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ORIGINAL REPORT

Long-Term Prognosis of Acute Myeloid Leukemia According to the New Genetic Risk Classification of the European LeukemiaNet Recommendations: Evaluation of the Proposed Reporting System

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ABSTRACT

Purpose
The current European LeukemiaNet (ELN) recommendations for acute myeloid leukemia (AML) propose a new risk reporting system, integrating molecular and cytogenetic factors and subdividing the large heterogenous group of intermediate-risk patients into intermediate-I (IR-I) and intermediate-II (IR-II). We assessed the prognostic value of the new risk classification in a large cohort of patients.

Patients and Methods
Complete data for classification were available for 1,557 of 1,862 patients treated in the AML96 trial. Patients were assigned to the proposed genetic groups from the ELN recommendations, and survival analyses were performed using the Kaplan-Meier method and log-rank test for significance testing.

Results
The median age of all patients was 67 years. With a median follow-up of 8.3 years, significant differences between all risk categories were observed in patients age ≤ 60 years regarding the time to relapse, relapse-free survival, and overall survival (OS). Patients in the IR-II group had a better prognosis than patients in the IR-I group. The median OS times in young patients with favorable risk (FR), IR-I, IR-II, and adverse risk (AR) were 5.3, 1.1, 1.6, and 0.5 years, respectively. Separate analyses in the age group older than 60 years revealed significant differences between FR, AR, and IR as a whole, but not between IR-I and IR-II.

Conclusion
In younger patients with AML, the ELN classification seems to be the best available framework for prognostic estimations to date. Caution is advised concerning its use for prospective treatment allocation before it has been prospectively validated. In elderly patients, alternative prognostic factors are desirable for further risk stratification of IR.

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INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease with large differences in prognosis. Balancing risks and benefits of different treatment approaches in accordance with the individual prognostic profile of patients is the basic principle of treatment in AML. The karyotype of AML cells was identified as a strong prognostic factor in a large patient population of the Medical Research Council (MRC) trial in 1998,[1] and several analyses have confirmed the strong impact of cytogenetic aberrations on prognosis.[2-9] Although there is consensus on classification and prognostic value of favorable risk (FR) and adverse risk (AR) aberrations, most patients display neither favorable nor adverse genetic features, which results in a large and heterogeneous group of intermediate risk (IR). To refine the risk profile of patients with AML, molecular factors have been identified, with mutations in the genes *FLT3*,[10-13] *NPM1*,[8,14-19] and *CEBPα*[20-25] being the most frequent and prognostically relevant aberrations. On the basis of a literature review and expert consensus, the authors of the recently published European LeukemiaNet (ELN) recommendations on diagnosis and management of AML proposed a subdivision of the IR group into an intermediate-I (IR-I) group and a less favorable intermediate-II

Table 1. Standardized Reporting for Correlation of Cytogenetic and Molecular Genetic Data in Acute Myeloid Leukemia With Clinical Data According to the ELN Guideline

ELN Genetic Risk Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* (normal karyotype) Mutated *CEBPα* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* and *FLT3-ITD* (normal karyotype) Wild-type *NPM1* without *FLT3-ITD* (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype

Abbreviation: ELN, European LeukemiaNet.

(IR-II) group. Furthermore, as opposed to the original MRC classification, patients with normal karyotype and either mutated *NPM1* or *CEBPα* genes and absent *FLT3-ITD* mutation were assigned to the FR group. All other patients with a normal karyotype were classified as IR-I. Patients with cytogenetic aberrations not classified as favorable or adverse form the second intermediate group, IR-II.[26] The ELN guideline classification is provided in Table 1.

Although several publications suggested prognostic differences in the molecular subgroups just mentioned, the proposed classification is not based on an actual AML patient cohort. It remains unclear whether the risk of relapse of patients with a normal karyotype, no *FLT3-ITD* mutation, and either mutated *NPM1* or *CEBPα* is comparable to that of core-binding factor (CBF) leukemias. Furthermore, it is questionable whether patients with no cytogenetic and no molecular aberrations have the same prognosis as *FLT3-ITD*–positive patients with a high *FLT3-ITD* allelic ratio. To answer these questions, to evaluate the risk classification in a large cohort of patients, and to consider implications for clinical practice, we conducted the analysis presented here by assigning patients treated in the AML96 trial between 1996 and 2005 to the proposed genetic groups from the ELN recommendations.

PATIENTS AND METHODS

Patients and Treatment

Patients treated within the AML96 trial of the Süddeutsche Hämoblastosegruppe (Southern German Hemoblastosis Group, now Deutsche Studieninitiative Leukämie/Study Alliance Leukemia) from 1996 to 2005 formed the cohort for the analysis. The AML96 trial included 1,862 patients ≥ 18 years old with primary and secondary or treatment-related AML and refractory anemia with excess of blasts according to the French-American-British (FAB) classification. All AML FAB subtypes were eligible for study apart from patients with acute promyelocytic leukemia (FAB M3). The trial protocol defined different treatment strategies for patients age 18 to 60 years and for elderly patients older than 60 years. Patients up to age 60 years received two cycles of induction chemotherapy with mitoxantrone (10 mg/m^2 on days 4 through 8), cytarabine (100 mg/m^2 on days 1 through 8), and etoposide (100 mg/m^2 on days 4 through 8); *m*-amsacrine (100 mg/m^2 on days 1 through 5) and cytarabine (1,000 mg/m^2 twice per day on days 1 through 5); and a risk-adapted postremission treatment as follows: IR and AR patients ≤ 55 years with available HLA-matched family donor received allogeneic hematopoietic stem-cell transplantation (SCT), and AR patients ≤ 45 years received transplantation from a matched unrelated donor if no family donor was available. All FR patients and those with no available donor were consolidated with one cycle of intermediate-dose or high-dose cytarabine plus mitoxantrone (cytarabine 1,000 or 3,000 mg/m^2 twice per day on days 1 through 6; mitoxantrone 10 mg/m^2 on days 4 through 6). The second consolidation therapy consisted of busulfan, cyclophosphamide, etoposide, or total-body irradiation plus cyclophosphamide followed by autologous stem-cell rescue. If autologous stem cells were not available, a second consolidation was given with *m*-amsacrine plus cytarabine. Patients older than 60 years received two courses of induction therapy with cytarabine and daunorubicin (cytarabine 100 mg/m^2 on days 1 through 7; daunorubicin 45 mg/m^2 on days 3 through 5) and one cycle of consolidation with *m*-amsacrine plus cytarabine. The treatment flow is shown in CONSORT diagrams in Figures 1 and 2.

The study was approved by the institutional review boards of the 40 participating centers. Informed consent was obtained from all patients according to the Declaration of Helsinki. The AML96 trial was registered at the ClinicalTrials.gov Web site (study identifier NCT00180115).

Treatment response was assessed by central cytomorphologic evaluation according to standard criteria.[27] Overall survival (OS) was defined as the time from study entry to death from any cause or relapse of the disease. Analyses of relapse-free survival (RFS), and time to relapse (TTR) included only patients attaining a complete remission (CR). RFS and TTR were measured from the time of CR achievement as proposed by the ELN guidelines.[26]

Cytogenetic and Molecular Analyses and Grouping of Patients

Samples of peripheral blood and bone marrow were processed in reference laboratories of the Süddeutsche Hämoblastosegruppe study group. Cytogenetic analyses were performed using standard techniques for chromosome banding and fluorescence in situ hybridization. According to the modified MRC classification, the following aberrations were defined as FR: t(8;21), inv(16), and t(16;16). Patients in the AR group had either −7, −5, 5q–, 7q–, t(6;9), inv(3q), t(9;22), or ≥ three cytogenetic aberrations. All remaining patients were defined as IR. Molecular analyses for mutations of *FLT3-ITD*, *NPM1*, and *CEBPα* were performed by standard polymerase chain reaction techniques.[10,17] Mutations in the *NPM1* or *CEBPα* gene will subsequently be referred to as *NPM1*+ or *CEBPα*+, whereas wild-type *NPM1*/*CEBPα* will be referred to as *NPM1* – or *CEBPα*–. Patients carrying the *FLT3-ITD* mutation will be referred to as *FLT3-ITD*+; other mutations or the wild-type form of *FLT3* will be abbreviated to *FLT3-ITD*–. The ELN guideline classification as published in 2010 was used for assigning patients to the following four groups: FR, IR-I, IR-II, and AR[26] (Table 1).

Statistical Analyses

Descriptive analyses were performed for the patient characteristics of age; sex; primary versus secondary AML; karyotype; *FLT3-ITD*, *NPM1*, or *CEBPα* mutation; and ELN risk group. Univariate analyses for the influence of the guideline variables on CR rates were performed using the χ^2 test; the log-rank test was used to evaluate TTR, RFS, and OS. Statistical analyses were performed with SPSS software, version 17.0 (SPSS, Chicago, IL).

RESULTS

Patients

Complete data for classification were available for 1,557 of 1,862 patients treated in the AML96 trial between 1996 and 2005. The median age of patients was 67 years (range, 18 to 87 years); roughly half of the patients were older than age 60 years. Sex distribution was

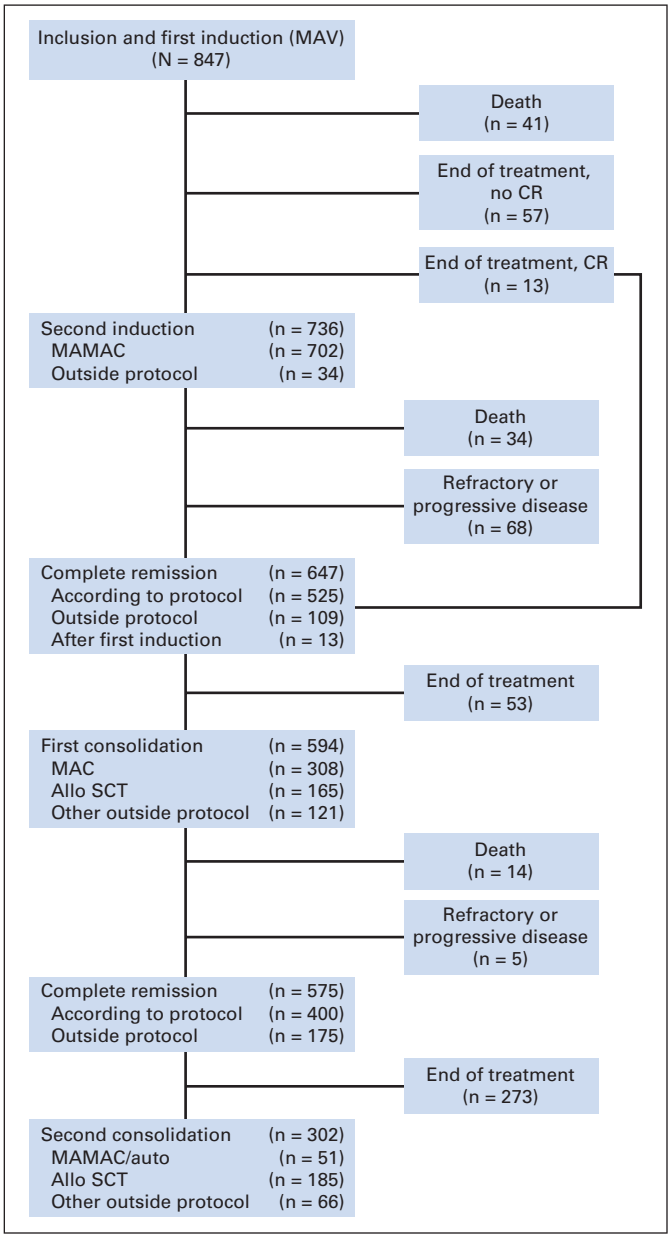

Fig 1. Modified CONSORT flow diagram of patients with acute myeloid leukemia ≤ 60 years old, showing patient numbers, treatments, and outcomes. Allo SCT, allogeneic stem-cell transplantation; auto, autologous stem-cell transplantation; CR, complete remission; MAMAC, *m*-amsacrine and cytarabine; MAV, mitoxantrone, cytarabine, and etoposide.

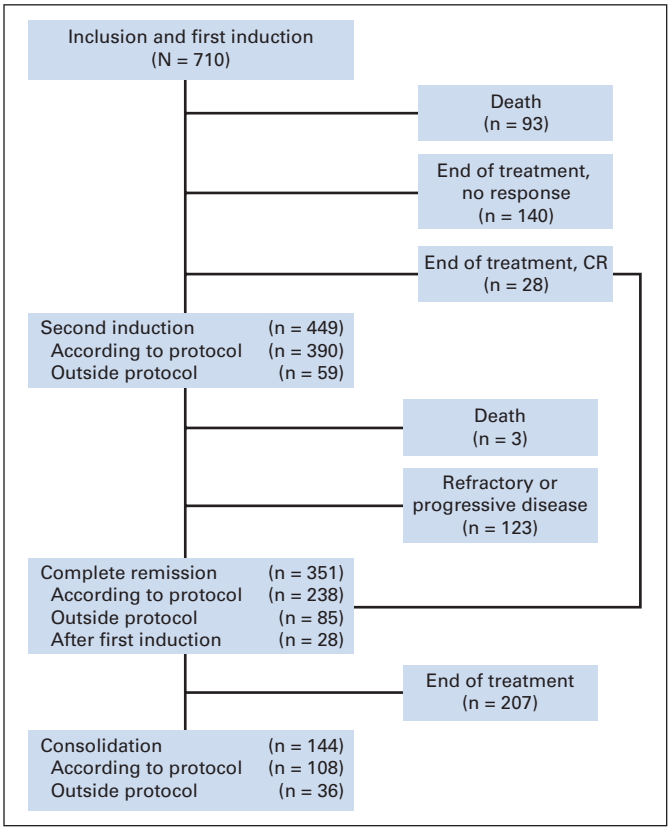

Fig 2. Modified CONSORT flow diagram of patients with acute myeloid leukemia older than 60 years showing patient numbers, treatments, and outcomes. CR, complete remission.

equal. The incidence of favorable, intermediate, and adverse karyotype was 10%, 67%, and 23%, respectively, according to the modified MRC classification. Application of the ELN classification resulted in a higher number of patients in the FR group (27%) and a subdivision of the now smaller intermediate group into IR-I (31%) and IR-II (19%). Patient characteristics are listed in Table 2, and patient distribution according to the modified MRC criteria and the ELN criteria is shown in Figure 3.

Course of Treatment and CR Rates

The treatments and outcomes are shown for patients age ≤ 60 years and more than 60 years in two separate modified CONSORT diagrams in Figures 1 and 2. A considerable number of patients did not complete protocol treatment as randomly assigned. Reasons for this were concerns of some participating physicians about tolerability of high-dose cytarabine, patients' preferences not to continue treatment, and physicians' reluctance to apply consolidation treatment after treatment-related toxicity during induction therapy. A CR was achieved in 64% of all patients (76% in patients ≤ 60 years and 51% in elderly patients). In patients ≤ 60 years, CR rates in FR, IR-I, IR-II, and AR patients were 88%, 76%, 77%, and 58%, respectively. In elderly patients, CR rates in FR, IR-I, IR-II, and AR patients were 72%, 53%, 47%, and 30%, respectively. CR rates are shown in Appendix Table A1 (online only). The described differences were significant between FR, AR, and IR as a whole, but not between IR-I and IR-II.

TTR, RFS, and OS

The median follow-up time for all patients by the time of analysis was 8.3 years. The median TTR was 20.5 months (95% CI, 15.2 to 25.8 months) for the entire cohort, 58.8 months (95% CI, 18.2 to 99.5 months) for younger patients, and 10.8 months (95% CI, 8.4 to 13.2 months) for elderly patients. In patients ≤ 60 years who did not receive an allogeneic SCT, a clear separation of all four ELN groups became evident. The comparison of TTR in ELN groups by log-rank test showed significant differences between all four groups. Notably, IR-II was associated with a better prognosis than IR-I. In patients ≤ 60 years who received an allogeneic SCT, TTR was generally longer than in patients who did not receive transplantation. In the SCT group, no

Table 2. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 1,557)	%
Age, years		
18 to 60	847	54.4
61 to 65	287	18.4
> 65	423	27.2
Sex		
Female	753	48.4
Male	804	51.6
Disease status		
De novo	1,253	80.5
Pre-existing MDS	229	14.7
Treatment associated	62	4.0
Unknown	13	0.8
Karyotype*		
Favorable risk	156	10.0
Intermediate risk	1,049	67.4
High risk	352	22.6
Normal karyotype	746	47.9
FLT3-ITD mutation		
Positive	320	20.6
Ratio ≥ 0.8	107	6.9
Ratio < 0.8	191	12.3
Ratio not done	22	1.4
Negative	1,103	70.8
Not done	134	8.6
NPM1 mutation		
Positive	404	25.9
Wild type	999	64.2
Not done	154	9.9
CEBPα mutation		
Positive	94	6.0
Wild type	1,272	81.7
Not done	191	12.3
ELN risk group		
Favorable	419	26.9
Intermediate-I	485	31.1
intermediate-II	298	19.1
Adverse	355	22.8

Abbreviations: ELN, European LeukemiaNet; MDS, myelodysplastic syndrome.
*Karyotype grouping is according to the modified Medical Research Council classification as follows: favorable risk: t(8;21), inv(16), and t(16;16); and high risk: either −7, −5, 5q−, 7q−, t(6;9), inv(3q), t(9;22), or ≥ three cytogenetic aberrations. All remaining patients were defined as intermediate risk.

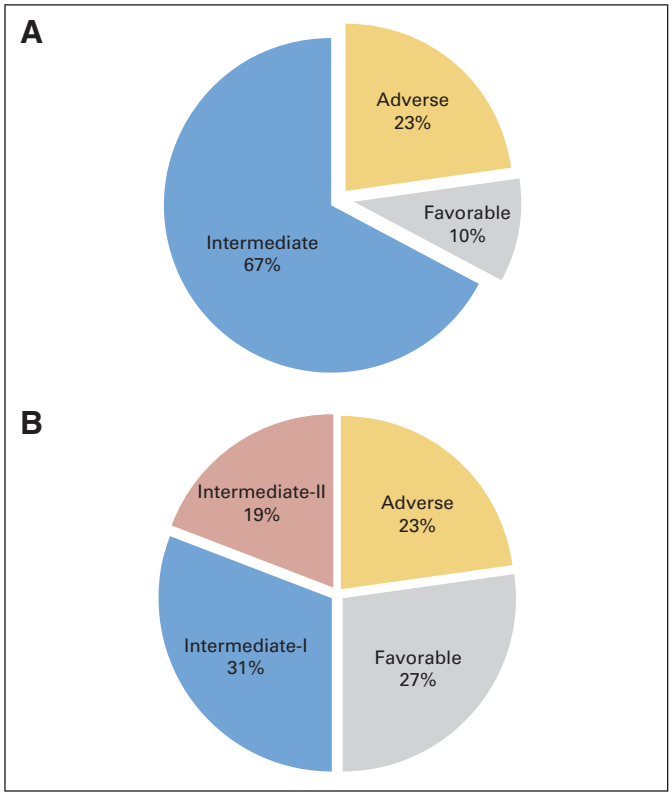

Fig 3. Distribution of patients according to the (A) Medical Research Council and (B) European LeukemiaNet criteria.

clear differences between FR, IR-I, and IR-II could be detected, whereas AR patients had a significantly poorer prognosis.

No clear differences between IR-I and IR-II were detected in elderly patients. Kaplan-Meier plots of probability of relapse in young and elderly patients are shown in Figure 4, and median TTR is provided in Table 3.

When analyzed for RFS and OS, similar patterns could be seen. The median RFS was 13.7 months (95% CI, 11.7 to 15.8 months) in the entire cohort, 19.2 months (95% CI, 12.6 to 25.8 months) in patients up to 60 years old, and 9.4 months (95% CI, 7.8 to 10.9 months) in elderly patients. The median OS was 12.4 months (95% CI, 11.3 to 13.6 months) in the entire cohort, 18.9 months (95% CI, 15.4 to 22.4 months) in patients up to 60 years old, and 8.7 months (95% CI, 7.8 to 9.7 months) in elderly patients. Significant differences were detected between all four ELN risk groups in the younger patient group with no allogeneic SCT, whereas no significant differences between the IR-I and IR-II groups were seen in elderly patients and in the entire cohort. Again, younger patients with IR-II had a better prognosis than patients in the IR-I group. Kaplan-Meier plots of RFS and OS are shown in Figure 4, and median RFS and OS are provided in Table 3.

Because the ELN guidelines suggest subsuming patients with CBF mutations together with patients displaying *NPM1+/FLT3-ITD−* and *CEBPα+/FLT3-ITD−* under the favorable risk category, we calculated their OS separately to assess whether the prognoses of these patient subgroups were comparable. The median OS times of patients with a CBF AML, *NPM1+/FLT3-ITD* − AML, and *CEBPα+/FLT3-ITD* − AML were 135.4 months, 22.7 months (95% CI, 12.6 to 32.7 months), and 28.4 months (95% CI, 0.0 to 60.2 months), respectively. In contrast, median OS times for IR-I and IR-II groups were 13.1 months (95% CI, 11.0 to 15.2 months) and 13.1 months (95% CI, 10.8 to 15.4 months), respectively. The corresponding Kaplan-Meier plots are shown in Figure 5. The results indicate a superior survival of patients with CBF AML compared with *NPM1+/FLT3-ITD* − and *CEBPα+/FLT3-ITD* − patients with normal karyotype. Still, the latter groups have a significantly better prognosis than IR-I or IR-II, with a practically doubled median OS.

To evaluate the influence of allogeneic SCT on prognosis in younger patients with AML, we compared OS in patients ≤ 60 years who had not received an allogeneic SCT and patients in the same age group who received transplantation with an allogeneic graft in first CR. OS in patients without allogeneic SCT was generally worse than in patients who received an allogeneic SCT, as shown in Table 3. No significant differences between FR, IR-I, and IR-II patients were seen

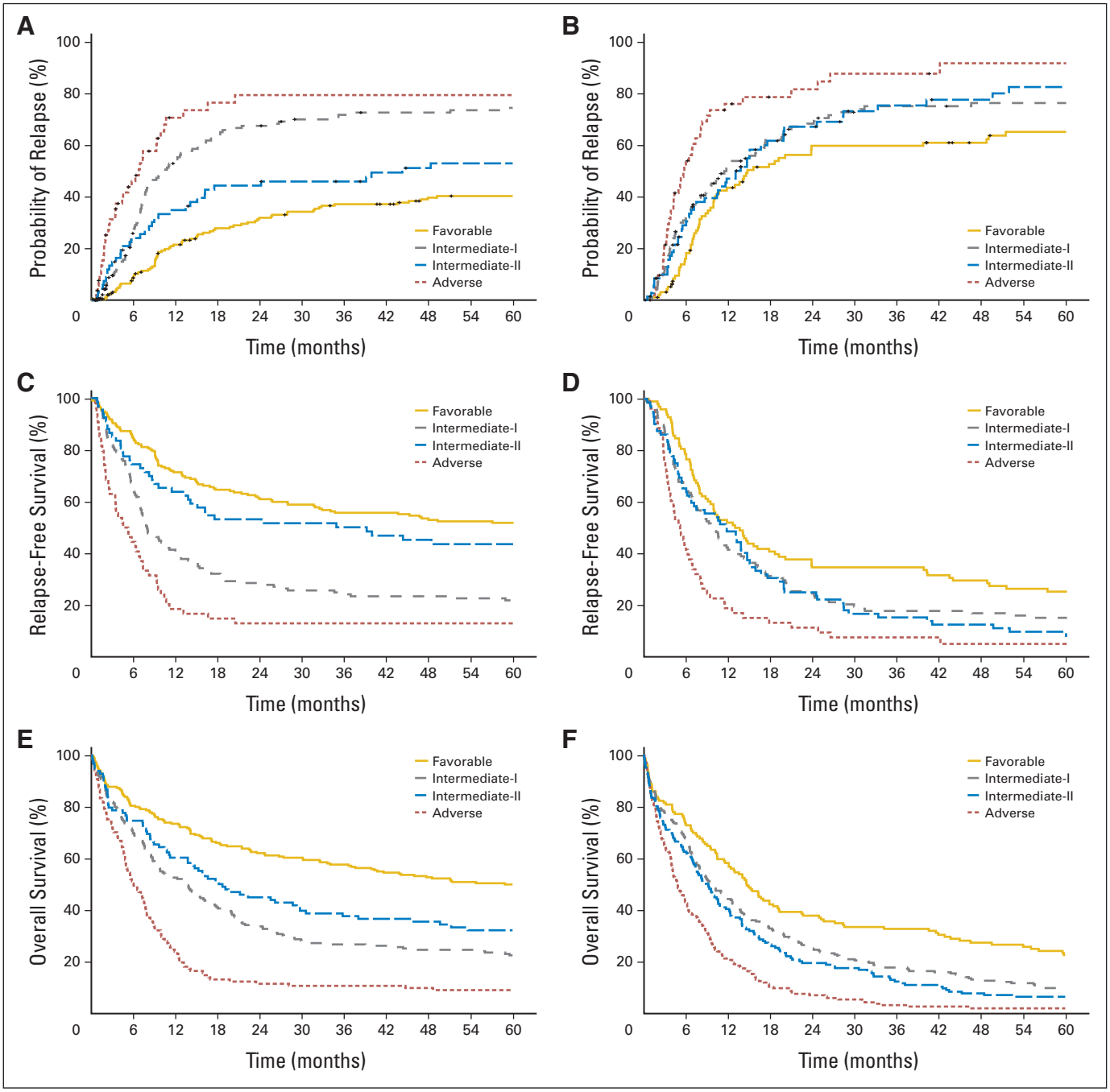

Fig 4. Probability of relapse, relapse-free survival, and overall survival in younger (A,C,E; age 18 to 60 years) and elderly (B,D,F; age > 60 years) patients with acute myeloid leukemia predicted by European LeukemiaNet risk categories.

in the transplantation group, whereas the prognosis of AR patients was generally poor.

From our previous experience, the *FLT3-ITD* ratio, rather than *FLT3-ITD* positivity or negativity, is of prognostic importance.[10] Although the ELN classification does not refer to the ratio, we analyzed the IR group with respect to an *FLT3-ITD* ratio threshold of 0.8. This resulted in a clear difference in OS in younger patients with AML, with a median survival of 10.4 months (95% CI, 8.2 to 12.6 months) in patients with a ratio ≥ 0.8 and 20.6 months (95% CI, 15.5 to 25.6 months) in patients with a lower *FLT3-ITD* load. The *FLT3-ITD* ratio had no significant impact on the prognosis of patients older than 60 years.

DISCUSSION

In our cohort of 1,557 patients with AML, the prognostic value of the ELN classification varied between younger and elderly patients with AML. In patients up to age 60 years, the classification resulted in the

Table 3. Median TTR, RFS, and OS in Patients ≤ 60 Years Who Did Not Receive an alloSCT, Patients ≤ 60 Years Who Received an alloSCT, and Patients > 60 Years, Stratified According to ELN Risk

	TTR (months)						RFS (months)						OS (months)					
	Age ≤ 60 Years, No alloSCT		Age ≤ 60 Years, alloSCT		Age > 60 Years		Age ≤ 60 Years, No alloSCT		Age ≤ 60 Years, alloSCT		Age > 60 Years		Age ≤ 60 Years, No alloSCT		Age ≤ 60 Years, alloSCT		Age > 60 Years	
Risk Group	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Favorable	NR	—	NR	—	14.7	8.6 to 20.8	66.1	—	NR	—	12.9	8.6 to 17.2	63.6	10.7 to 116.6	NR	—	14.6	11.7 to 17.6
Intermediate-I	10.2	6.9 to 13.5	NR	—	11.4	7.0 to 15.8	7.9	6.0 to 9.8	94.0	—	9.6	7.2 to 11.9	13.6	9.8 to 17.4	NR	—	9.5	7.3 to 11.7
Intermediate-II	44.3	0 to 114.1	NR	—	13.0	8.8 to 17.2	39.1	8.4 to 70.0	104.8	11.8 to 197.8	11.6	6.9 to 16.3	18.7	9.6 to 27.7	109.2	24.3 to 194.1	9.2	7.1 to 11.3
Adverse	6.7	4.2 to 9.3	24.4	11.3 to 37.5	5.7	4.1 to 7.4	4.5	1.8 to 7.2	9.0	2.0 to 16.1	5.1	3.6 to 6.7	6.0	4.2 to 7.8	12.2	4.9 to 19.4	4.8	3.7 to 5.9

Abbreviations: alloSCT, allogeneic stem-cell transplantation; ELN, European LeukemiaNet; NR, not reached; OS, overall survival; RFS, relapse-free survival; TTR, time to relapse.

separation of four patient groups with significant differences for TTR, RFS, and OS. Given these results, the ELN grouping system seems to represent the best available prognostic framework for younger patients with AML to date. In our patient group, the prognosis of IR-II is significantly better than that of IR-I. Possible reasons for this finding could be cytogenetic aberrations that might actually confer a more favorable prognosis, such as t(9;11), 9q–,[9] or –Y,[28] which were present in 14, 12, and 10 of 298 IR-II patients, respectively. Alternatively, a higher proportion of patients with an *FLT3-ITD* allelic ratio ≥ 0.8 in the IR-I group (20%) compared with the IR-II group (6%) may have contributed to these results. However, the impact of *FLT3-ITD* in patients with cytogenetic aberrations remains unclear.

We compared OS between CBF leukemias, *NPM1+/FLT3-ITD–*, *CEBPα+/FLT3-ITD–*, IR-I, and IR-II and found a superior survival of CBF AML as opposed to the group of *NPM1+/FLT3-ITD–* and *CEBPα+/FLT3-ITD–* patients with normal karyotype. Still, the latter patients have a significantly better prognosis than IR-I or IR-II patients, with a practically doubled median OS. Given these results, it seems justifiable to assign *NPM1+/FLT3-ITD–* and *CEBPA+/FLT3-ITD–* patients with normal karyotype to the FR group as proposed by the guideline authors.

Additional or alternative prognostic factors and on-treatment evaluations seem desirable for the prediction of OS in the group without favorable or adverse genetic features in elderly patients with AML. No significant difference between IR-I and IR-II could be shown in this patient group. Although differences in the distribution of high *FLT3-ITD* ratios were present between IR-I (16%) and IR-II (4%) patients, the prognostic impact of *FLT3-ITD* in this patient group seems negligible.[29-32] Because of generally short survival times and small numbers of patients with FR features, differences between CBF, *CEBPα+*, and *NPM1+* and between IR-I and IR-II were rather small (data not shown), and a clear separation between the FR group, including *NPM1+/CEBPα+*, and the IR groups could not be shown.

According to our results, the ELN classification is a valuable tool for prognostic purposes, particularly in younger patients, because it allows a more detailed stratification of patients with significantly different prognoses. The grouping seems to mirror differences in AML biology and the corresponding clinical course. On the basis of the stratification results of the *FLT3-ITD* ratio threshold of 0.8, quantitative rather than qualitative information on *FLT3-ITD* could be useful for further improvement of the risk stratification in the future.

It is important to note that the ELN classification has not been evaluated for specific treatment approaches and is therefore not shown to be predictive. Thus, decisions on the optimum postremission therapy for patients in the FR and IR groups cannot yet be based on prognostic systems such as the ELN risk groups. As an example, according to a landmark analysis of the Acute Myeloid Leukemia Cooperative Group, patients with an *NPM1* mutation have a favorable outcome after allogeneic transplantation, with a 6-year OS rate of 91%.[33] Recently, a retrospective comparative donor versus no donor analysis was published in a cohort of *NPM1+/FLT3-ITD* – patients showing no significant difference between both groups.[20] Because of the retrospective character of these analyses and the mentioned selection bias associated with a donor versus no donor comparison, a prospective study is warranted to reliably assess the value of allogeneic transplantation in both *NPM1+/FLT3-ITD* – and *CEBPα+/FLT3-ITD* – patients. So far, we think that given the considerable risk of relapse as opposed to CBF AML (Fig 5), this patient group should not be excluded from allogeneic treatment options outside a clinical trial. However, although our data suggest an advantage in OS for patients younger than age 60 years receiving allogeneic SCT, the allocation to this treatment in a nonrandomized fashion precludes any definitive statements on the role of this modality.

Both of the questions addressing the predictive value of the ELN classification in FR and IR groups and the influence of allogeneic SCT on prognosis will be evaluated in a prospective randomized study

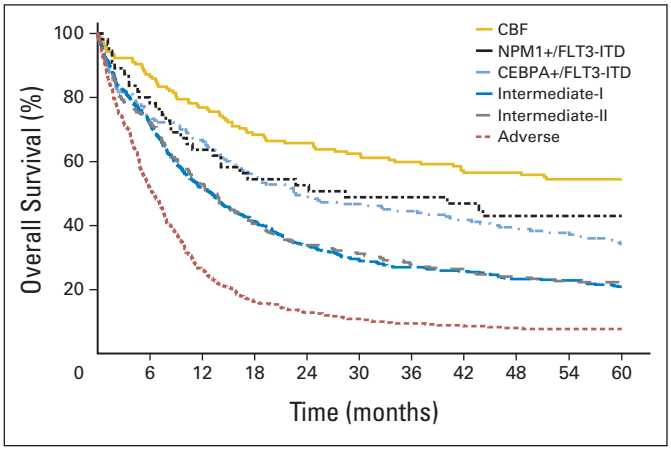

Fig 5. Overall survival in all analyzed patients with acute myeloid leukemia (AML) according to the European LeukemiaNet risk categories including a stratification for the following subgroups of favorable risk: core-binding factor (CBF) AML, *NPM1+/FLT3-ITD–* AML, and *CEBPα+/FLT3-ITD–*.

starting in Germany in 2011. In the Evaluation of Transplantation in Acute Myeloid Leukemia (ETAL) trial, patients with IR and an available donor will be randomly assigned to conventional cytarabine-based consolidation or allogeneic transplantation. Because the definition of IR in this trial will be based on the MRC classification, patients with normal karyotype and mutated *NPM1* or *CEBPα* will also be included and randomly assigned in a stratified manner.

In light of recently detected new molecular factors, gene-expression profiling technology, and sequencing, a refinement of the existing classifications by adding new factors and including quantitative information on *FLT3-ITD* mutations will hopefully enable us to specify prognostic statements, prospectively evaluate the impact of different treatments on long-term outcomes, and establish predictive factors for individually tailored treatment options and improvement of survival in all patients with AML.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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