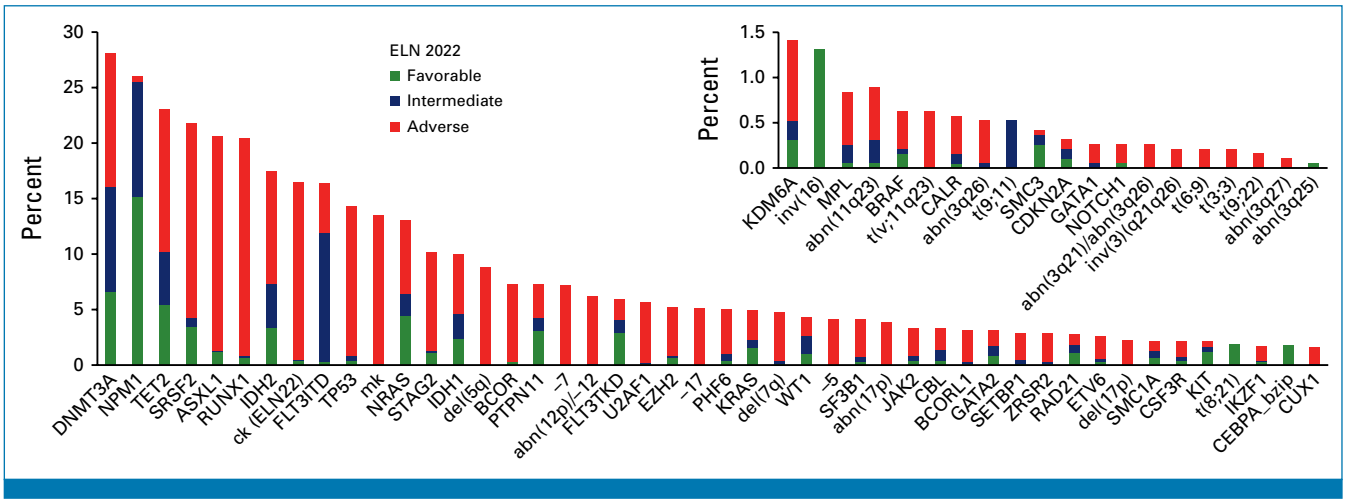

FIG 2. Mutational landscape of the patient cohort. Driver events found in 1,910 elderly patients with newly diagnosed AML. Each bar represents a driver lesion, including gene mutations and chromosomal abnormalities. The colors (green, blue, red) in each bar represent the ELN 2022 risk class (favorable, intermediate, adverse) among each driver lesion. abn, abnormality in; ck, complex karyotype (annotated according to the 2022 ELN risk classification); ELN, European LeukemiaNet; mk, monosomal karyotype.

P < .001, respectively). All other baseline clinical variables and distributions of somatic gene mutations and cytogenetic alterations were not significantly different between the AML development and AML validation cohorts (Data Supplement, Table S2 and Fig S6). The median follow-up times in the AML development, AML validation, and HR-MDS test cohorts were 58.9 months (range, 0.2-117), 38.4 (0.2-50.6), and 49.0 (0.2-115), respectively. OS was similar between the AML development versus AML validation and HR-MDS test cohorts (29% ± 1% *v* 32% ± 2%, 23% ± 1% at 4-years; P = .39; Data Supplement, Fig S7).

To identify the optimum combination of patient-specific and genetic and cytogenetic variables to risk stratify patients, we used a machine learning random survival forest algorithm (Data Supplement for details) to determine the importance toward stratifying OS (Data Supplement, Table S3 and Fig S8).

Next, we used the top discriminatory variables sequentially in a Cox regression analysis for OS to define the optimal model (Fig 3A). The three most important variables at diagnosis in predicting survival were the presence of a *TP53* mutation (HR, 2.42 [95% CI, 1.83 to 3.21]), monosomal karyotype (HR, 2.06 [95% CI, 1.56 to 2.73]), and age >65 years (HR, 1.50 [1.31 to 1.72]) of the nine variables identified. Finally, these nine variables were assigned points on the basis of their rounded HRs. Mutated *TP53* and monosomal karyotype were assigned three points, age >65 years was assigned two points, WBC >20 × 10e9/L, male sex, *FLT3* internal tandem duplication (ITD), and mutations in *DNMT3A*, *ASXL1*, and *RUNX1* were each assigned one point. *FLT3-ITD* was the only gene found of all the mutations in genes encoding signaling molecules. The median individual total score in the development cohort was three points (range, 0-10; Fig 3B). OS decreased with increasing scores (Data Supplement, Fig S9). Using quartiles of the score distribution, we collapsed patients of the development cohort into four groups defined as favorable (score 0-1 points; n = 170, 14.1%), intermediate (score 2-3; n = 485, 40.3%), poor (score 4-6; n = 339, 28.2%), and very poor (score 7-10; n = 210, 17.4%, Fig 3B).

The favorable-risk group had relatively younger, mostly female patients and was depleted in adverse-risk molecular features. By contrast, the very poor-risk group was enriched with patients with high-risk cytogenetics and/or mutated *TP53* (Data Supplement, Fig S10 and Table S4). Importantly, CR/CRi rate was 90.3% for favorable-risk patients, which decreased to 57.3% for very poor-risk patients with AML. Similarly, the transplant rate was 45.0% in the favorable-risk group, which was lower in the intermediate- (33.2%), poor- (24.5%), and very poor-risk (29.4%) groups.

Outcomes for the AML60+ Classification

The new risk model, termed the AML60+ classification, showed strong prognostic separation of OS in the AML development, AML validation, and HR-MDS test cohorts (Figs 3C-3E). OS at 4 years decreased progressively in substantial steps across the four risk groups, in the AML development (favorable: 54% ± 4%, intermediate: 38% ± 2%, poor: 21% ± 2%, very poor: 4% ± 1%), AML validation (52% ± 9%, 43% ± 4%, 27% ± 4%, 4% ± 3%), and HR-MDS test cohorts (54% ± 10%, 33% ± 6%, 14% ± 5%, 0% ± 3%). These differences in outcome were similarly observed when censored at allo-HCT (Data Supplement, Fig S11). The performance of the AML60+ classification for OS discrimination as measured by the C-index was 0.694 ± 0.015 (AML development), 0.666 ± 0.023 (AML validation), and 0.738 ± 0.037 (HR-MDS test). Calibration was excellent in all three cohorts (Data Supplement, Fig S12). The AML60+ classification was

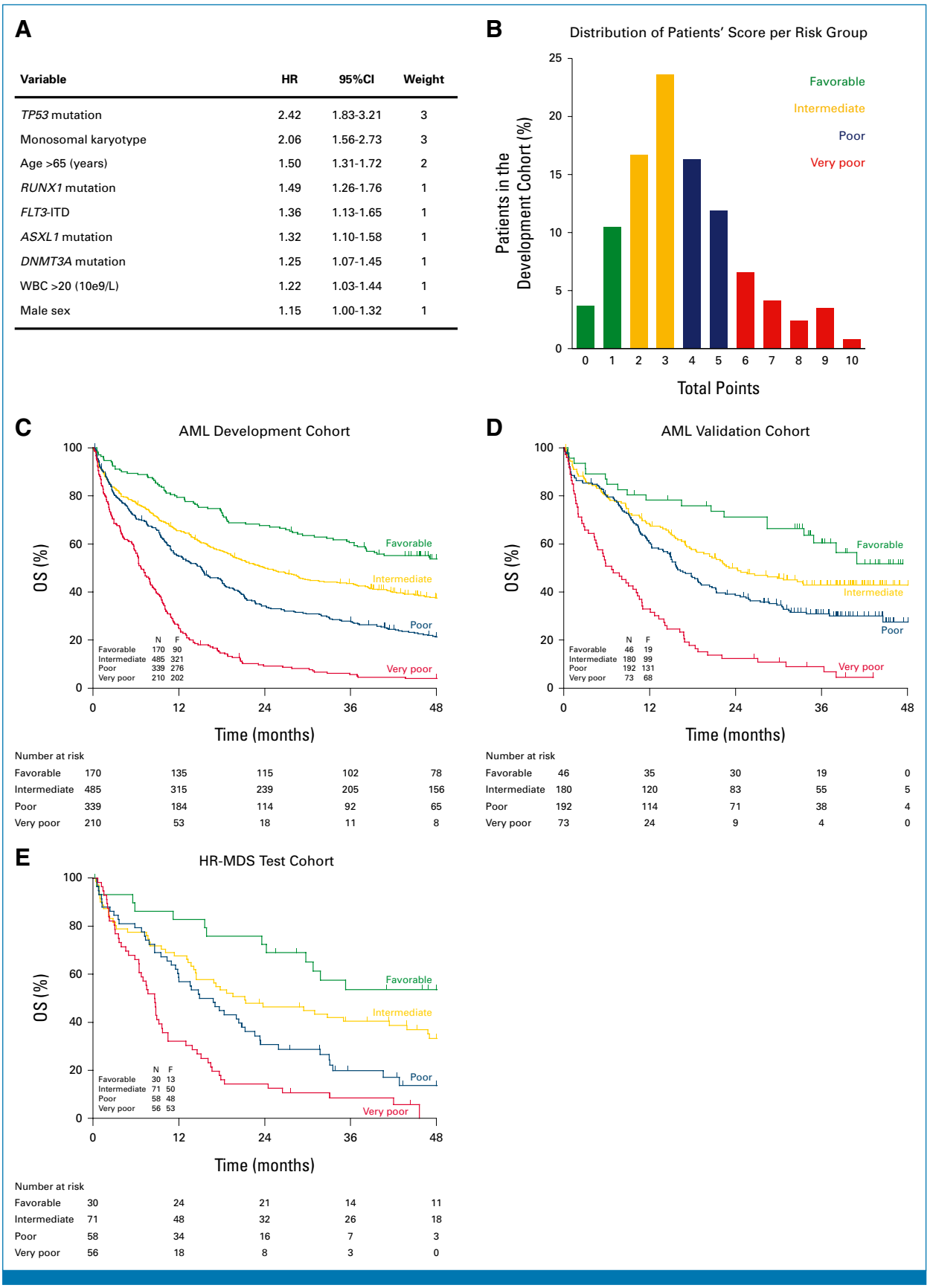

FIG 3. AML60+ classification model development. (A) Cox regression analysis for OS using the top predictors identified by the random survival forest. Patients are assigned points on the basis of the presence of predictors; (B) shows the distribution of patients across the total sum of points and four risk groups in the development cohort. OS by risk categories (continued on following page)

FIG 3. (Continued). of the novel risk score in the (C) AML development cohort, (D) AML validation cohort, and (E) HR-MDS test cohort. Time is measured from the date of study entry. F, number of failures (ie, death); HR, hazard ratio; HR-MDS, high-risk myelodysplastic syndrome; N, number of patients at risk; OS, overall survival.

also associated with highly different event-free survival for all patients and relapse-free survival for patients in CR/CRi (Data Supplement, Fig S13).

Restratification of Patients From ELN2022 to the AML60+ Classification

Since the ELN2022 model was not developed for older patients with AML, we first asked how patients with AML in the three ELN2022 risk groups would be distributed among the four AML60+ prognostic groups (Fig 4A). This analysis showed that each ELN2022 risk group is heterogeneous with respect to the AML60+ risk groups. For example, 37% of the ELN2022 adverse-risk group contains AML60+ favorable- and intermediate-risk patients. Conversely, the ELN2022 favorable-risk group contains 75% of AML60+ intermediate- or higher-risk patients.

Next, we directly compared OS using the AML60+ classification for each ELN2022 risk group (Figs 4B-4D). Strikingly, in each ELN response category, AML60+ markedly improved the stratification of patients. For example, in ELN favorable-risk patients, where the 4-year OS is 53% ± 3%, AML60+ further partitioned patients into three subgroups where OS ranges from 66% ± 5% (AML60+ favorable) to 53% ± 4% (AML60+ intermediate) and 43% ± 5% (AML60+ poor; Fig 4B). In the remaining two ELN2022 subgroups, intermediate-risk and adverse-risk, AML60+ similarly also provided additional prognostic information (Figs 4C and 4D). Within the ELN2022 adverse-risk group, comprising >57% of our cohort, the AML60+ favorable and intermediate subgroups were associated with the better OS at 4 years of 48% ± 6% and 32% ± 3% compared with 19% ± 1% in the ELN adverse-risk group as a whole, which was similar to the AML60+ poor-risk group (15% ± 2%). However, AML60+ also identified a very poor-risk subgroup within the ELN2022 adverse-risk group with a 4-year OS of only 3% ± 1% (Fig 4D).

Thus, for each ELN2022 risk category, AML60+ provided additional prognostic information, showing its substantial added value. We repeated this analysis to demonstrate how AML60+ would perform within the ALFA classification model[12] (Data Supplement, Fig S14), which is based on an age-appropriate prognostic risk classification. This analysis showed that AML60+ also outperforms the ALFA classification.[12]

Impact of allo-HCT in the AML60+ Classification

To address the clinically important question of which older patients with AML maximally benefit from allo-HCT in first CR/CRi, we analyzed 4-year OS measured from CR/CRi, with allo-HCT considered as a time-varying covariate (Fig 5).[15] OS at 4 years was improved by allo-HCT in the intermediate- and very poor-risk AML60+ subgroup compared with no allo-HCT (51% ± 5% *v* 39% ± 3%, $P = .01$; and 12% ± 5% *v* 2% ± 1%, $P = .03$), whereas OS was not significantly different in the favorable-risk and poor-risk subgroup (62% ± 5% *v* 53% ± 5%, $P = .24$; and 35% ± 5% *v* 22% ± 2%, $P = .07$). In the favorable-, intermediate-, and poor-risk groups, the relative risk of relapse was reduced with allo-HCT toward one third, but was counterbalanced by two- to three-fold increased nonrelapse mortality (NRM; Data Supplement, Figs S15-S17).

DISCUSSION

There is a clinical need to predict outcome more accurately for older patients with AML treated with curative intent and specifically to identify those patients who will benefit from allo-HCT, the most important curative consolidation therapy in this age group. To address this, to our knowledge, we present the largest study combining the genomic landscape with clinical outcomes of intensively treated patients older than 60 years with AML and HR-MDS. The study was conducted with the aim of providing a clinically applicable, validated, age-specific prognostic classification that also identifies patients who are most likely to benefit from allo-HCT. Using an unsupervised assessment of widely available diagnostic patient-specific and genetic variables, combined with a statistical evaluation of the importance of each variable, we propose a new prognostic risk classification for this patient group, called AML60+ that stratifies older intensively treated patients with AML into four risk groups with variable outcomes on the basis of nine commonly available clinical and genetic variables. AML60+ improves on the current widely used ELN2022 risk classification that is based on data from patients with AML younger than 60 years. AML60+ better discriminates patient outcomes for each of the current ELN2022 risk groups. Importantly, AML60+ also provides a prognostic scoring system for patients with HR-MDS treated with intensive chemotherapy and allo-HCT concordant with the notion that HR-MDS (10%-19% blasts) and AML are overlapping diseases with respect to treatment outcomes with intensive chemotherapy as highlighted by the International Consensus Classification.[21]

As the most potent curative post-remission therapy for this age group is allo-HCT, it is critical to identify which older patients with AML treated with curative intent will benefit from this potentially toxic therapy. We demonstrated a significant OS benefit of allo-HCT in the patients with AML assigned to the AML60+ intermediate- and very poor-risk

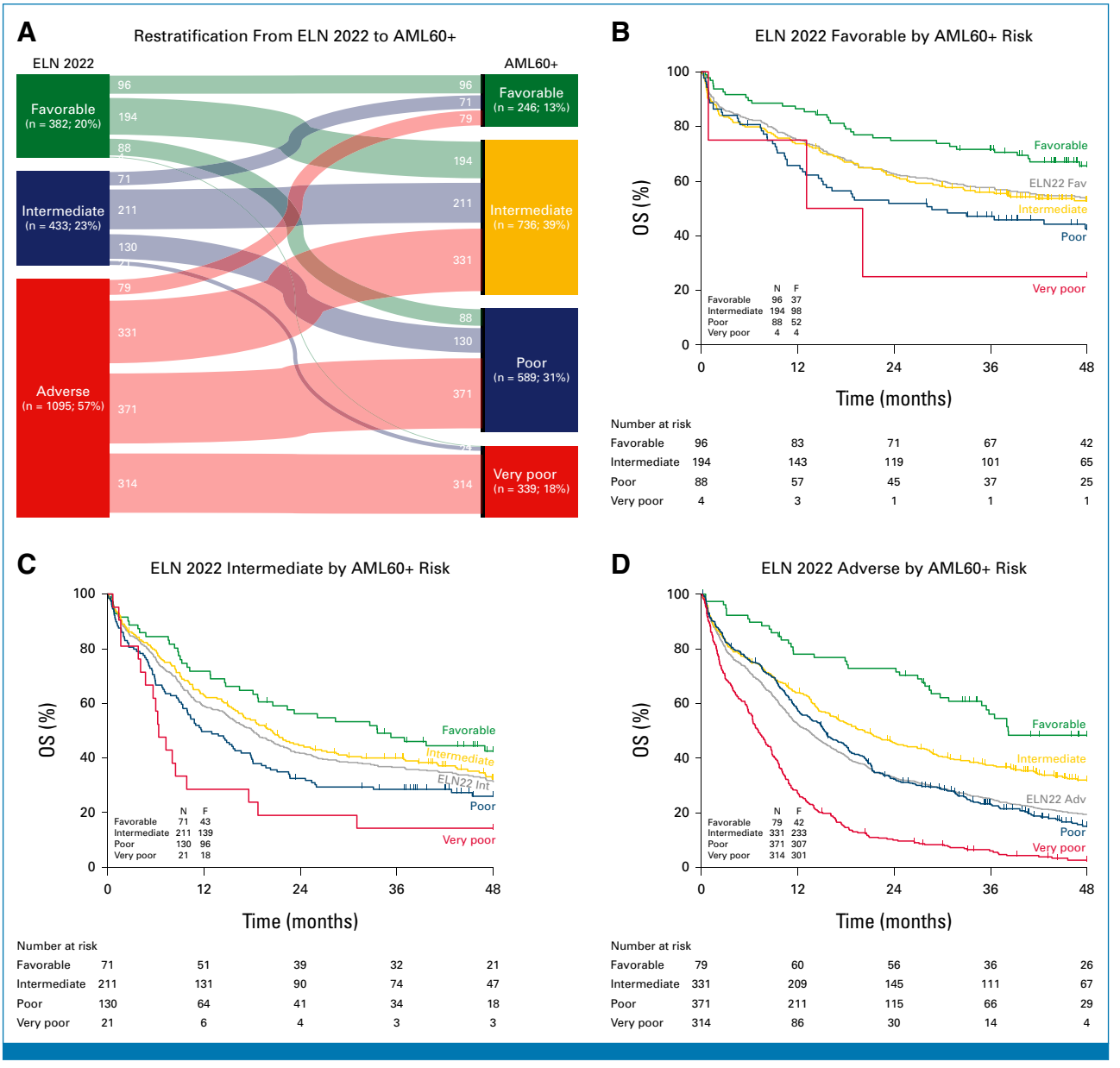

FIG 4. Restratification and OS of patients from ELN 2022 to AML60+ classification. (A) Restratification of patients from ELN 2022 risk classification to the new AML60+ classification. OS by the new AML60+ classification in the ELN 2022 (B) favorable-, (C) intermediate-, and (D) adverse-risk groups. The corresponding outcome curve of each ELN 2022 group is shown in gray in (B), (C), and (D). Time is measured from the date of study entry. ELN, European LeukemiaNet; F, number of failures (ie, death); N, number of patients at risk; OS, overall survival.

group and an indication for better OS in the AML60+ poor-risk group. Although the OS benefit of allo-HCT in these older patients appeared to be relatively modest, the cumulative incidence of relapse was reduced by allo-HCT in all risk groups, indicating a strong graft-versus-leukemia effect. However, as this benefit was counterbalanced by increased NRM in all risk groups, it emphasizes the importance of patient-specific evaluation of NRM (eg, by transplant risk models Hematopoietic Cell Transplantation-comorbidity index, European Society for Blood and Marrow Transplantation risk score) and deployment of existing, and new, strategies to reduce the risk of NRM. Importantly, AML60+ defines a very poor-risk group that has a survival of only 12% ± 5% with allo-HCT and only 2% ± 1% without allo-HCT at 4 years. This patient group should be prioritized for innovative therapeutic strategies in clinical trials even in the frontline setting.

The majority (65.3%) of older intensively treated patients with AML have myelodysplastic-related cytogenetic changes and/or mutations in genes associated with secondary AML (65.3%), whereas only 9.1% of patients have a clinical diagnosis of secondary AML. The 4-year OS for patients with genetic secondary AML is identical to those with clinical secondary AML supporting the notion that much of secondary AML is not clinically recognized.[17] Consistent with

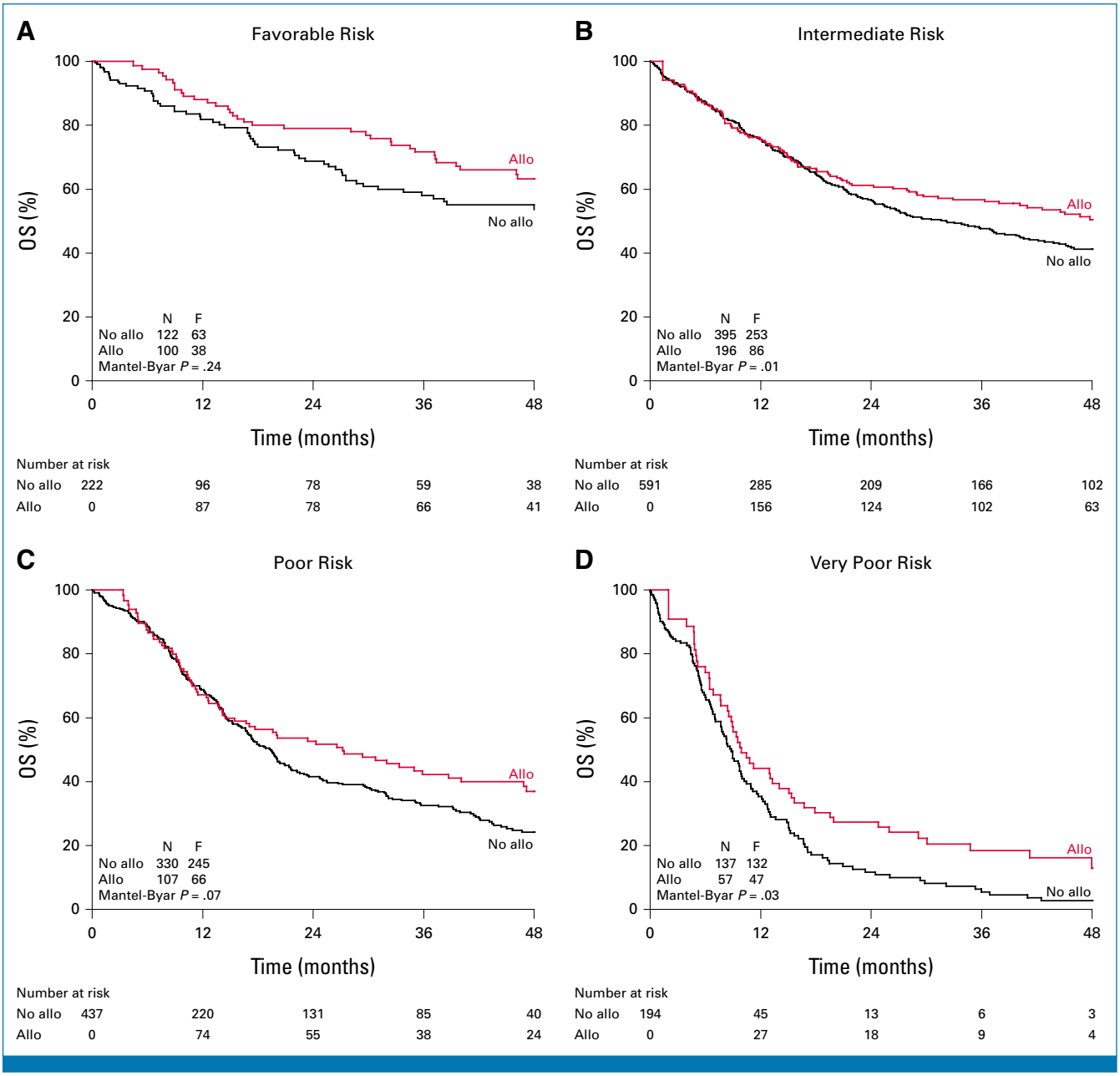

FIG 5. OS of allo-HCT versus no allo-HCT in first CRi in AML60+ risk groups. OS by the (A) favorable, (B) intermediate, (C) poor, and very poor (D) groups of the AML60+ classification in which allo-HCT is considered as a time-dependent covariate according to a Simon-Makuch plot.[15] Time is measured from the date of CRI, and patients switch from the no allo-HCT to the allo-HCT at the time of allo-HCT if they received allo-HCT. allo-HCT, allogeneic hematopoietic cell transplantation; CRi, complete remission with incomplete count recovery; F, number of failures (ie, death); N, number of patients at risk; OS, overall survival.

previous reports, *TP53* mutations and chromosomal abnormalities associated with *TP53* mutations (complex and monosomal karyotype) were associated with very poor outcomes.[22-24]

There are several limitations of this study. It is retrospective with multiple patient cohorts treated over a 12-year period. Although patients were treated in clinical trials, different intensive chemotherapy regimens were given. For example, a proportion of patients in the NCRI-AML18 trial received gemtuzumab ozogamicin with intensive chemotherapy, which was not used in the HOVON protocols. However, this also means that the results are likely to be relevant regardless of the type of intensive chemotherapy schedule used. Sixteen percent of the patients with AML had *FLT3*-ITD, but only 10% of those patients received a *FLT3* inhibitor (quizartinib) in the development cohort. Further analysis in a large cohort of patients uniformly treated with *FLT3* inhibitors will be needed to establish if *FLT3*-ITD remains a poor prognosis biomarker in older patients. Our analyses did not include assessment of measurable residual disease (MRD),[25-28] either after intensive therapy or pre– or post–

allo-HCT. Future studies will be needed to assess the impact of MRD. Although patients were not randomly assigned to allo-HCT and patient selection cannot be excluded, these data reflect real-world allo-HCT clinical practice. Finally, our cohort consisted of a predominantly White population; further work will be required in other ethnicities, given the emerging data on diverse prognostic implications of AML mutations.[29]

Similar to all prognostic classifications, AML60+ will have to be refined as optimal treatment evolves. As targeted therapies for specific genetic subtypes are tested, it is likely that genetic subtype–specific, as well as age- and treatment-specific, prognostic risk scores will be needed. Furthermore, it is likely that intensive chemotherapy will be compared with venetoclax-HMA backbone regimens, especially for more adverse-risk patients and for patients who can have targeted therapies in triplet combination with venetoclax-HMA. These novel treatment regimens also including other novel agents (eg, CPX-351, oral azacitidine) require large, international, adequately powered studies to develop the next generation of risk classifications. In this regard, the data generated here furnish an important reference for future investigation.

In summary, AML60+ provides a novel prognostic score that is easy to apply to current routine clinical practice and crucially provides information on survival post–allo-HCT. By using AML60+, clinicians will better be able to assess the relative benefit from allo-HCT and balance that against the potential NRM assessed by specific risk scores.[30–33] AML60+ is available as an online tool.[34]

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Risk Stratification in Older Intensively Treated Patients With AML

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