

Measurable Residual Disease and Fusion Partner Independently Predict Survival and Relapse Risk in Childhood *KMT2A*-Rearranged Acute Myeloid Leukemia: A Study by the International Berlin-Frankfurt-Münster Study Group

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abstract

PURPOSE A previous study by the International Berlin-Frankfurt-M nster Study Group (I-BFM-SG) on childhood *KMT2A*-rearranged (*KMT2A*-r) AML demonstrated the prognostic value of the fusion partner. This I-BFM-SG study investigated the value of flow cytometry-based measurable residual disease (flow-MRD) and evaluated the benefit of allogeneic stem-cell transplantation (allo-SCT) in first complete remission (CR1) in this disease.

METHODS A total of 1,130 children with *KMT2A*-r AML, diagnosed between January 2005 and December 2016, were assigned to high-risk (n = 402; 35.6%) or non-high-risk (n = 728; 64.4%) fusion partner-based groups. Flow-MRD levels at both end of induction 1 (EOI1) and 2 (EOI2) were available for 456 patients and were considered negative (<0.1%) or positive ( 0.1%). End points were 5-year event-free survival (EFS), cumulative incidence of relapse (CIR), and overall survival (OS).

RESULTS The high-risk group had inferior EFS (30.3% high risk v 54.0% non-high risk; $P < .0001$), CIR (59.7% v 35.2%; $P < .0001$), and OS (49.2% v 70.5%; $P < .0001$). EOI2 MRD negativity was associated with superior EFS (n = 413; 47.6% MRD negativity v n = 43; 16.3% MRD positivity; $P < .0001$) and OS (n = 413; 66.0% v n = 43; 27.9%; $P < .0001$), and showed a trend toward lower CIR (n = 392; 46.1% v n = 26; 65.4%; $P = .016$). Similar results were obtained for patients with EOI2 MRD negativity within both risk groups, except that within the non-high-risk group, CIR was comparable with that of patients with EOI2 MRD positivity. Allo-SCT in CR1 only reduced CIR (hazard ratio, 0.5 [95% CI, 0.4 to 0.8]; $P = .00096$) within the high-risk group but did not improve OS. In multivariable analyses, EOI2 MRD positivity and high-risk group were independently associated with inferior EFS, CIR, and OS.

CONCLUSION EOI2 flow-MRD is an independent prognostic factor and should be included as risk stratification factor in childhood *KMT2A*-r AML. Treatment approaches other than allo-SCT in CR1 are needed to improve prognosis.

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INTRODUCTION

Most pediatric AML study groups (SGs) currently base risk stratification on genetics, including fusion genes and molecular aberrations, and early treatment response, either morphologically or more accurately assessed by

detection of flow cytometry-based measurable residual disease (flow-MRD).¹ Detection of flow-MRD in bone marrow (BM) after induction therapy is considered a strong indicator of relapse,²⁻⁷ and can aid risk-directed postremission therapy,^{2,5,6} including allogeneic stem-cell

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

This study investigated whether flow cytometry-based measurable residual disease (flow-MRD) at end of induction 2 (EOI2) is of prognostic significance in childhood *KMT2A*-rearranged (*KMT2A*-r) AML. Moreover, the benefit of allogeneic stem-cell transplantation (allo-SCT) in first complete remission (CR1) was evaluated.

Knowledge Generated

To our knowledge, this study is the first to demonstrate that EOI2 flow-MRD positivity is an independent adverse prognosticator in childhood *KMT2A*-r AML, in addition to the high-risk *KMT2A* fusion partner-based group. Patients within the high-risk fusion partner-based group with EOI2 MRD positivity have dismal outcomes. Additionally, allo-SCT in CR1 reduces relapse risk in patients with high-risk *KMT2A* fusion partners.

Relevance (S. Bhatia)

This study shows the utility of using EOI2 flow-MRD as an independent prognosticator for risk stratification in children with *KMT2A*-r AML, highlighting the need for novel therapeutic strategies for this subgroup of patients because of the dismal prognosis.*

*Relevance section written by JCO Associate Editor Smita Bhatia, MD, MPH, FASCO.

transplantation (allo-SCT) in first complete remission (CR1).

A heterogeneous genetic pediatric AML subtype for which international consensus on risk stratification is lacking⁸ is 11q23/*KMT2A*-rearranged (*KMT2A*-r) AML, which occurs in 20%-25% of children with AML.¹ In a large International Berlin-Frankfurt-Münster (I-BFM)-SG collaborative study⁹ and in some smaller SG studies,^{10,11} the prognosis of this subtype has been shown to be influenced by the fusion partner. Considerably better survival rates have been reported for 1q21,⁹ whereas 6q27, 10p12, 10p11.2, 4q21, and 19p13.3 are considered high-risk *KMT2A* translocation partners, which independently predict poor prognosis.^{9,10} However, the prognostic value of flow-MRD in this specific disease is unknown and was questioned by the I-BFM-SG because of the relatively high number of relapses observed in patients with flow-MRD negativity (<0.1%).

The benefit of allo-SCT in CR1 remains a debatable subject in pediatric AML, as its enhanced antileukemic activity needs to outweigh the risk of transplant-related mortality.^{1,12,13} In previous pediatric *KMT2A*-r AML studies, allo-SCT in CR1 did not improve relapse risk, nor survival.^{9,10} However, exposure to gemtuzumab ozogamicin (GO; Mylotarg, Pfizer, New York, NY) before transplantation seemed to improve the post-transplantation prognosis in these patients.¹⁰

We aimed to evaluate the prognostic significance of end of induction 2 (EOI2) flow-MRD response and allo-SCT in CR1 in childhood *KMT2A*-r AML overall and within fusion partner-based risk groups.

METHODS

Study Design and Patients

A retrospective study was conducted within the I-BFM-SG, including 15 pediatric AML SGs/countries. Eligible patients

were younger than 19 years and were newly diagnosed with *KMT2A*-r AML between January 1, 2005, and December 31, 2016. Patients with a diagnosis of myeloid leukemia in Down syndrome, isolated myeloid sarcoma, or acute promyelocytic leukemia were excluded, as well as patients who were initially treated, for more than one week, for a diagnosis other than AML. Not all SGs/countries provided eligible patients for the entire study period, and treatment was given according to national or international pediatric AML SG trials (Data Supplement [Table S1], online only), which were all cytarabine-/anthracycline-based.^{2,4,6,14-24} Institutional ethics committees approved these trials, and patients and/or parents provided written consent according to the Declaration of Helsinki. All data were checked for accuracy and corrected in consultation with the SGs/countries.

Assignment to Fusion Partner Groups and Risk Classification

The karyotype (G-, Q-, or R-banding), fluorescence in situ hybridization, and reverse transcription polymerase chain reaction (PCR) results were reviewed within the SGs/countries for the presence of *KMT2A* rearrangements. Patients were assigned to 10 different fusion partner groups or the *KMT2A*-other group, as previously reported by Balgobind et al.⁹ The group assignment was reviewed by two authors (R.W. and C.H.). The fusion partners of *KMT2A*-other group patients were reviewed to identify novel groups, with a minimum of 10 patients. Patients with unidentified fusion partners or those occurring in less than 10 patients remained within the *KMT2A*-other group.

On the basis of previously published classifications,^{9,10} patients with 6q27 (*KMT2A*::*AFDN*), 4q21 (*KMT2A*::*AFF1*), 10p12 (*KMT2A*::*MLLT10*), 10p11.2 (*KMT2A*::*ABI1*), and 19p13.3 (*KMT2A*::*MLLT1*) were assigned to the high-risk group, while all others were assigned to the non-high-risk

group. The *KMT2A*-other group was excluded because their fusion partners could not be risk group–assigned owing to their unknown prognostic impact.

Flow-MRD Analysis

Flow-MRD analysis was implemented in most, but not yet in all, trials/treatment protocols used by the SGs/countries during the study period. Additionally, some SGs/countries could not provide flow-MRD data because of ongoing trials. Ten SGs/countries provided flow-MRD data, which were mainly detected using 4- to 10-color antibody panels. Two SGs also used the different from normal approach. Details on the BM cellularity were not collected.

Definitions and Statistical Analysis

CR was defined as <5% BM blasts, the absence of cells with Auer rods and extramedullary disease, and peripheral blood cell regeneration.¹ Refractory disease was defined as ≥5% BM blasts, either morphologically, cytogenetically, or by a high positive PCR result, or proven extramedullary disease after induction therapy. Relapse was defined as ≥5% BM blasts or reappearance of blasts in peripheral blood, or the development of extramedullary disease after initial morphologic CR.¹ End of induction 1 (EOI1) and EOI2 BM responses were morphologically categorized as M1 (<5% blasts), M2 (≥5%–<20% blasts), or M3 (≥20% blasts). EOI1 and EOI2 flow-MRD responses <0.1% were considered negative and ≥0.1% positive. Event-free survival (EFS) was defined as the time from diagnosis to induction failure, relapse, secondary malignancy, death in CR, or last follow-up, whichever occurred first. Induction failure was included as an event at $t = 0$. Cumulative incidence of relapse (CIR) and nonrelapse mortality (NRM) were defined as the time from EOI1, for patients in CR, to relapse and to death without relapse, respectively. The competing event for CIR was death without relapse and for NRM death with relapse. Overall survival (OS) was defined as the time from diagnosis to death, or last follow-up.

Median (IQR) follow-up time of patients was 5.2 years (3.5–7.8). Differences in proportions were tested using Pearson's χ^2 test. Medians between two groups were compared using the Mann-Whitney U test. EFS and OS estimates were calculated using the Kaplan-Meier method and compared using the log-rank test. The CIR was estimated by adjusting for competing risks and was compared using Gray's test. Hazard ratios (HR) were calculated using Cox proportional hazard models, wherein allo-SCT in CR1 was included as a time-dependent covariate. Covariates with two-sided P values < .05 in univariable analysis were included in multivariable analysis. To visually compare the CIR, NRM, and OS of allo-SCT versus no allo-SCT in CR1 overall and stratified by treatment era (2005–2010 v 2011–2016), a 90-day landmark was used. Multivariable analyses were performed excluding morphologic BM and flow-MRD response, referred to as the crude models containing the highest number of patients, and including morphologic BM and flow-MRD response separately from each other.

Analyses were performed using R version 4.0.3. Two-sided P values ≤ .01 were considered statistically significant.

RESULTS

Patients

Of the 1,256 eligible patients, 126 (10.0%) were assigned to the *KMT2A*-other group and excluded (Fig 1). *KMT2A*-other group patients were younger and had more often a WBC at diagnosis $\geq 100 \times 10^9/L$ than the remaining 1,130 patients (Data Supplement, Tables S2 and S3). Table 1 presents the clinical characteristics of these 1,130 patients and stratified by *KMT2A* risk group (non-high risk: $n = 728$, 64.4%; high risk: $n = 402$, 35.6%). High-risk group patients tended to be more often age 10 years and older (30.1% high-risk group v 23.4% non-high-risk group; $P = .013$), had a higher median WBC at diagnosis ($25.7 \times 10^9/L$ v $16.2 \times 10^9/L$; $P = .0056$), and had less frequently good morphologic EOI1 BM responses (ie, M1; 71.0% v 83.8%; $P < .0001$), with a trend for less frequent EOI2 M1 BM responses (91.9% v 95.6%; $P = .015$).

Of the 1,130 included patients, 456 (40.4%) had available EOI1 and EOI2 MRD data (Fig 1). No significant differences in clinical characteristics and outcomes were detected between patients with and without available MRD data at both time points (Data Supplement, Tables S4 and S5). These 456 patients were classified as either EOI2 MRD-negative ($n = 413$; 90.6%), including patients with negative-negative (– –; $n = 362$; 79.4%) and positive-negative (+ –; $n = 51$; 11.2%) MRD responses at the respective time points, or EOI2 MRD-positive ($n = 43$; 9.4%), including patients with positive-positive (+ +; $n = 31$; 6.8%) and negative-positive (– +; $n = 12$; 2.6%; see Data Supplement, Table S6, for characteristics) MRD responses. The proportions of patients with EOI2 MRD negativity and MRD positivity were similar within both *KMT2A* risk groups (Table 1).

Data on allo-SCT in CR1 were available for 931/962 (96.8%) patients who achieved CR, of whom 20.7% (193/931) underwent transplantation. The Data Supplement, Table S7, details the transplantation characteristics. The transplantation rates within the non-high-risk and high-risk groups were 17.0% (103/605) and 27.6% (90/326), respectively. Pre-SCT MRD data were available for 68 patients, of whom eight were MRD-positive and 60 MRD-negative.

Outcome in Childhood *KMT2A*-r AML and Prognostic Significance of EOI2 Flow-MRD Response

Of the 1,095 patients who were known to have started chemotherapy, 962 (87.9%) achieved CR. The cohort's 5-year EFS, CIR, and OS rates were 45.3% (95% CI, 42.3 to 48.5), 44.0% (40.8–47.2), and 62.8% (59.8–65.8), respectively (Table 1). The high-risk group had inferior EFS (30.3% [95% CI, 25.9 to 35.4] v 54.0% [95% CI, 50.3 to 58.0]; $P < .0001$), CIR (59.7% [95% CI, 54.1 to 64.8] v 35.2% [95% CI, 31.3 to 39.0]; $P < .0001$), and OS (49.2% [95% CI, 44.2 to 54.7] v 70.5% [95% CI, 67.1 to 74.2]; $P < .0001$) than the non-high-risk group.

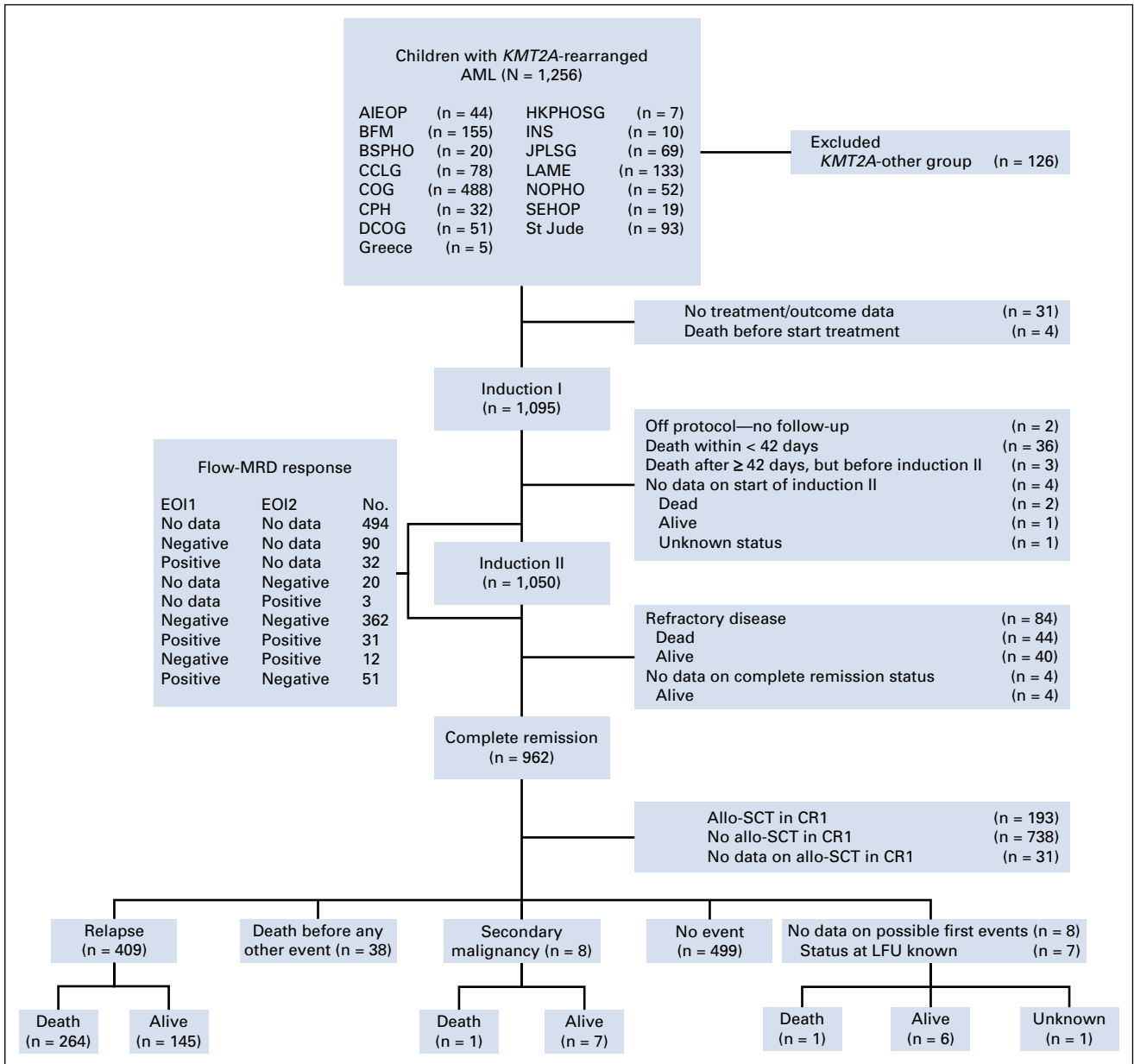


FIG 1. Flow diagram of the cohort of children with *KMT2A*-rearranged AML recruited by the collaborative study groups/countries between January 1, 2005, and December 31, 2016. Patients with unidentified fusion partners or those occurring in less than 10 patients were assigned to the *KMT2A*-other group. Fusion partners in the *KMT2A*-other group could not be risk group-assigned because of their unknown prognostic impact and were excluded. AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica (Italy); allo-SCT, allogeneic stem-cell transplantation; BFM, Berlin-Frankfurt-Münster (Germany and Austria); BSPHO, Belgian Society of Pediatric Hematology Oncology (Belgium); CCLG, Children’s Cancer and Leukaemia Group (United Kingdom); COG, Children’s Oncology Group (United States); CPH, Czech Pediatric Hematology (Czech Republic); CR1, first complete remission; DCOG, Dutch Childhood Oncology Group (the Netherlands); EOI1, end of induction 1; EOI2, end of induction 2; HKPHOSG, Hong Kong Pediatric Hematology and Oncology Study Group (Hong Kong); I-BFM, International Berlin-Frankfurt-Münster; INS, Israel National Study (Israel); JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group (Japan); LAME, Leucémie Aiguë Myéloblastique Enfant (France); LFU, last follow-up; MRD, measurable residual disease; No., number of patients; NOPHO, Nordic Society for Pediatric Hematology and Oncology (Scandinavia); SEHOP, Spanish Society of Pediatric Hematology and Oncology (Spain); St Jude, St Jude Children’s Research Hospital (United States).

Patients with EOI2 MRD negativity had better EFS (n = 413; 47.6% [95% CI, 42.9 to 52.7] v n = 43; 16.3% [95% CI, 8.3 to 32.1]; P < .0001) and OS (n = 413; 66.0% [95% CI, 61.4 to 70.9] v n = 43; 27.9% [95% CI, 17.3 to 45.1]; P < .0001) than patients with EOI2 MRD positivity, and showed a trend toward lower CIR (n = 392; 46.1% [95% CI, 41.1 to 51.1] v n = 26; 65.4% [95% CI, 43.0 to 80.8]; P = .016; Table 1; Figs 2A-2C). Similarly, within both *KMT2A* risk groups, patients with EOI2 MRD negativity had significantly better EFS and OS than patients with EOI2 MRD positivity (Table 1; Figs 2D

TABLE 1. Clinical Characteristics and Outcomes of the Cohort of 1,130 Children With *KMT2A*-Rearranged AML and Stratified by Fusion Partner-Based Risk Group

Characteristic	Total Cohort (N = 1,130)	KMT2A Risk Group ^a		P									
		Non-High Risk (n = 728)	High Risk (n = 402)										
Sex, No. (%) (n = 1,110)													
Male	582 (52.4)	362 (50.8)	220 (55.3)	.16									
Female	528 (47.6)	350 (49.2)	178 (44.7)										
Age at diagnosis, years, No. (%) (n = 1,130)													
Median (IQR)	3.0 (1.0-10.1)	2.7 (1.0-9.1)	3.0 (1.0-12.1)	.24									
<1	244 (21.6)	153 (21.0)	91 (22.6)	.53									
≥1	886 (78.4)	575 (79.0)	311 (77.4)										
<2	463 (41.0)	295 (40.5)	168 (41.8)	.68									
≥2	667 (59.0)	433 (59.5)	234 (58.2)										
<10	839 (74.2)	558 (76.6)	281 (69.9)	.013									
≥10	291 (25.8)	170 (23.4)	121 (30.1)										
WBC, ×10 ⁹ /L, No. (%) (n = 1,062)													
Median (IQR)	21.0 (5.4-79.4)	16.2 (5.0-75.2)	25.7 (7.7-84.9)	.0056									
<100	834 (78.5)	539 (78.8)	295 (78.0)	.77									
≥100	228 (21.5)	145 (21.2)	83 (22.0)										
CNS involvement, No. (%) (n = 660)													
Negative	532 (80.6)	356 (81.8)	176 (78.2)	.27									
Positive	128 (19.4)	79 (18.2)	49 (21.8)										
FAB type, No. (%) (n = 777)													
FAB-M0	14 (1.8)	8 (1.6)	6 (2.2)	.27									
FAB-M1	30 (3.9)	15 (2.9)	15 (5.6)										
FAB-M2	18 (2.3)	15 (2.9)	3 (1.1)										
FAB-M4	104 (13.4)	71 (13.9)	33 (12.3)										
FAB-M5	561 (72.2)	364 (71.5)	197 (73.5)										
FAB-M7	29 (3.7)	21 (4.1)	8 (3.0)										
FAB unspecified	21 (2.7)	15 (2.9)	6 (2.2)										
BM response by morphology at EO11, No. (%) (n = 871)													
M1	688 (79.0)	455 (83.8)	233 (71.0)	<.0001									
M2	122 (14.0)	60 (11.0)	62 (18.9)										
M3	61 (7.0)	28 (5.2)	33 (10.1)										
BM response by morphology at EO12, No. (%) (n = 891)													
M1	840 (94.3)	545 (95.6)	295 (91.9)	.015									
M2	35 (3.9)	20 (3.5)	15 (4.7)										
M3	16 (1.8)	5 (0.9)	11 (3.4)										
Flow-MRD response, No. (%) (n = 456)													
MRD-negative at EO12 (--/+ -)	413 (90.6)	252 (91.6)	161 (89.0)	.34									
MRD-positive at EO12 (++/- +)	43 (9.4)	23 (8.4)	20 (11.0)										
Clinical Outcome	Total Cohort				Non-High Risk				High Risk				P
	No.	%	95% CI	P	No.	%	95% CI	P	No.	%	95% CI	P	
5-year pEFS	1,077	45.3	42.3 to 48.5		685	54.0	50.3 to 58.0		392	30.3	25.9 to 35.4		<.0001
MRD-negative at EO12 (--/+ -)	413	47.6	42.9 to 52.7	<.0001	252	55.9	50.0 to 62.5	.00030	161	34.6	27.9 to 42.8	<.0001	<.0001
MRD-positive at EO12 (++/- +)	43	16.3	8.3 to 32.1		23	30.4	16.4 to 56.5		20	0.0	—		.011

(continued on following page)

TABLE 1. Clinical Characteristics and Outcomes of the Cohort of 1,130 Children With *KMT2A*-Rearranged AML and Stratified by Fusion Partner-Based Risk Group (continued)

Clinical Outcome	Total Cohort				Non-High Risk				High Risk				P
	No.	%	95% CI	P	No.	%	95% CI	P	No.	%	95% CI	P	
5-year pCIR	953	44.0	40.8 to 47.2		612	35.2	31.3 to 39.0		341	59.7	54.1 to 64.8		<.0001
MRD-negative at EO12 (- -/+ -)	392	46.1	41.1 to 51.1	.016	239	37.5	31.3 to 43.7	.19	153	59.6	51.2 to 67.0	.011	<.0001
MRD-positive at EO12 (+ +/+ +)	26	65.4	43.0 to 80.8		16	50.0	23.3 to 71.9		10	NC ^b	—		.068
5-year pOS	1,093	62.8	59.8 to 65.8		698	70.5	67.1 to 74.2		395	49.2	44.2 to 54.7		<.0001
MRD-negative at EO12 (- -/+ -)	413	66.0	61.4 to 70.9	<.0001	252	74.8	69.4 to 80.6	<.0001	161	52.3	44.9 to 60.9	<.0001	<.0001
MRD-positive at EO12 (+ +/+ +)	43	27.9	17.3 to 45.1		23	43.5	27.3 to 69.3		20	10.0	2.7 to 37.2		.048

NOTE. Values in bold indicate statistical significance.

Abbreviations: BM, bone marrow; EO11, end of induction 1; EO12, end of induction 2; FAB, French-American-British; MRD, measurable residual disease; NC, not calculable; No., number of patients; pCIR, probability of cumulative incidence of relapse; pEFS, probability of event-free survival; pOS, probability of overall survival.

^aThe non-high-risk group included patients with the fusion partners 9p22 (n = 544), 19p13.1 (n = 75), 1q21 (n = 28), 19p13 (n = 23), Xq24 (n = 22), 1p32 (n = 13), 17q21 (n = 13), and 17q12 (n = 10). The high-risk group included patients with the fusion partners 10p12 (n = 218), 6q27 (n = 92), 19p13.3 (n = 56), 10p11.2 (n = 24), and 4q21 (n = 12).

^bThe pCIR could not be extrapolated to 5 years for patients within the high-risk group with EO12 MRD positivity because all patients had an event before that time point.

and 2F). With regard to CIR, within the non-high-risk group, patients with EO12 MRD negativity and MRD positivity had similar CIR (n = 239; 37.5% [95% CI, 31.3 to 43.7] v n = 16; 50.0% [95% CI, 23.3 to 71.9]; P = .19), whereas within the high-risk group, patients with EO12 MRD negativity showed a trend toward lower CIR (n = 153; 59.6% [95% CI, 51.2 to 67.0] v n = 10; 5-year CIR not calculable because all events occurred before this time point; P = .011; Table 1; Fig 2E).

Conversely, among patients with EO12 MRD negativity, the high-risk group had inferior EFS (n = 161; 34.6% [95% CI, 27.9 to 42.8] v n = 252; 55.9% [95% CI, 50.0 to 62.5]), CIR (n = 153; 59.6% [95% CI, 51.2 to 67.0] v n = 239; 37.5% [95% CI, 31.3 to 43.7]), and OS (n = 161; 52.3% [95% CI, 44.9 to 60.9] v n = 252; 74.8% [95% CI, 69.4 to 80.6]) than the non-high-risk group (all P < .0001; Table 1). Among patients with EO12 MRD positivity the high-risk group showed a trend toward inferior EFS (n = 20; 0.0% v n = 23; 30.4% [95% CI, 16.4 to 56.5]; P = .011), whereas CIR and OS were similar for the *KMT2A* risk groups (Table 1).

Univariable and Multivariable Analyses

In univariable analyses (Data Supplement, Table S8), EO12 MRD positivity and the high-risk group were significantly associated with inferior EFS, CIR, and OS. Age 2 years and older and age 10 years and older were significantly associated with inferior OS. WBC $\geq 100 \times 10^9/L$ showed a trend toward inferior EFS and was significantly associated with poorer OS. EO11 M2 and M3 BM responses were significantly associated with inferior EFS. Additionally, EO11 and EO12 M3 BM responses were significantly associated with inferior OS.

Overall, allo-SCT in CR1 showed a trend toward decreased CIR (HR 0.7 [95% CI, 0.5 to 0.9]; P = .011) but did not improve OS (HR 1.0 [95% CI, 0.7 to 1.3]; P = .99; Figs 3A and 3B for 90-day landmark), nor within either *KMT2A* risk group. Within the high-risk group, allo-SCT in CR1 decreased CIR (HR 0.5

[95% CI, 0.4 to 0.8]; P = .00096), but not within the non-high-risk group (HR 0.6 [95% CI, 0.4 to 1.0]; P = .058; Figs 3C and 3D for 90-day landmark). Within smaller groups on the basis of *KMT2A* risk group and EO12 MRD response, allo-SCT in CR1 did not significantly decrease CIR or improve OS (Data Supplement, Table S8). The Data Supplement, Figures S1 and S2, present 90-day NRM landmark analyses for allo-SCT versus no allo-SCT in CR1 and 90-day NRM, CIR, and OS landmark analyses for these patients stratified by treatment era (2005-2010 v 2011-2016).

The Data Supplement, Table S9, presents the crude multivariable models and those including morphologic BM response. In multivariable analyses including flow-MRD response (Table 2), EO12 MRD positivity and the high-risk group were independently associated with inferior EFS (HR 3.4 [95% CI, 2.4 to 4.9]; P < .0001; HR 2.0 [95% CI, 1.5 to 2.5]; P < .0001, respectively), CIR (HR 2.3 [95% CI, 1.4 to 3.7]; P = .0013; HR 2.1 [95% CI, 1.5 to 2.8]; P < .0001, respectively), and OS (HR 1.9 [95% CI, 1.6 to 2.3]; P < .0001; HR 2.1 [95% CI, 1.5 to 2.9]; P < .0001, respectively). Age 10 years and older was independently associated with poorer OS (HR 1.7 [95% CI, 1.2 to 2.3]; P = .0023).

DISCUSSION

After our previous I-BFM-SG study showing the prognostic value of the *KMT2A* fusion partner,⁹ this novel study on childhood *KMT2A*-r AML is, to our knowledge, the first to demonstrate that EO12 MRD positivity is an independent adverse prognostic factor in this disease, in addition to the fusion partner. This further demonstrates the need for risk stratification in childhood *KMT2A*-r AML, which constitutes 20%-25% of pediatric AML cases. In addition, allo-SCT in CR1 reduced relapse risk within the high-risk group but did not improve OS, as it

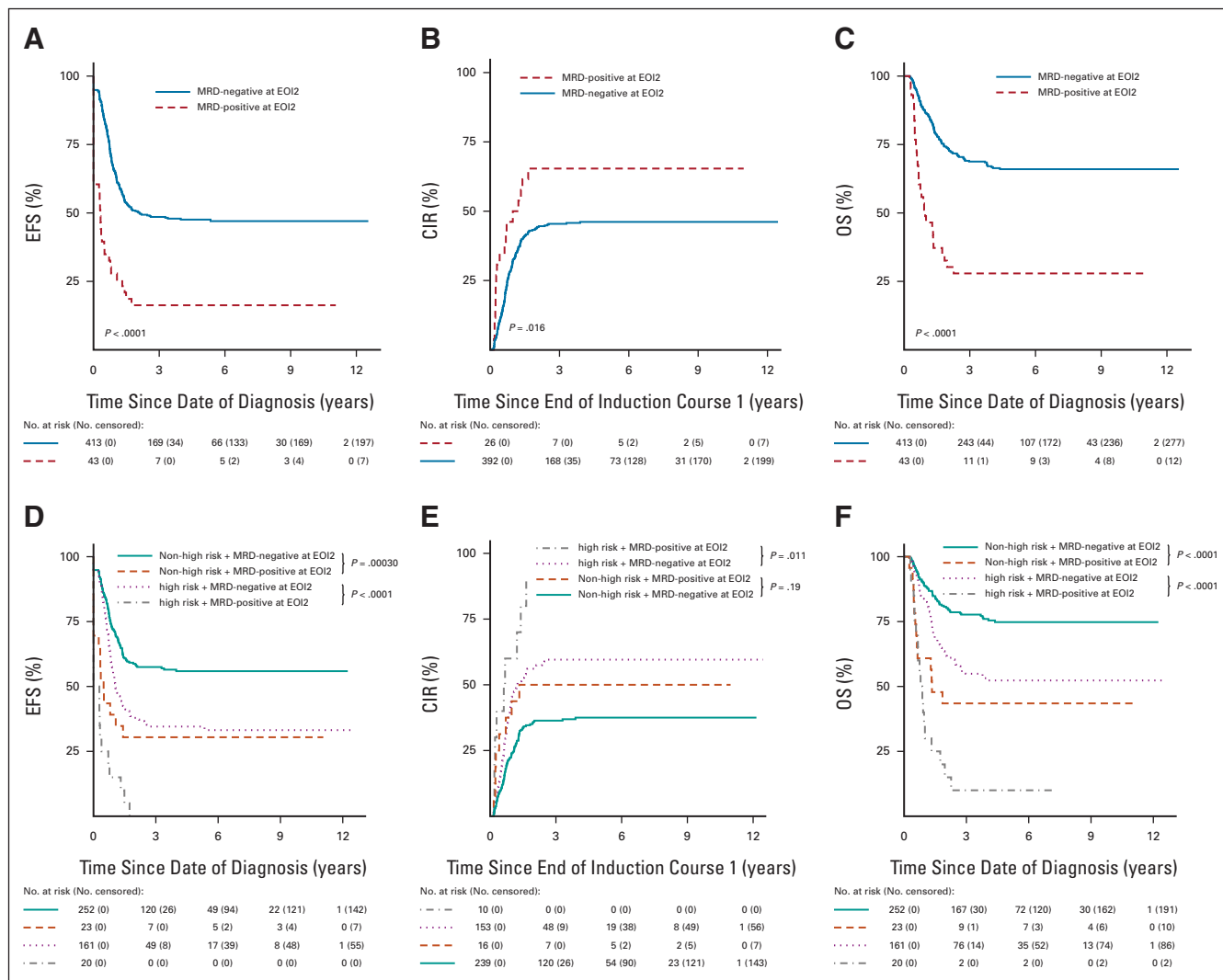


FIG 2. (A) EFS, (B) CIR, and (C) OS curves of patients with EO12 MRD negativity and MRD positivity. (D) EFS, (E) CIR, and (F) OS curves of patients with EO12 MRD negativity and MRD positivity stratified by *KMT2A* fusion partner-based risk group. The group of patients with EO12 MRD negativity included patients who were EO11 MRD-negative and EO12 MRD-negative (– –), as well as patients who were EO11 MRD-positive and EO12 MRD-negative (+ –). The group of patients with EO12 MRD positivity included patients who were EO11 MRD-positive and EO12 MRD-positive (+ +), as well as patients who were EO11 MRD-negative and EO12 MRD-positive (– +). CIR, cumulative incidence of relapse; EFS, event-free survival; EO11, end of induction 1; EO12, end of induction 2; MRD, measurable residual disease; OS, overall survival.

was counterbalanced by enhanced procedure-related toxicity.

We confirmed the independent adverse prognostic significance of previously defined high-risk *KMT2A* translocation partners (ie, 4q21, 6q27, 10p11.2, 10p12, and 19p13.3).^{9,10} Therefore, our study serves as a consensus statement on fusion partner-based risk classification of childhood *KMT2A*-r AML, which will enable intergroup clinical trials and facilitate the performance of retrospective collaborative studies. The Children’s Oncology Group (COG), as well as other SGs, incorporated these high-risk translocations into the initial risk stratification of their ongoing AAML1831 trial (ClinicalTrials.gov identifier: [NCT04293562](https://clinicaltrials.gov/ct2/show/study/NCT04293562)).^{25,26} Hopefully, more SGs will follow.

Interestingly, the EFS and OS rates of patients within the non-high-risk group with EO12 MRD positivity were quite similar to those of patients within the high-risk group with EO12 MRD negativity (EFS, 30.4% v 34.6%; OS, 43.5% v 52.3%). Notably, despite their good initial treatment response, the CIR rate of patients with EO12 MRD negativity was 46%, which is markedly higher than the reported CIR rates of 17% and 32% of patients with EO12 MRD negativity in pediatric AML in general.^{2,5} This finding demonstrates the aggressive nature of childhood *KMT2A*-r AML. Relapses may be inherent to *KMT2A* genetic features, causing the emergence of leukemic stem cells not detected by flow-MRD after killing the leukemic cell bulk.²⁷ Leukemic stem-cell frequency assessment at

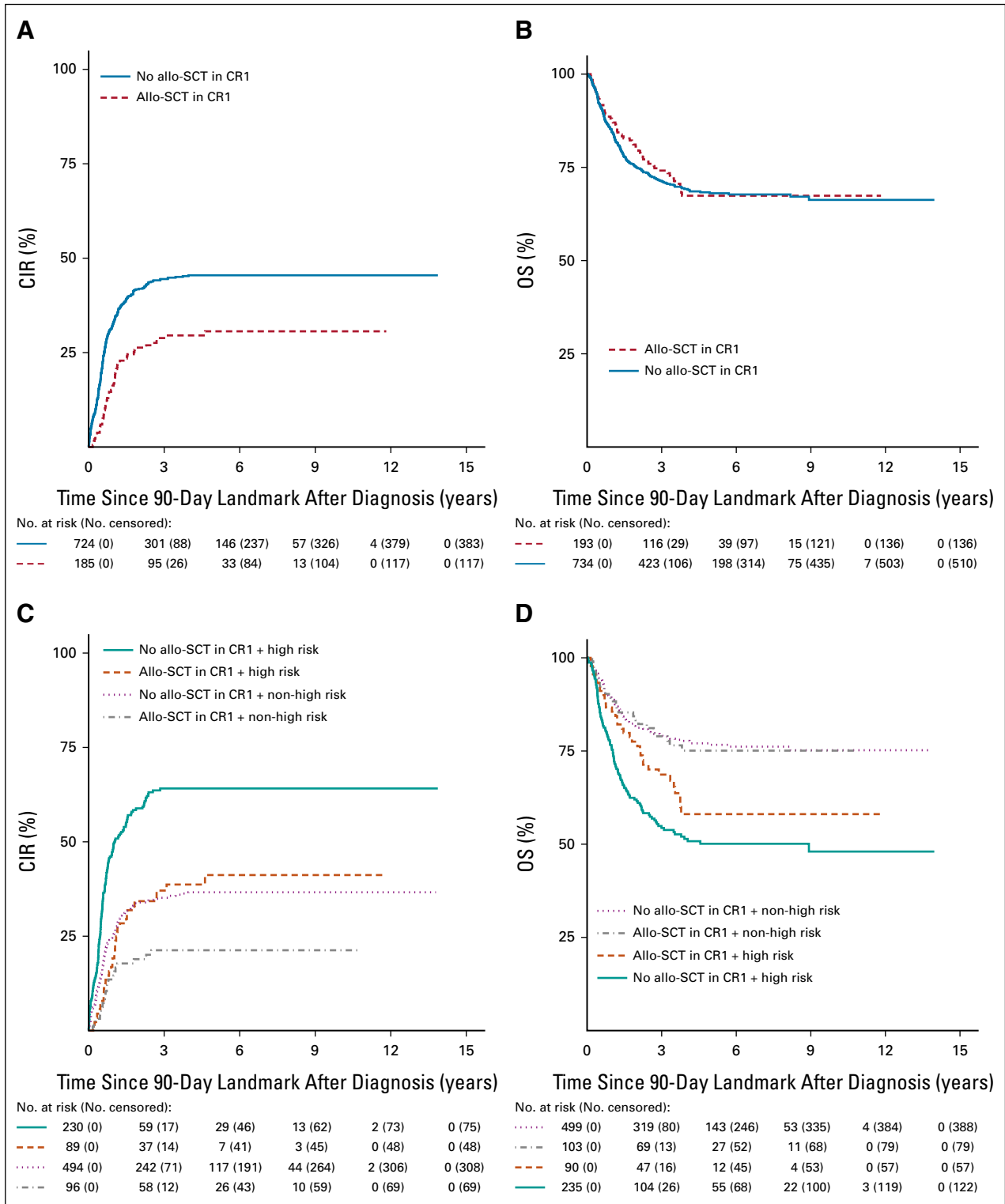


FIG 3. (A) CIR and (B) OS curves to visually compare (with a 90-day landmark) patients who did and did not receive allo-SCT in CR1. (C) CIR and (D) OS curves to visually compare (with a 90-day landmark) patients who did and did not receive allo-SCT in CR1 stratified by *KMT2A* fusion partner-based risk group. *P* values are not shown as these figures are only used for visual comparison. allo-SCT, allogeneic stem-cell transplantation; CIR, cumulative incidence of relapse; CR1, first complete remission; OS, overall survival.

TABLE 2. Multivariable Analyses of Event-Free Survival, Cumulative Incidence of Relapse, and Overall Survival in Children With *KMT2A*-Rearranged AML

Multivariable	pEFS				pCIR				pOS			
	No.	HR	95% CI	P	No.	HR	95% CI	P	No.	HR	95% CI	P
<i>KMT2A</i> risk group												
Non-high risk	269	1.0			247	1.0			269	1.0		
High risk	175	2.0	1.5 to 2.5	<.0001	152	2.1	1.5 to 2.8	<.0001	175	2.1	1.5 to 2.9	<.0001
Age at diagnosis, years												
<10	—	—			—	—			321	1.0		
≥10	—	NA ^a	—	—	—	NA ^a	—	—	123	1.7	1.2 to 2.3	.0023
WBC, ×10 ⁹ /L												
<100	350	1.0			—	—			350	1.0		
≥100	94	0.8	0.6 to 1.1	.15	—	NA ^a	—	—	94	0.8	0.6 to 1.2	.35
Receiving allo-SCT in CR1												
No	—	—			325	1.0			—	—		
Yes	—	NA ^b	—	—	74	0.8	0.5 to 1.2	.22	—	NA ^a	—	—
Flow-MRD response												
MRD-negative at EO12 (− −/+ −)	402	1.0			374	1.0			402	1.0		
MRD-positive at EO12 (+ +/+ +)	42	3.4	2.4 to 4.9	<.0001	25	2.3	1.4 to 3.7	.0013	42	1.9	1.6 to 2.3	<.0001

NOTE. Allo-SCT in CR1 was included as a time-dependent covariate. Values in bold indicate statistical significance.

Abbreviations: allo-SCT, allogeneic stem-cell transplantation; CR1, first complete remission; EFS, event-free survival; EO12, end of induction 2; HR, hazard ratio; MRD, measurable residual disease; NA, not applicable; No., number of patients; pCIR, probability of cumulative incidence of relapse; pEFS, probability of event-free survival; pOS, probability of overall survival; WBC, white blood cell count.

^aOnly covariates with two-sided *P* values < .05 in univariable analysis were included in multivariable analysis.

^bReceiving allo-SCT in CR1 was not included in the multivariable analysis of EFS because, to receive allo-SCT in CR1, patients had to achieve CR, and EFS analysis also included induction failures.

diagnosis and during treatment may be included in future studies to further improve the identification of children with *KMT2A*-r AML at risk of relapse.^{28,29} Alternatively, the limited sensitivity of the 4- to 10-color antibody panels used for flow-MRD detection in our study may have played a role. It needs to be determined whether flow-MRD detection on the basis of up-to-date methodology with 10 or more color approaches and centralized quality control,^{30,31} PCR-based techniques, or next-generation sequencing (NGS) may at least partially overcome this limitation in sensitivity.

Among patients with EO12 MRD negativity, the high-risk group showed significantly poorer outcomes than the non-high-risk group, consistent with a previous study on children with AML with MRD negativity that identified t(6;11) and t(10;11)—breakpoints that were not further specified—as independent adverse prognostic factors.³² By contrast, among patients with EO12 MRD positivity, prognosis was not significantly influenced by the *KMT2A* risk group.

On the basis of our findings, patients within the high-risk group, irrespective of flow-MRD response, and patients within the non-high-risk group with EO12 MRD positivity may benefit from high-risk-based treatment or novel treatment approaches, including experimental therapy. Allo-SCT in CR1 is generally used as high-risk-based treatment. The allo-SCT in CR1 rate in our study was slightly higher than in the

previous I-BFM-SG study⁹ (21% v 14%) but relatively low by modern standards, and given the high relapse risk of children with *KMT2A*-r AML. This may be explained by the fact that in the treatment protocols used during our study period, high-risk *KMT2A* translocations were not always considered a transplantation indication or that transplantation was restricted to those with available human leukocyte antigen-matched donors. To our knowledge, we are the first to show that allo-SCT in CR1 reduced the relapse risk in patients within the high-risk group, but not in patients within the non-high-risk group, nor within smaller groups on the basis of *KMT2A* risk group and EO12 MRD response. This should be interpreted cautiously, as the overall transplantation rate was low and this study was not powered to assess the effect of allo-SCT in CR1. Furthermore, allo-SCT in CR1 did not improve OS, consistent with previous findings.^{9,10} This is most likely due to insufficient eradication of the disease and, although significantly reduced in the most recent years, transplantation-related mortality.

Our results highlight the need for new treatment approaches to improve the prognosis of children with *KMT2A*-r AML. The COG demonstrated that GO added to induction therapy improved EFS and reduced relapse risk in these patients.¹⁰ Additionally, GO seemed to improve post-transplantation prognosis.¹⁰ These results need to be further confirmed to definitively establish which children with *KMT2A*-r

AML show the greatest benefit from intensified treatment strategies. In the current MyeChild01 (ClinicalTrials.gov identifier: [NCT02724163](https://clinicaltrials.gov/ct2/show/study/NCT02724163)) and Japanese Pediatric Leukemia/Lymphoma SG-AML-20 (jRCTs041210015) trials,³³ GO added to induction and postinduction therapy is being studied, respectively. Other potentially promising agents are menin inhibitors, which have shown a significant reduction in leukemic cell load in mice engrafted with *KMT2A-r* AML.³⁴ Additionally, in two recent phase I studies, treatment with the menin inhibitors SNDX-5613 (revumenib)³⁵ and KO-539 (ziftomenib)³⁶ appeared safe and showed encouraging clinical responses in patients with relapsed/refractory *KMT2A-r* acute leukemia and AML, respectively.

Although flow cytometry is applicable in approximately 90% of children with AML, MRD cannot be detected in all patients because it requires extensive expertise to distinguish AML cells from normal, regenerating BM, which may only be available in larger experienced laboratories.^{5,30,37} Considerable efforts are being made to standardize sample preparation and analyses.^{5,30}

This largest cohort of children with *KMT2A-r* AML serves as a highly valuable historical cohort for future pediatric AML SG collaborations in the pre-menin inhibitor era. Our study was limited by its retrospective design, the use of nonuniform treatment protocols with different risk stratifications across SGs, the overall low transplantation rate, and the lack of flow-MRD data at both time points in more

than half of the patients. In some cases, MRD availability might have interacted with risk stratification and/or treatment allocation, including allo-SCT in CR1. Nonetheless, the relatively old and largely nonstandardized flow-MRD data from our cohort allowed us to discern flow-MRD–based risk associations independent of the fusion partner-based risk group.

We conclude that EO12 flow-MRD response and fusion partner-based risk group should be included as risk stratification factors in childhood *KMT2A-r* AML. Patients within the non–high-risk group with EO12 MRD negativity may be assigned to the standard-risk arm of treatment protocols but should be closely monitored for MRD after remission. All other patients (Data Supplement, Figure S3) should be assigned to the high-risk arm. Future studies should establish whether allo-SCT in CR1 will be the best risk-adapted treatment for all patients assigned to the high-risk-arm. New treatment approaches, including GO and menin inhibitors, are urgently needed for this subset of patients. The implementation of optimized stratification approaches, the increased availability of flow-MRD assays, quantitative PCR, and NGS among pediatric AML SGs worldwide, and the use of agents able to kill *KMT2A-r* AML cells more efficiently could contribute to improved survival of children with *KMT2A-r* AML, for whom international collaborative research remains indispensable.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Individual participant data are not available to share. Participating study groups should be contacted directly for the original data.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Measurable Residual Disease and Fusion Partner Independently Predict Survival and Relapse Risk in Childhood *KMT2A*-Rearranged Acute Myeloid Leukemia: A Study by the International Berlin-Frankfurt-Münster Study Group**

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