Chromosomal Abnormalities and Prognosis in NPM1-Mutated Acute Myeloid Leukemia: A Pooled Analysis of Individual Patient Data From Nine International Cohorts

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PURPOSE Nucleophosmin 1 (NPM1) mutations are associated with a favorable prognosis in acute myeloid leukemia (AML) when an internal tandem duplication (ITD) in the fms-related tyrosine kinase 3 gene (FLT3) is absent (FLT3-ITD<sup>neg</sup>) or present with a low allelic ratio (FLT3-ITD<sup>low</sup>). The 2017 European LeukemiaNet guidelines assume this is true regardless of accompanying cytogenetic abnormalities. We investigated the validity of this assumption.

METHODS We analyzed associations between karyotype and outcome in intensively treated patients with NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> AML who were prospectively enrolled in registry databases from nine international study groups or treatment centers.

RESULTS Among 2,426 patients with NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> AML, 2,000 (82.4%) had a normal and 426 (17.6%) had an abnormal karyotype, including 329 patients (13.6%) with intermediate and 83 patients (3.4%) with adverse-risk chromosomal abnormalities. In patients with NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> AML, cytogentic were associated with lower complete remission rates (87.7%, 86.0%, and 66.3% for normal, aberrant intermediate, and adverse karyotype, respectively; P < .001), inferior 5-year overall (52.4%, 44.8%, 19.5%, respectively; P < .001) and event-free survival (40.6%, 36.0%, 18.1%, respectively; P < .001), and a higher 5-year cumulative incidence of relapse (43.6%, 44.2%, 51.9%, respectively; P = .0012). These associations remained in multivariable mixed-effects regression analyses adjusted for known clinicopathologic risk factors (P < .001 for all end points). In patients with adverse-risk chromosomal aberrations, we found no significant influence of the NPM1 mutational status on outcome.

CONCLUSION Karyotype abnormalities are significantly associated with outcome in NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> AML. When adverse-risk cytogenetics are present, patients with NPM1<sup>mut</sup> share the same unfavorable prognosis as patients with NPM1 wild type and should be classified and treated accordingly. Thus, cytogenetic risk predominates over molecular risk in NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> AML.

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INTRODUCTION

Mutations in the nucleophosmin 1 (NPM1) gene have been associated with a favorable prognosis in the absence of concomitant internal tandem duplications (ITD) of the fms-related tyrosine kinase 3 (FLT3) gene in cytogenetically normal acute myeloid leukemia (AML).<sup>1,6</sup> It was later observed that patients with an NPM1 mutation (NPM1<sup>mut</sup>) and a low allelic ratio FLT3-ITD (FLT3-ITD<sup>low</sup>) had similar outcomes to patients with an NPM1 mutation but no FLT3-ITD.<sup>7,8</sup>

Thus, both groups are now being classified as favorable risk in the 2017 update of the European LeukemiaNet recommendations on genetic risk classification (ELN 2017).<sup>9</sup>

Another key change in ELN 2017 has been to consider the NPM1<sup>mut/FLT3-ITD<sup>neg/low</sup> status favorable regardless of coexisting chromosomal abnormalities, as in the case of core-binding factor AML.<sup>9</sup> However, the
Central Cytogenetic Review and Genetic Analyses

All karyotypes were centrally reviewed by a hematologist and a geneticist, L.A. and R.E., following International System for Human Cytogenomic Nomenclature 2016 guidelines.12 Cytogenetic abnormalities were classified as favorable, intermediate, or adverse as defined in ELN 2017.9 Among patients with FLT3-ITD-positive disease, only those with an allelic ratio of less than 0.5 (FLT3-ITD<0.5) were included.9

Statistical Analyses

Baseline variables were compared using χ² or Fisher’s exact test for categorical and Mann-Whitney or Kruskal-Wallis test for continuous variables. Time-to-event variables and complete remission (CR) were defined as described in ELN 2017,9 with the exception that overall survival (OS) and event-free survival (EFS) were measured from initial AML diagnosis. Furthermore, because induction strategies and time points of response evaluation differed between cohorts, for reasons of comparability, response to induction was based on a patient’s status at day 90, counting induction failure as an event at day 90 for EFS.13 Survival probabilities were determined with the Kaplan-Meier and the Aalen-Johansen estimator and compared using log-rank and Gray’s test, respectively; all survival probabilities are given at 5 years. Follow-up time was calculated by the reverse Kaplan-Meier method. Multivariable mixed-effects Cox proportional hazard, cause-specific hazard, and logistic regression models were generated to assess statistical significance of prognostic factors with respect to OS, EFS, cumulative incidence of relapse (CIR), and CR. Cytogenetic risk was adjusted for age, type of AML (de novo vs secondary), WBC count, and FLT3-ITD mutational status (present with low allelic ratio v absent). A registry center–specific random effects term was included in the multivariable models to account for potential heterogeneity in baseline risk among centers. The proportional hazards assumption was verified for each variable individually by inspection of scaled Schoenfeld residuals. The consistency of association with outcomes across subgroups was examined with Cox proportional hazard models and test for interaction. To evaluate associations of allogeneic HSCT as postremission therapy with prognosis, time-to-event variables were measured from CR1, and allogeneic HSCT was introduced as a time-dependent covariable. The time-dependent association was plotted according to the method of Simon and Makuch.14 Missing data were not imputed. Two-sided P values < .05 were considered significant. All analyses were performed using R (www.r-project.org), version 3.5.1.

RESULTS

Association With Clinical and Molecular Features

A total of 2,426 patients with NPM1mut/FLT3-ITDneg/low AML were identified (Fig 1). Of these, 2,000 (82.4%) had evidence supporting this modification is limited, and previous studies have so far only compared the impact of abnormal versus normal cytogenetics, without specific focus on the rare co-occurrence of NPM1 mutations and karyotype abnormalities that are classically associated with an adverse risk, such as deletions or monosomies of chromosomes 5 or 7, abnormalities of chromosome 17p, or complex or monosomal karyotypes, among others.10,11 Even though the combination of an NPM1 mutation with these abnormalities is rare, the prognostic effect of adverse cytogenetics in NPM1mut AML has important implications for postremission treatment decisions, in particular, the current recommendation that patients who are NPM1mut/FLT3-ITDneg/low not receive allogeneic hematopoietic stem cell transplantation (HSCT), given their presumed low risk of relapse might be altered if the adverse karyotype increased the risk. We evaluated the potential prognostic impact of karyotype in 2,426 intensively treated patients with NPM1mut/FLT3-ITDneg/low AML in a pooled analysis of individual patient data from nine study group registries or treatment centers worldwide.

METHODS

Patients

Individual patient data were collected from nine international AML study group registries or treatment centers: Study Alliance Leukemia, Programa Español para el Tratamiento de las Hemopatías Malignas, Acute Leukemia French Association, Toulouse-Bordeaux AML database, MD Anderson Cancer Center, Swedish AML Registry, Czech Leukemia Study Group for Life, Australasian Leukemia and Lymphoma Group, and Fred Hutchinson Cancer Research Center. Only intensively treated patients with AML 18 years of age or older with a known karyotype and who carried an NPM1 mutation in the absence of an FLT3-ITD mutation with a high (≥ 0.5)19 allelic ratio were included. From each cohort, data on intensively treated patients with NPM1 wild type (NPM1wt) and adverse cytogenetics as defined in the ELN 2017 guidelines were used as an adverse-risk reference cohort. For each patient, a predefined minimal data set was collected, including the variables age, sex, date of AML diagnosis, type of AML (de novo or secondary), bone marrow (BM) blast count, WBC count, karyotype, NPM1/FLT3-ITD mutational status including mutant/wild-type ratio, type of and response to induction chemotherapy, date of allogeneic HSCT in first complete remission (CR1), date of allogeneic HSCT beyond CR1, events (induction failure, relapse, death), and date of last contact. Patients with myelodysplastic syndromes or acute promyelocytic leukemia were excluded. This study was performed in accordance with the Declaration of Helsinki, all registries were approved by the local institutional review boards, and written informed consent was obtained from all patients through the participating centers.
a normal karyotype and 426 (17.6%) had an abnormal karyotype, including 329 patients (13.6%) with chromosomal abnormalities of intermediate risk (ie, with aberrations not classified as adverse or favorable according to ELN 2017), 83 (3.4%) with chromosomal abnormalities of adverse risk, and 14 (0.6%) with favorable core-binding factor cytogenetics. A total of 1,845 patients with NPM1wt/FLT3-ITDneg/low and adverse-risk cytogenetics were identified.

Baseline characteristics are listed in Table 1. In patients with NPM1mut/FLT3-ITDneg/low AML, the presence of adverse-risk cytogenetics was associated with older age (P = .0097), male sex (P < .001), secondary AML (P = .032), and negative FLT3-ITD status (P < .001). There were no significant differences in rates of allogeneic HSCT between cytogenetic risk groups in patients with NPM1mut/FLT3-ITDneg/low (P = .40). Compared with patients with NPM1wt/FLT3-ITDneg/low with adverse cytogenetics, patients with NPM1mut/FLT3-ITDneg/low with adverse cytogenetics were older, had higher BM blast counts, and had higher WBC counts. Rearrangements of 11q23, -5/del(5q), and a monosomal karyotype were underrepresented in patients with NPM1mut/FLT3-ITDneg/low with adverse-risk karyotype compared with the NPM1wt reference group. Rates of allogeneic HSCT were higher in patients with adverse-risk cytogenetics with NPM1wt than in those with NPM1mut (41.5% v 30.1%; P = .082).

### Karyotype and Outcome in NPM1mut/FLT3-ITDneg/low AML

The 83 patients with NPM1mut/FLT3-ITDneg/low AML and adverse cytogenetics had a lower CR rate (66.3%) than...
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NPM1 Mutated, Karyotype</th>
<th>NPM1 Wild Type, Karyotype</th>
<th>( P^* )</th>
<th>( P^† )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2,000</td>
<td>1,845</td>
<td>.0097§</td>
<td>.034§</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>56 (18-84)</td>
<td>62 (28-79)</td>
<td>.0097§</td>
<td>.034§</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>875 (43.8)</td>
<td>50 (60.2)</td>
<td>&lt; .001</td>
<td>.31</td>
</tr>
<tr>
<td>Female</td>
<td>1,125 (56.2)</td>
<td>33 (39.8)</td>
<td>1,007 (54.6)</td>
<td></td>
</tr>
<tr>
<td>AML type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>1,805 (90.2)</td>
<td>68 (81.9)</td>
<td>1,350 (73.2)</td>
<td></td>
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<tr>
<td>Secondary</td>
<td>176 (8.8)</td>
<td>14 (16.9)</td>
<td>456 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>19 (0.9)</td>
<td>1 (1.2)</td>
<td>39 (2.1)</td>
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</tr>
<tr>
<td>WBC, ( \times 10^9/L )</td>
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<td></td>
<td>.68§</td>
<td>&lt; .001§</td>
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<tr>
<td>Median (range)</td>
<td>20 (0-453)</td>
<td>14 (0-221)</td>
<td>5 (0-468)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9 (0.4)</td>
<td>3 (3.6)</td>
<td>5 (0.3)</td>
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</tr>
<tr>
<td>BM blasts</td>
<td></td>
<td></td>
<td>.73§</td>
<td>&lt; .001§</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66 (0-100)</td>
<td>67 (16-96)</td>
<td>52 (1-100)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>120 (6.0)</td>
<td>14 (16.9)</td>
<td>108 (5.9)</td>
<td></td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td></td>
<td></td>
<td>&lt; .001†</td>
<td>.47¶</td>
</tr>
<tr>
<td>Absent</td>
<td>1,592 (79.6)</td>
<td>80 (96.4)</td>
<td>1,799 (97.5)</td>
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</tr>
<tr>
<td>Present with low allelic ratio</td>
<td>408 (20.4)</td>
<td>3 (3.6)</td>
<td>46 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Allergic HSCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1,409 (70.5)</td>
<td>58 (69.9)</td>
<td>1,074 (58.2)</td>
<td>.082</td>
</tr>
<tr>
<td>CR1</td>
<td>330 (16.5)</td>
<td>17 (20.5)</td>
<td>441 (23.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; CR1</td>
<td>254 (12.7)</td>
<td>8 (9.6)</td>
<td>321 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>7 (0.4)</td>
<td>0 (0.0)</td>
<td>9 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990-2008</td>
<td>628 (31.4)</td>
<td>31 (37.3)</td>
<td>598 (32.4)</td>
<td>.58</td>
</tr>
<tr>
<td>2009-2013</td>
<td>768 (38.4)</td>
<td>30 (36.1)</td>
<td>760 (41.2)</td>
<td></td>
</tr>
<tr>
<td>2014-2018</td>
<td>604 (30.2)</td>
<td>22 (26.5)</td>
<td>487 (26.4)</td>
<td></td>
</tr>
<tr>
<td>Adverse cytogenetic abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(6;9)</td>
<td>—</td>
<td>—</td>
<td>41 (2.2)</td>
<td>.42¶</td>
</tr>
<tr>
<td>t(11q23)</td>
<td>—</td>
<td>—</td>
<td>182 (9.9)</td>
<td>.0039¶</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>—</td>
<td>2 (2.4)</td>
<td>29 (1.6)</td>
<td>.39¶</td>
</tr>
<tr>
<td>inv(3)(t;3:3)</td>
<td>—</td>
<td>2 (2.4)</td>
<td>106 (5.7)</td>
<td>.32¶</td>
</tr>
<tr>
<td>t(5;11)</td>
<td>—</td>
<td>17 (20.5)</td>
<td>653 (35.4)</td>
<td>.0053</td>
</tr>
<tr>
<td>–7</td>
<td>—</td>
<td>17 (20.5)</td>
<td>509 (27.6)</td>
<td>.16</td>
</tr>
<tr>
<td>abn(17p)</td>
<td>—</td>
<td>15 (18.1)</td>
<td>461 (25.0)</td>
<td>.15</td>
</tr>
<tr>
<td>Monosomal</td>
<td>—</td>
<td>21 (25.3)</td>
<td>859 (46.6)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Complex</td>
<td>—</td>
<td>59 (71.1)</td>
<td>1,129 (61.2)</td>
<td>.070</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>5 (0-468)</td>
<td>108 (5.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CR1, first complete remission; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication.

*P values for comparison of characteristics in patients with NPM1 mutations according to cytogenetic risk.

†P values for comparison of characteristics in patients with adverse cytogenetics according to NPM1 mutational status.

‡Karyotype with cytogenetic aberrations classified as neither favorable nor adverse risk.

§Kruskal-Wallis or Mann-Whitney test.

||K2 test.

¶Fisher’s exact test.
patients with NPM1mut/FLT3-ITDneg/low AML and a normal karyotype (87.7%) or intermediate-risk cytogenetic abnormalities (86.0%; \( P < .001 \)), but a similar CR rate to patients with NPM1mut/FLT3-ITDneg/low carrying adverse cytogenetic abnormalities (57.5%; \( P = .11 \)). Median follow-up time for all patients was 4.23 years (95% CI, 4.05 to 4.46 years). Among patients with NPM1mut/FLT3-ITDneg/low, 5-year EFS rates were lower in the presence of adverse cytogenetics (18.1%) than with aberrant intermediate cytogenetics (86.0%; \( P < .001 \)), but a similar CR rate to NPM1mut/FLT3-ITDneg/low AML and a normal karyotype. Most importantly, we found no significant hazard risk of death (HR, 2.63; 95% CI, 2.05 to 3.38; \( P < .001 \)) when comparing patients with NPM1mut/FLT3-ITDneg/low and NPM1mut/FLT3-ITDneg/low with adverse-risk.
cytogenetic abnormalities. When comparing intermediate and normal cytogenetics in patients with NPM1\textsuperscript{mut}/FLT3-ITD\textsuperscript{neg/low}, intermediate cytogenetics remained associated with inferior OS (HR, 1.27; 95% CI, 1.07 to 1.50; \(P = .0060\)) and EFS (HR, 1.21; 95% CI, 1.04 to 1.41; \(P = .014\)), but not with a higher CIR (HR, 1.18; 95% CI, 0.97 to 1.44; \(P = .10\)) after adjustment for age, AML type, WBC, and FLT3-ITD status. We found no significant difference in outcome between normal karyotype and favorable cytogenetic abnormalities among patients with NPM1\textsuperscript{mut}/FLT3-ITD\textsuperscript{neg/low} genotype (Data Supplement).

Recently, the categorization of NPM1\textsuperscript{mut} AML with an FLT3-ITD\textsuperscript{low} mutation as favorable risk has been questioned.\(^{15}\) Thus, we reanalyzed the data excluding the 448 patients with an FLT3-ITD\textsuperscript{low} mutation. Again, adverse cytogenetic abnormalities remained associated with an unfavorable

<table>
<thead>
<tr>
<th>TABLE 2. Multivariable Regression Analyses in Patients With NPM1\textsuperscript{mut}/FLT3-ITD\textsuperscript{neg/low} AML</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 10-year increase</td>
<td>0.64</td>
<td>0.58 to 0.72</td>
</tr>
<tr>
<td>Type of AML, secondary v de novo</td>
<td>0.84</td>
<td>0.58 to 1.23</td>
</tr>
<tr>
<td>WBC, per 50 (\times 10^9/L) increase</td>
<td>0.80</td>
<td>0.73 to 0.88</td>
</tr>
<tr>
<td>FLT3-ITD, present with low allelic ratio v absent</td>
<td>0.98</td>
<td>0.70 to 1.36</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate abnormal v normal</td>
<td>0.84</td>
<td>0.59 to 1.19</td>
</tr>
<tr>
<td>Adverse v normal</td>
<td>0.29</td>
<td>0.17 to 0.48</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 10-year increase</td>
<td>1.45</td>
<td>1.38 to 1.53</td>
</tr>
<tr>
<td>Type of AML, secondary v de novo</td>
<td>1.11</td>
<td>0.92 to 1.35</td>
</tr>
<tr>
<td>WBC, per 50 (\times 10^9/L) increase</td>
<td>1.19</td>
<td>1.14 to 1.25</td>
</tr>
<tr>
<td>FLT3-ITD, present with low allelic ratio v absent</td>
<td>1.40</td>
<td>1.20 to 1.64</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate abnormal v normal</td>
<td>1.27</td>
<td>1.07 to 1.50</td>
</tr>
<tr>
<td>Adverse v normal</td>
<td>2.97</td>
<td>2.29 to 3.87</td>
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<tr>
<td>Event-free survival</td>
<td></td>
<td></td>
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<tr>
<td>Age, per 10-year increase</td>
<td>1.34</td>
<td>1.28 to 1.41</td>
</tr>
<tr>
<td>Type of AML, secondary v de novo</td>
<td>1.10</td>
<td>0.92 to 1.31</td>
</tr>
<tr>
<td>WBC, per 50 (\times 10^9/L) increase</td>
<td>1.16</td>
<td>1.11 to 1.22</td>
</tr>
<tr>
<td>FLT3-ITD, present with low allelic ratio v absent</td>
<td>1.29</td>
<td>1.12 to 1.48</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate abnormal v normal</td>
<td>1.21</td>
<td>1.04 to 1.41</td>
</tr>
<tr>
<td>Adverse v normal</td>
<td>2.63</td>
<td>2.05 to 3.38</td>
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<tr>
<td>Cumulative incidence of relapse</td>
<td></td>
<td></td>
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<tr>
<td>Age, per 10-year increase</td>
<td>1.29</td>
<td>1.22 to 1.37</td>
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<tr>
<td>Type of AML, secondary v de novo</td>
<td>0.94</td>
<td>0.74 to 1.21</td>
</tr>
<tr>
<td>WBC, per 50 (\times 10^9/L) increase</td>
<td>1.14</td>
<td>1.07 to 1.21</td>
</tr>
<tr>
<td>FLT3-ITD, present with low allelic ratio v absent</td>
<td>1.36</td>
<td>1.14 to 1.63</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate abnormal v normal</td>
<td>1.18</td>
<td>0.97 to 1.44</td>
</tr>
<tr>
<td>Adverse v normal</td>
<td>2.52</td>
<td>1.75 to 3.62</td>
</tr>
</tbody>
</table>

NOTE. Odds ratios (ORs) greater or less than 1.0 indicate higher or lower complete remission rates, respectively, for the higher values of the continuous variables and the first category listed for the categorical variables. Hazard ratios (HRs) greater or less than 1.0 indicate an increased or decreased risk, respectively, of an event for the higher values of the continuous variables and the first category listed for the categorical variables. Because of missing values, 32 of 2,412 patients (1.3%) were excluded in the multivariable models for overall survival, event-free survival, and complete remission, and 27 of 2,092 patients (1.3%) in the model for cumulative incidence of relapse.

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication.
FIG 3. Overall survival according to cytogenetics and NPM1 mutational status by selected baseline categories. (A) Normal versus adverse cytogenetics in NPM1mut/FLT3-ITDneg/low acute myeloid leukemia (AML). (B) NPM1mut/FLT3-ITDneg/low (continued on following page)
outcome in patients with $NPM1^{\text{wt}}/FLT3-ITD^{\text{neg/low}}$ disease after adjustment for age, AML type, and WBC (HR for death, 2.94; 95% CI, 2.25 to 3.84; HR for event, 2.62; 95% CI, 2.03 to 3.38; HR for relapse, 2.45; 95% CI, 1.68 to 3.57; all $P < .001$; Data Supplement). Of note, the $FLT3-ITD^{\text{neg/low}}$ genotype was virtually absent in the adverse karyotype group regardless of $NPM1$ mutational status (Table 1).

### Cytogenetics and Prognosis by Subgroup

We found a significant interaction of age with OS according to karyotype abnormalities in patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ disease ($P_{\text{interaction}} = .0096$; Fig 3) such that the risk of death associated with adverse cytogenetics was 3.97 in younger patients (< 60 years) but only 1.95 in older patients (≥ 60 years) with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ AML. Similar results were obtained for EFS (HR, 3.07 and 1.88, respectively; $P_{\text{interaction}} = .086$; Data Supplement) and CIR (HR, 3.59 and 1.25, respectively; $P_{\text{interaction}} = .0046$; Data Supplement). Younger patients with adverse cytogenetics had a two-thirds reduced likelihood of achieving a CR (OR, 0.29; 95% CI, 0.12 to 0.71; $P = .0062$) and an increased risk of death (HR, 4.71; 95% CI, 3.11 to 7.14; $P < .001$), experiencing an event (HR, 3.56; 95% CI, 2.38 to 5.31; $P < .001$) or relapse (HR, 4.62; 95% CI, 2.81 to 7.60; $P < .001$) after adjustment for age, AML type, WBC, and $FLT3-ITD^{\text{status}}$ compared with patients with normal cytogenetics (Data Supplement). Also in older patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$, adverse cytogenetics remained associated with inferior CR (OR, 0.28; 95% CI, 0.15 to 0.52; $P < .001$), OS (HR, 2.16; 95% CI, 1.53 to 3.05; $P < .001$), and EFS (HR, 2.07; 95% CI, 1.50 to 2.87; $P < .001$), but not with CIR (HR, 1.43; 95% CI, 0.83 to 2.46; $P = .20$) in multivariable analyses (Data Supplement). We found no significant heterogeneity of associations between cytogenetic risk and OS by sex, type of AML, $FLT3-ITD$ status, WBC, BM blast counts, treatment period, or cohort (Fig 3).

### Individual Adverse-Risk Cytogenetic Abnormalities

There were no obvious differences in the association of individual adverse cytogenetic abnormalities with risk of death when comparing patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ in the five largest adverse-risk cytogenetic subgroups, but the number of deaths was small (−5/del(5q): 14; −7: 12; abn(17p): 13; complex karyotype: 47; monosomy karyotype: 18; Fig 3; Data Supplement).

### Allogeneic HSCT in CR1 in Patients With $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$

To evaluate the association of postremission allogeneic HSCT with survival, time-to-event variables were measured from CR1. Because of the low frequency of allogeneic HSCT in CR1 in patients 60 years of age or older (9.2%), only younger patients (< 60 years) were included in these analyses. Of 1,466 younger patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}, 1,345 (91.7%) achieved a CR and 345 of these (25.7%) subsequently received allogeneic HSCT. Baseline characteristics of patients in CR1 stratified by postremission therapy are shown in the Data Supplement. Patients undergoing transplantation in CR1 more frequently had secondary AML ($P = .0079$) or an $FLT3-ITD$ mutation ($P < .001$). Survival for all patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ according to postremission therapy is shown in Figures 4A and 4B. Patients who underwent transplantation had a lower CIR (22.6% vs 41.4%; $P < .001$) but a higher nonrelapse mortality (NRM, 18.3% vs 7.4%; $P < .001$) compared with patients who did not undergo transplantation in CR1. There were no differences in OS between patients who underwent transplantation and those who did not (65.6% vs 67.2%; $P = .34$).

However, among patients with $NPM1^{\text{mut}}/FLT3-ITD^{\text{neg/low}}$ with adverse cytogenetics, those who received allogeneic HSCT in CR1 had a four-fold lower risk of death than patients who did not receive allogeneic HSCT in CR1 (HR, 0.27; 95% CI, 0.09 to 0.82; $P_{\text{interaction}} = .012$; Fig 4C). We found no significant interaction of cytogenetics and postremission treatment (transplantation vs no transplantation) with CIR ($P_{\text{interaction}} = .41$) or NRM ($P_{\text{interaction}} = .53$). Among patients with adverse cytogenetics, the association of allogeneic HSCT in CR1 with better OS was more pronounced in patients with $NPM1^{\text{mut}}$ (HR for death, 0.27; 95% CI, 0.09 to 0.82) than in patients with $NPM1^{\text{wt}}$ (HR for death, 0.71; 95% CI, 0.58 to 0.87; $P_{\text{interaction}} = .073$).

### DISCUSSION

Pretreatment cytogenetic and molecular abnormalities are routinely used to assess risk of relapse in AML and thus to guide treatment strategies in AML, in particular, use of allogeneic HSCT in CR1.8 In the absence of $FLT3-ITD$ with a high allelic ratio, $NPM1$ mutations have been considered to confer a favorable prognosis regardless of concomitant cytogenetic abnormalities, most influentially in the most
recent ELN 2017 genetic risk classification.⁹ This view was based on two reports investigating the prognostic effects of an abnormal karyotype in patients with NPM1mut/FLT3-ITDneg AML. In the larger cohort (n = 355, derived from two independent cohorts),¹⁰ no significant impact of cytogenetic abnormalities on survival for NPM1mut/FLT3-ITDneg AML was found, whereas in the smaller cohort (n = 95),¹¹ a significantly inferior EFS, but not OS, was reported for patients with abnormal cytogenetics. In both studies, however, the individual cytogenetic abnormalities were not reported for patients with the NPM1mut/FLT3-ITDneg genotype, and no distinction was made between chromosomal abnormalities of intermediate and adverse risk, owing to the rarity of the latter in NPM1mut AML.

In contrast, in this study, we were able to distinguish between intermediate and adverse cytogenetics consequent to the inclusion of 2,426 patients with NPM1mut/FLT3-ITDneg/low AML from sites in Europe, Australia, and the United States. As expected, the majority of these patients had a normal karyotype, whereas cytogenetic abnormalities were found in 17.6% of patients, including 329 patients with intermediate and 83 with adverse-risk aberrations. However, it has to be noted that our analysis was performed retrospectively in patients who were, in part, not originally classified according to ELN 2017 guidelines. Thus, NPM1/FLT3 genetic analyses might have been underperformed in patients with an aberrant karyotype, and patients with an abnormal karyotype might have been under-represented in our study.

We found that concomitant chromosomal abnormalities were significantly associated with prognosis in patients with NPM1mut/FLT3-ITDneg/low AML. Whereas the difference in 5-year OS and EFS between normal and intermediate aberrant karyotypes was modest (OS, 52.4% and 44.8%, respectively; EFS, 40.6% and 36.0%, respectively), patients with NPM1mut/FLT3-ITDneg/low with adverse chromosomal

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**FIG 4.** Survival by transplantation status in NPM1mut/FLT3-ITDneg/low acute myeloid leukemia. (A) Overall survival and (B) cumulative incidence of relapse (CIR) and nonrelapse mortality (NRM) according to postremission therapy in younger patients in first complete remission (CR1). (C) Overall survival according to allogeneic hematopoietic stem cell transplantation (alloSCT) status in subgroups by cytogenetic risk. Diamonds represent the pooled unadjusted hazard ratios (HRs). Horizontal lines represent the 95% CIs. The dotted vertical line represents the HR from the complete cohort. The P value for interaction is from the χ² test comparing the interaction HRs across subgroups and represents heterogeneity. AlloSCT was included as a time-dependent covariable.
aberrations had a considerably poorer prognosis (OS, 19.5%; EFS, 18.1%). In fact, patients carrying adverse-risk cytogenetics shared a virtually identical unfavorable outcome, regardless of whether the otherwise beneficial $NPM1^{mut}/FLT3-ITD^{neg/low}$ status was present or not. The type of the adverse chromosomal abnormality did not seem to influence this effect, although low numbers might obscure detection of heterogeneity among individual aberrations. Furthermore, we found similar results when repeating the analyses excluding patients with an $FLT3-ITD^{low}$ mutation. Thus, it is unlikely that varying assays for $FLT3-ITD$ mutational status and allelic ratio significantly affected our analyses. Given that only three patients with $NPM1^{mut}$ AML and adverse cytogenetics also had an $FLT3-ITD^{low}$ mutation, the impact of adverse cytogenetics in this particular genotype remains unclear.

Chromosome aberrations in $NPM1^{mut}$ AML are considered secondary genetic events, and the $NPM1$ mutation is stable during the course of the disease. In the latest update of WHO classification of myeloid neoplasms, AML with mutated $NPM1$ has become a distinct entity. Our data, however, suggest that adverse karyotype abnormalities seem to predominate over the favorable biologic impact of the $NPM1$ founder mutation and dictate the course of the disease. However, because of the methodology of detection without use of subclone analysis, we were unable to dissect whether $NPM1$ mutations and concurrent genetic abnormalities occurred in the same or in different leukemic cell populations. We also did not have access to relapse samples, lacking the possibility to test whether the $NPM1$ mutation, the cytogenetic abnormalities, or both are retained during the course of the disease.

Allogeneic HSCT is widely accepted as the best post-remission treatment of transplant-eligible patients with adverse cytogenetics. The results of our analysis support previous data from smaller cohorts that allogeneic HSCT in CR1 is also associated with a reduction in risk of relapse in the total cohort of patients with $NPM1^{mut}/FLT3-ITD^{neg/low}$, including those with normal cytogenetics. However, the reduced risk of relapse did not translate into a superior OS. We found no excessive NRM (18.3%) in our cohort. It is likely that effective salvage treatments in relapsing patients, who did not receive allogeneic HSCT as primary post-remission consolidation, offset the potential beneficial effect of transplantation in CR1. Minimal residual disease–guided treatment decisions might further reduce the effect of primary allogeneic HSCT in patients with $NPM1^{mut}/FLT3-ITD^{neg/low}$, especially those with intermediate-risk cytogenetics. Given the retrospective nature of our study, these results demand additional validation within prospective trials. In contrast, in patients with $NPM1^{mut}$/FLT3-ITD$^{neg/low}$ with adverse cytogenetics, allogeneic HSCT in CR1 was associated with a significantly improved survival compared with consolidation chemotherapy, further emphasizing that these patients should be classified as high risk and managed as such.

In summary, this international collaborative study clearly shows that cytogenetic abnormalities are important determinants of outcome in $NPM1^{mut}/FLT3-ITD^{neg/low}$ AML. Most importantly, patients with $NPM1$ mutations with the $FLT3-ITD^{neg/low}$ genotype and adverse-risk cytogenetics share the same unfavorable prognosis as their counterparts with $NPM1^{mut}$ and should be classified accordingly.

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