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REGULAR ARTICLE

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Optimized cytogenetic risk-group stratification of *KMT2A*-rearranged pediatric acute myeloid leukemia

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Key Points

- We clinically characterized 3 additional, recurring *KMT2A*-r groups and identified specific ACAs of independent prognostic significance.
- We present an optimized, fusion-based risk-group stratification of *KMT2A*-r pediatric AML.

A comprehensive international consensus on the cytogenetic risk-group stratification of *KMT2A*-rearranged (*KMT2A*-r) pediatric acute myeloid leukemia (AML) is lacking. This retrospective (2005-2016) International Berlin-Frankfurt-Münster Study Group study on 1256 children with *KMT2A*-r AML aims to validate the prognostic value of established recurring *KMT2A* fusions and additional cytogenetic aberrations (ACAs) and to define additional, recurring *KMT2A* fusions and ACAs, evaluating their prognostic relevance. Compared with our previous study, 3 additional, recurring *KMT2A*-r groups were defined: Xq24/*KMT2A*::*SEPT6*, 1p32/*KMT2A*::*EPS15*, and 17q12/t(11;17)(q23;q12). Across 13 *KMT2A*-r groups, 5-year event-free survival probabilities varied significantly (21.8%-76.2%; $P < .01$). ACAs occurred in 46.8% of 1200 patients with complete karyotypes, correlating with inferior overall survival (56.8% vs 67.9%; $P < .01$). Multivariable analyses confirmed independent associations of 4q21/*KMT2A*::*AFF1*, 6q27/*KMT2A*::*AFDN*, 10p12/*KMT2A*::*MLLT10*, 10p11.2/*KMT2A*::*ABI1*, and 19p13.3/*KMT2A*::*MLLT1* with adverse

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Individual participant data are not available to share. Participating study groups/countries should be contacted directly for the original data. Any overlap in our data set has been published in https://doi.org/10.1200/JCO.22.02120.

The full-text version of this article contains a data supplement.

outcomes, but not those of 1q21/*KMT2A*::*MLLT11* and trisomy 19 with favorable and adverse outcomes, respectively. Newly identified ACAs with independent adverse prognoses were monosomy 10, trisomies 1, 6, 16, and X, add(12p), and del(9q). Among patients with 9p22/*KMT2A*::*MLLT3*, the independent association of French-American-British–type M5 with favorable outcomes was confirmed, and those of trisomy 6 and measurable residual disease at end of induction with adverse outcomes were identified. We provide evidence to incorporate 5 adverse-risk *KMT2A* fusions into the cytogenetic risk-group stratification of *KMT2A*-r pediatric AML, to revise the favorable-risk classification of 1q21/*KMT2A*::*MLLT11* to intermediate risk, and to refine the risk-stratification of 9p22/*KMT2A*::*MLLT3* AML. Future studies should validate the associations between the newly identified ACAs and outcomes and unravel the underlying biological pathogenesis of *KMT2A* fusions and ACAs.

Introduction

KMT2A-rearranged (*KMT2A*-r) acute myeloid leukemia (AML) is a heterogeneous pediatric AML subtype involving chromosomal rearrangement of the *KMT2A* (formerly known as *MLL*) gene located at chromosome 11q23.[1] Outcome of this subtype is highly variable and related to the *KMT2A* fusion partner, as determined in our previous International Berlin-Frankfurt-Münster (I-BFM) Study Group (SG; I-BFM-SG) analysis (1993-2005).[2] Our more recent (2005-2016) I-BFM-SG cohort demonstrated that the outcome of childhood *KMT2A*-r AML is also dependent on flow cytometry–based measurable residual disease (flow-MRD) at end of induction 2 (EOI2).[3]

The most frequently occurring *KMT2A* translocation, t(9;11)(p22;q23) (9p22/*KMT2A*::*MLLT3* fusion), has been associated with an intermediate prognosis.[2,4] However, among patients with 9p22/*KMT2A*::*MLLT3*, significantly better survival was repeatedly reported for those with the French-American-British (FAB)–type M5.[2,5] The translocation t(1;11)(q21;q23) (1q21/*KMT2A*::*MLLT11* fusion) has been associated with a favorable outcome,[2] although not confirmed by others.[4] Markedly inferior outcomes have been reported for the translocations t(4;11)(q21;q23) (4q21/*KMT2A*::*AFF1* fusion), t(6;11)(q27;q23) (6q27/*KMT2A*::*AFDN* fusion), t(10;11)(p12;q23) (10p12/*KMT2A*::*MLLT10* fusion), t(10;11)(p11.2;q23) (10p11.2/*KMT2A*::*ABI1* fusion), and t(11;19)(q23;p13.3) (19p13.3/*KMT2A*::*MLLT1* fusion),[2,4] which are often considered as adverse risk. In our more recent I-BFM-SG analysis,[3] these 5 fusions were clustered into an adverse-risk fusion-based group, which was independently associated with a poor outcome, like in the study by Pollard et al.[4]

The Children's Oncology Group incorporated these 5 distinct adverse-risk *KMT2A* fusions as unfavorable prognostic markers into the treatment stratification algorithm of their ongoing AAML1831 trial (ClinicalTrials.gov identifier: NCT04293562).[6,7] However, other SGs did not consider these fusions, incorporated only few, or relied more on flow-MRD as a prognostic factor because of the lack of a comprehensive international consensus on risk-group stratification of childhood *KMT2A*-r AML.[8,9]

Additional cytogenetic aberrations (ACAs) have been reported to be of prognostic value in childhood *KMT2A*-r AML.[2,5] Trisomy 8 was associated with a favorable outcome, whereas trisomy 19 and structural aberrations were associated with adverse outcomes.[5]

The aims of this large I-BFM-SG study were to validate the prognostic value of previously defined recurring *KMT2A* fusions and reported ACAs and to define additional, recurring *KMT2A* fusions and ACAs, evaluating their prognostic relevance. The overall aim was to provide evidence to optimize the cytogenetic risk-group stratification of *KMT2A*-r pediatric AML.

Methods

Study design and patients

This retrospective study included patient data from 1256 children with *KMT2A*-r AML, assembled from 15 pediatric AML SGs/countries affiliated with the I-BFM-SG (supplemental Table 1). This same cohort was used in our previous study, analyzing the impact of flow-MRD and use of allogeneic stem cell transplantation (allo-SCT) in first complete remission (CR1) on the outcome of patients with *KMT2A*-r AML.[3] Patients were treated according to national or SG pediatric AML clinical trials,[10-23] approved by the institutional ethics committees of all collaborating centers. The study included patients aged<19 years with de novo *KMT2A*-r AML, diagnosed between 1 January 2005 and 31 December 2016. Patients with a diagnosis of acute promyelocytic leukemia, isolated myeloid sarcoma, myeloid leukemia of Down syndrome, and/or who had received previous anticancer treatment for diseases other than AML for >1 week were excluded a priori. Data were validated for accuracy and correctness.

Cytogenetic analysis

KMT2A rearrangements were detected by cytogenetics (G-, Q-, or R-banding according to local practice), with some confirmed by fluorescence in situ hybridization, or reverse transcription polymerase chain reaction within the local centers. Karyotypes were reviewed by 2 authors (R.E.v.W. and C.J.H.) and written according to the International System for Human Cytogenetic Nomenclature 2020.[24] Patients were assigned to 1 of 10 individual, recurring fusion-based *KMT2A*-r groups or the *KMT2A*-other group, as

previously described by Balgobind et al.[2] Two authors (R.E.v.W. & C.J.H.) validated the group assignments and defined additional, recurring *KMT2A*-r groups when the same fusion was observed in at least 10 patients. Unknown fusions and those present in <10 patients remained assigned to the *KMT2A*-other group.

An ACA was defined as the presence of an acquired chromosomal abnormality in addition to the *KMT2A* rearrangement. Constitutional abnormalities did not constitute ACA. Patients with incomplete karyotypes were excluded from the ACA analysis. Ploidy changes were regarded as a single ACA. Patients with ACAs were categorized into having numerical, structural, or both numerical and structural aberrations. Numerical aberrations were defined as the loss or gain of whole chromosomes, whereas structural aberrations involved changes to chromosome short (p) or long (q) arms. Within the category of both numerical and structural aberrations, patients with separate numerical, and structural aberrations were included, as well as gains of structurally abnormal chromosomes, for example, +der(9p) and +i(8q). The gain of a marker chromosome was classified as a numerical aberration.

Statistical analyses

CR was defined as <5% blasts in the bone marrow after 2 induction courses, with regeneration of peripheral blood cells and the absence of extramedullary disease and cells with Auer rods. Patients who did not achieve CR after induction therapy were considered refractory to treatment. Relapse was defined as ≥5% blasts in the bone marrow, reappearance of leukemic blasts in the peripheral blood, or the presence of extramedullary disease after initial CR. Event-free survival (EFS) was calculated from the date of diagnosis to the date of the first event or last follow-up. Events included induction failure (ie, death before the start of intended treatment, death within 42 days after the start of treatment [early death], death after >42 days but before CR assessment, or refractory disease), death in CR, relapse, and secondary malignancy. Induction failure was considered an event at time zero. Cumulative incidence of relapse (CIR) was defined as the time from end of induction 1 until relapse for patients in CR, with deaths without a relapse considered competing events. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up.

The χ^2 test was used to compare differences in proportions of clinical characteristics and groups. The Mann-Whitney *U* and Kruskal-Wallis tests were used to compare differences in medians of 2 or >2 groups, respectively. The prognostic impact of recurring ACAs, occurring in at least 10 patients, was explored. Probabilities of EFS and OS with 95% confidence intervals (CIs) were estimated with the Kaplan-Meier method and compared using the log-rank test. CIR estimates with 95% CIs were compared using the Gray test for competing risks. Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% CIs. Variables with a 2-sided *P*-value < .05 in univariable Cox regression analyses were included in multivariable Cox regression models. Subsequently, variables with a 2-sided *P*-value > .10 were omitted from the final multivariable models by stepwise backward elimination. To correct for multiple testing, 2-sided *P*-values ≤ .01 were considered statistically significant. SPSS version 28 and R version 4.1.2 were used.

Results

Patient characteristics and ACA distribution

A total of 1256 children with *KMT2A*-r AML were included, of whom 1130 (90.0%) were assigned to 1 of 13 *KMT2A*-r groups and 126 (10.0%) to the *KMT2A*-other group (Figure 1). 9p22/*KMT2A*::*MLLT3* (n = 544, 43.3%), 10p12/*KMT2A*::*MLLT10* (n = 218, 17.4%), 6q27/*KMT2A*::*AFDN* (n = 92, 7.3%), and t(11;19)(q23;p13.1) (19p13.1/*KMT2A*::*ELL* fusion) (n = 75, 6.0%) were most frequent, together accounting for around 75% of cases. As compared with Balgobind et al,[2] 3 additional, recurring *KMT2A*-r groups were defined: t(X;11)(q24;q23) (Xq24/*KMT2A*::*SEPT6* fusion) (n = 22, 1.8%), t(1;11)(p32;q23) (1p32/*KMT2A*::*EPS15* fusion) (n = 13, 1.0%), and t(11;17)(q23;q12) (17q12, variable at the molecular level) (n = 10, 0.8%).

Among the 1256 patients, only 56 (4.5%) had incomplete karyotypes. There were no statistically significant differences between patients with and without complete karyotypes in terms of sex, median age, white blood cell (WBC) count at diagnosis, central nervous system involvement, FAB-type, *KMT2A*-r groups, and clinical outcome (supplemental Table 2). Of the 1200 patients with complete karyotypes, 562 (46.8%) had ACAs (Figure 1). The number of ACAs ranged from 0 to 17. The median number of ACAs among patients with ACAs was 2 (interquartile range, 1.0-3.0).

Table 1 shows the clinical characteristics and outcomes of the total cohort, stratified by *KMT2A*-r group. There were statistically significant differences in median age and WBC count at diagnosis and in the proportions of FAB-type and type of ACAs between these groups (Table 1). In all *KMT2A*-r groups, the median age at diagnosis was <4 years except for the 19p13.3/*KMT2A*::*MLLT1*, t(11;19)(q23;p13) (19p13, subband unknown), and 6q27/*KMT2A*::*AFDN* groups, in which the median ages were 6.8, 9.2, and 10.5 years ($P < .01$), respectively. The median WBC count at diagnosis was higher in patients with 19p13 (50.8×10^9/L), 6q27/*KMT2A*::*AFDN* (65.8×10^9/L), and 4q21/*KMT2A*::*AFF1* (114.3×10^9/L) than in other *KMT2A*-r groups ($P < .01$). Most patients were classified as FAB-M5 (n = 619, 71.5%) or FAB-M4 (n = 121, 14.0%), but these proportions were not similar across all groups ($P < .01$). For example, most children with 1q21/*KMT2A*::*MLLT11* were classified as FAB-M4.

Supplemental Tables 3 and 4 show the frequency distributions of all numerical and structural ACAs, respectively, in total and stratified by *KMT2A*-r group. There were 28 recurring ACAs (supplemental Table 5), of which trisomy 8 (n = 210, 37.4% of all ACA cases) was the most common. Analyses to test for associations between specific ACAs and *KMT2A*-r groups were not possible because of the small numbers.

The type of ACAs differed significantly across *KMT2A*-r groups ($P < .01$; Table 1). For example, numerical aberrations were more common in patients with 9p22/*KMT2A*::*MLLT3* (44.9%), 17q12 (50%), 19p13 (63.6%), Xq24/*KMT2A*::*SEPT6* (66.7%), and t(11;17)(q23;q21) (17q21, fusion unknown) (83.3%) than in other *KMT2A*-r groups. Associations between the presence and type of ACAs and clinical characteristics are shown in supplemental Table 6. The median WBC count at diagnosis was lower in patients with ACAs than in patients without ACAs, whereas ACAs

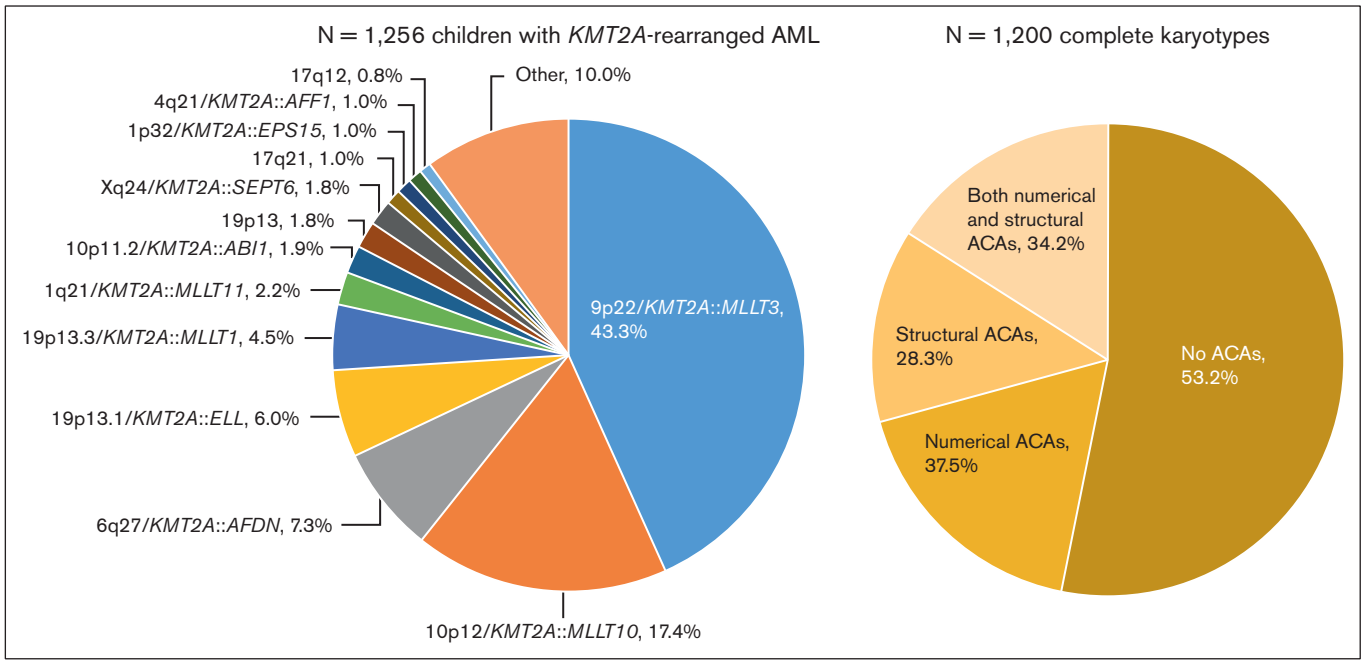


Figure 1. Distribution of the fusion-based groups and the presence and type of ACAs in our cohort of childhood *KMT2A*-r AML. 9p22/*KMT2A*::*MLLT3* refers to t(9;11)(p22;q23) (n = 544), 10p12/*KMT2A*::*MLLT10* to t(10;11)(p12;q23) (n = 218), 6q27/*KMT2A*::*AFDN* to t(6;11)(q27;q23) (n = 92), 19p13.1/*KMT2A*::*ELL* to t(11;19)(q23;p13.1) (n = 75), 19p13.3/*KMT2A*::*MLLT1* to t(11;19)(q23;p13.3) (n = 56), 1q21/*KMT2A*::*MLLT11* to t(1;11)(q21;q23) (n = 28), 10p11.2/*KMT2A*::*ABI1* to t(10;11)(p11.2;q23) (n = 24), 19p13 to t(11;19)(q23;p13) without ascertained subband (n = 23), Xq24/*KMT2A*::*SEPT6* to t(X;11)(q24;q23) (n = 22), 17q21 to t(11;17)(q23;q21) (n = 13), 1p32/*KMT2A*::*EPS15* to t(1;11)(p32;q23) (n = 13), 4q21/*KMT2A*::*AFF1* to t(4;11)(q21;q23) (n = 12), and 17q12 to t(11;17)(q23;q12) (n = 10). Of the 1200 patients with complete karyotypes, 638 had no ACAs and 562 had ACAs, of whom 211 had solely numerical ACAs, 159 solely structural aberrations, and 192 both numerical and structural ACAs. Figure created with BioRender.com.

in general were more likely to occur in patients with FAB-M7 and FAB-M0.

Outcome

Of the 1219 patients known to have commenced chemotherapy, 1066 (87.5%) achieved CR, with no significant differences in CR rates among *KMT2A*-r groups ($P = .02$; Table 1). However, EFS, CIR, and OS estimates of the *KMT2A*-r groups differed significantly (all $P < .01$; Table 1; Figure 2). Good outcomes were observed in patients with Xq24/*KMT2A*::*SEPT6* and 1p32/*KMT2A*::*EPS15*, with EFS and OS rates exceeding 75% and 90%, respectively, and CIR rates below 20%. Most patients that achieved CR in these 2 groups were treated with chemotherapy only and did not receive allo-SCT in CR1 (16/21 patients with Xq24/*KMT2A*::*SEPT6*; 9/10 patients with 1p32/*KMT2A*::*EPS15*). Relapses in these groups occurred only in patients who did not undergo transplantation, and all but 1 patient were salvaged. Patients with 10p11.2/*KMT2A*::*ABI1*, 6q27/*KMT2A*::*AFDN*, and 4q21/*KMT2A*::*AFF1* had very poor outcomes with EFS rates of 21.8% (95% CI, 4.9-38.7), 23.3% (95% CI, 14.3-32.3), and 25.0% (95% CI, 0.5-49.5), respectively. Patients with 10p12/*KMT2A*::*MLLT10* and 19p13.3/*KMT2A*::*MLLT1* also had poor outcomes, with EFS rates <40%. In these 5 *KMT2A*-r groups with poor outcomes, CIR rates were ≥50% (Table 1).

Patients with ACAs had inferior OS compared with patients without ACAs (56.8% [95% CI, 52.5-61.1] vs 67.9% [95% CI, 64.2-71.6]; $P < .01$), but EFS and CIR rates were not statistically significantly different (supplemental Table 7; supplemental Figure 1). Patients with numerical ACAs showed better outcomes than patients with structural or both numerical and structural ACAs (EFS, 52.0% [95% CI, 44.9-59.1] vs 33.7% [95% CI, 25.9-41.5] vs 37.3% [95% CI, 30.1-44.6]; $P < .01$; CIR, 34.5% [95% CI, 27.5-41.6] vs 57.0% [95% CI, 47.5-65.4] vs 51.7% [95% CI, 43.2-59.6]; $P < .01$; OS, 64.0% [95% CI, 57.1-70.9] vs 53.9% [95% CI, 47.7-62.1] vs 50.8% [95% CI, 43.0-58.6]; $P < .01$; supplemental Table 7). EFS curves for patients with and without recurring ACAs that were included in multivariable Cox regression analyses on the basis of entry criterion 2-sided P value $< .05$ in univariable Cox regression analyses (supplemental Table 5) are shown in Figure 3, and the CIR and OS curves of these patients are shown in supplemental Figure 2. Patients with trisomy 8 had statistically significantly superior EFS and a lower CIR than patients without trisomy 8. Patients with monosomy 10 and del(9q) had statistically significantly inferior EFS and OS and a higher CIR than patients without these ACAs. Patients with trisomies 4, 6, 12, 16, and X, and add(12p) had statistically significantly inferior EFS and/or higher CIR than patients without these ACAs. Patients with trisomy 1 had a statistically significantly inferior OS than patients without trisomy 1.

Multivariable analyses

In multivariable analyses (Table 2), age >10 years was independently associated with inferior OS (HR, 1.8; $P < .01$), and WBC count >100 × 10^9/L with inferior EFS (HR, 1.3; $P < .01$) and OS (HR, 1.5; $P < .01$). The 10p12/*KMT2A*::*MLLT10*, 6q27/*KMT2A*::*AFDN*, and

Table 1. Clinical characteristics and outcomes of 1256 children with *KMT2A*-r AML and stratified by fusion-based group

	Total	9p22/ *KMT2A*::*MLLT3*	10p12/ *KMT2A*::*MLLT10*	6q27/ *KMT2A*::*AFDN*	19p13.1/ *KMT2A*::*ELL*	19p13.3/ *KMT2A*::*MLLT1*	1q21/ *KMT2A*::*MLLT11*	10p11.2/ *KMT2A*::*ABI1*
No. (%)	1256 (100)	544 (43.3)	218 (17.4)	92 (7.3)	75 (6.0)	56 (4.5)	28 (2.2)	24 (1.9)
Sex, no. (%) (n = 1235)								
Male	638 (51.7)	276 (51.9)	127 (58.5)	44 (47.8)	39 (52.7)	30 (54.5)	9 (32.1)	14 (63.6)
Female	597 (48.3)	256 (48.1)	90 (41.5)	48 (52.2)	35 (47.3)	25 (45.5)	19 (67.9)	8 (36.4)
Age at diagnosis, y (n = 1256)								
Median (IQR)	2.5 (1.0-10.0)	3.0 (1.1-9.1)	1.6 (0.7-7.7)	10.5 (5.4-15.2)	3.6 (0.6-12.3)	6.8 (1.6-13.2)	1.2 (0.5-3.0)	1.5 (0.9-5.1)
WBC count, $\times 10^9$/L, (n = 1186)								
Median (IQR)	21.4 (5.7-87.8)	12.3 (4.4-74.2)	15.1 (5.2-57.7)	65.8 (20.4-120.8)	33.2 (11.0-93.7)	28.1 (12.1-92.3)	30.4 (9.0-63.0)	30.9 (7.5-45.9)
CNS involvement, No. (%) (n = 722)								
Negative	574 (79.5)	274 (83.3)	105 (80.8)	41 (83.7)	25 (69.4)	19 (65.5)	12 (80)	7 (63.6)
Positive	148 (20.5)	55 (16.7)	25 (19.2)	8 (16.3)	11 (30.6)	10 (34.5)	3 (20)	4 (36.4)
FAB-type, no. (%) (n = 866)								
FAB-M0	18 (2.1)	7 (1.8)	0 (0)	3 (5.2)	0 (0)	2 (6.1)	1 (5.3)	0 (0)
FAB-M1	33 (3.8)	9 (2.3)	1 (0.7)	12 (20.7)	3 (6.5)	0 (0)	1 (5.3)	0 (0)
FAB-M2	19 (2.2)	6 (1.5)	1 (0.7)	1 (1.7)	4 (8.7)	1 (3.0)	4 (21.1)	0 (0)
FAB-M4	121 (14.0)	29 (7.4)	11 (7.2)	15 (25.9)	17 (37.0)	6 (18.2)	9 (47.4)	1 (6.7)
FAB-M5	619 (71.5)	308 (78.6)	132 (86.3)	26 (44.8)	20 (43.5)	22 (66.7)	3 (15.8)	13 (86.7)
FAB-M7	31 (3.6)	21 (5.4)	6 (3.9)	0 (0)	0 (0)	2 (6.1)	0 (0)	0 (0)
FAB unspecified	25 (2.9)	12 (3.1)	2 (1.3)	1 (1.7)	2 (4.3)	0 (0)	1 (5.3)	1 (6.7)
ACA, no. (%) (n = 1200)								
No	638 (53.2)	271 (52.5)	100 (47.6)	60 (67.4)	44 (61.1)	26 (47.3)	20 (71.4)	14 (58.3)
Yes	562 (46.8)	245 (47.5)	110 (52.4)	29 (32.6)	28 (38.9)	29 (52.7)	8 (28.6)	10 (41.7)
ACA type, no. (%) (n = 562)								
Structural	159 (28.3)	53 (21.6)	44 (40.0)	6 (20.7)	4 (14.3)	9 (31.0)	3 (37.5)	7 (70)
Numerical	211 (37.5)	110 (44.9)	30 (27.3)	9 (31.0)	11 (39.3)	11 (37.9)	2 (25)	2 (20)
Both*	192 (34.2)	82 (33.5)	36 (32.7)	14 (48.3)	13 (46.4)	9 (31.0)	3 (37.5)	1 (10)
CR, no. (%) (n = 1219)	1066 (87.5)	464 (89.9)	187 (87.8)	77 (85.6)	62 (87.3)	50 (90.9)	22 (81.5)	22 (91.7)

Clinical outcome	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
5-y pEFS	1199	44.8 (41.9-47.7)	512	54.0 (49.5-58.5)	212	33.4 (26.7-40.1)	89	23.3 (14.3-32.3)	71	44.8 (33.0-56.6)	55	34.7 (21.6-47.8)	27	55.0 (36.0-74.0)	24	21.8 (4.9-38.7)
5-y pCIR	1057	44.8 (41.7-47.9)	459	36.2 (31.6-40.7)	186	57.4 (49.6-64.4)	77	66.3 (54.0-76.0)	61	41.9 (29.2-54.2)	50	54.1 (39.1-66.9)	22	27.9 (10.9-47.9)	22	71.4 (45.4-86.6)
5-y pOS	1217	62.6 (59.9-65.3)	522	70.2 (66.1-74.3)	214	54.0 (47.1-60.9)	90	39.0 (27.8-50.2)	72	67.8 (56.6-79.0)	55	51.7 (37.6-65.8)	27	73.3 (56.3-90.4)	24	50.9 (29.9-71.9)

Values in boldface indicate statistical significance. Fusion-based groups are displayed in descending order of occurrence. 9p22/*KMT2A*::*MLLT3* refers to t(9;11)(p22;q23), 10p12/*KMT2A*::*MLLT10* to t(10;11)(p12;q23), 6q27/*KMT2A*::*AFDN* to t(6;11)(q27;q23), 19p13 to t(11;19)(q23;p13) without ascertained subband, 19p13.1/*KMT2A*::*ELL* to t(11;19)(q23;p13.1), 19p13.3/*KMT2A*::*MLLT1* to t(11;19)(q23;p13.3), 1q21/*KMT2A*::*MLLT11* to t(1;11)(q21;q23), 10p11.2/*KMT2A*::*ABI1* to t(10;11)(p11.2;q23), Xq24/*KMT2A*::*SEPT6* to t(X;11)(q24;q23), 17q21 to t(11;17)(q23;q21), 4q21/*KMT2A*::*AFF1* to t(4;11)(q21;q23), 1p32/*KMT2A*::*EPS15* to t(1;11)(p32;q23), and 17q12 to t(11;17)(q23;q12).

CNS, central nervous system; No., number of patients; pCIR, probability of CIR; pEFS, probability of EFS; pOS, probability of OS.

*Including patients who had separate numerical and structural aberrations, as well as patients with gain of a chromosome with a structural aberration, for example, +der(9p) and +i(8q).

Table 1 (continued)

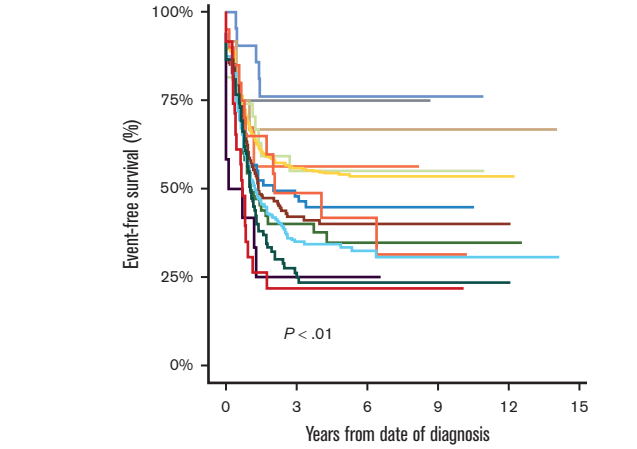
	19p13	Xq24/*KMT2A*::*SEPT6*	17q21	1p32/*KMT2A*::*EPS15*	4q21/*KMT2A*::*AFF1*	17q12	Other	*P* value
No. (%)	23 (1.8)	22 (1.8)	13 (1.0)	13 (1.0)	12 (1.0)	10 (0.8)	126 (10.0)	
Sex, no. (%) (n = 1235)								
Male	8 (38.1)	9 (42.9)	7 (53.8)	8 (61.5)	5 (41.7)	6 (60)	56 (44.8)	.24
Female	13 (61.9)	12 (57.1)	6 (46.2)	5 (38.5)	7 (58.3)	4 (40)	69 (55.2)	
Age at diagnosis, y (n = 1256)								
Median (IQR)	9.2 (1.0-13.0)	1.4 (0.9-5.7)	1.0 (0.3-3.8)	0.6 (0.3-1.6)	0.6 (0.1-1.9)	1.7 (0.6-13.9)	1.5 (0.6-7.7)	**<.01**
WBC count, ×10^9/L, (n = 1186)								
Median (IQR)	50.8 (11.4-103.0)	18.0 (5.4-48.1)	39.2 (8.4-127.4)	39.4 (13.5-56.9)	114.3 (24.3-401.0)	41.0 (8.8-102.3)	30.0 (8.2-145.8)	**<.01**
CNS involvement, no. (%) (n = 722)								
Negative	17 (94.4)	9 (75)	8 (72.7)	8 (80)	4 (66.7)	3 (75)	42 (67.7)	.10
Positive	1 (5.6)	3 (25)	3 (27.3)	2 (20)	2 (33.3)	1 (25)	20 (32.3)	
FAB-type, no. (%) (n = 866)								
FAB-M0	0 (0)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)	4 (4.5)	**<.01**
FAB-M1	0 (0)	2 (15.4)	0 (0)	0 (0)	2 (22.2)	0 (0)	3 (3.4)	
FAB-M2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (1.1)	
FAB-M4	4 (28.6)	3 (23.1)	6 (60)	1 (11.1)	0 (0)	2 (33.3)	17 (19.1)	
FAB-M5	10 (71.4)	8 (61.5)	4 (40)	8 (88.9)	4 (44.4)	3 (50)	58 (65.2)	
FAB-M7	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.2)	
FAB unspecified	0 (0)	0 (0)	0 (0)	0 (0)	2 (22.2)	0 (0)	4 (4.5)	
ACA, no. (%) (n = 1200)								
No	12 (52.2)	16 (72.7)	5 (45.5)	7 (53.8)	3 (25)	4 (40)	56 (48.7)	.02
Yes	11 (47.8)	6 (27.3)	6 (54.5)	6 (46.2)	9 (75)	6 (60)	59 (51.3)	
ACA type, no. (%) (n = 562)								
Structural	0 (0)	0 (0)	0 (0)	3 (50)	3 (33.3)	2 (33.3)	25 (42.4)	**<.01**
Numerical	7 (63.6)	4 (66.7)	5 (83.3)	2 (33.3)	2 (22.2)	3 (50)	13 (22.0)	
Both*	4 (36.4)	2 (33.3)	1 (16.7)	1 (16.7)	4 (44.4)	1 (16.7)	21 (35.6)	
CR, no. (%) (n = 1219)	20 (95.2)	21 (100)	12 (92.3)	10 (83.3)	6 (50)	9 (90)	104 (85.2)	.02

Clinical outcome	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	
5-y pEFS	20	41.8 (18.9-64.7)	21	76.2 (58.0-94.4)	12	66.7 (40.0-93.4)	12	75.0 (50.5-99.5)	12	25.0 (0.5-49.5)	10	56.3 (24.0-88.6)	122	39.9 (30.9-48.9)	**<.01**
5-y pCIR	19	43.4 (20.1-64.8)	21	19.0 (5.7-38.3)	11	9.1 (0.4-35.0)	10	10.0 (0.5-37.4)	6	50.0 (7.7-82.9)	9	37.5 (7.2-69.4)	104	52.2 (41.8-61.7)	**<.01**
5-y pOS	20	62.4 (39.9-84.9)	21	90.5 (78.0-100)	13	69.2 (44.1-94.3)	13	92.3 (78.0-100)	12	25.0 (0.5-49.5)	10	50.0 (13.5-86.5)	124	60.8 (52.0-69.6)	**<.01**

Values in boldface indicate statistical significance. Fusion-based groups are displayed in descending order of occurrence. 9p22/*KMT2A*::*MLLT3* refers to t(9;11)(p22;q23), 10p12/*KMT2A*::*MLLT10* to t(10;11)(p12;q23), 6q27/*KMT2A*::*AFDN* to t(6;11)(q27;q23), 19p13 to t(11;19)(q23;p13) without ascertained subband, 19p13.1/*KMT2A*::*ELL* to t(11;19)(q23;p13.1), 19p13.3/*KMT2A*::*MLLT1* to t(11;19)(q23;p13.3), 1q21/*KMT2A*::*MLLT11* to t(1;11)(q21;q23), 10p11.2/*KMT2A*::*ABI1* to t(10;11)(p11.2;q23), Xq24/*KMT2A*::*SEPT6* to t(X;11)(q24;q23), 17q21 to t(11;17)(q23;q21), 4q21/*KMT2A*::*AFF1* to t(4;11)(q21;q23), 1p32/*KMT2A*::*EPS15* to t(1;11)(p32;q23), and 17q12 to t(11;17)(q23;q12).

CNS, central nervous system; No., number of patients; pCIR, probability of CIR; pEFS, probability of EFS; pOS, probability of OS.

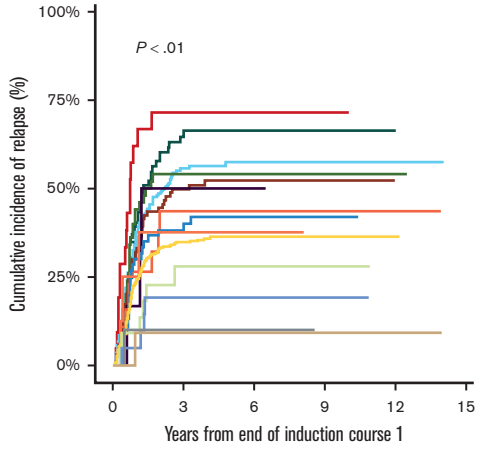
*Including patients who had separate numerical and structural aberrations, as well as patients with gain of a chromosome with a structural aberration, for example, +der(9p) and +i(8q).



Number at risk (number censored)

Xq24/KMT2A::SEPT6	21 (0)	12 (4)	5 (11)	4 (12)	0 (16)	0 (16)
1p32/KMT2A::EPS15	12 (0)	8 (1)	2 (7)	0 (9)	0 (9)	0 (9)
17q21	12 (0)	7 (1)	3 (5)	1 (7)	1 (7)	0 (8)
17q12	10 (0)	5 (1)	3 (3)	0 (6)	0 (6)	0 (6)
1q21/KMT2A::MLLT11	27 (0)	13 (2)	8 (7)	2 (13)	0 (15)	0 (15)
9p22/KMT2A::MLLT3	512 (0)	226 (63)	101 (181)	41 (241)	1 (281)	0 (282)
19p13.1/KMT2A::ELL	71 (0)	31 (4)	14 (19)	8 (25)	0 (33)	0 (33)
Other	122 (0)	46 (7)	16 (35)	6 (45)	1 (50)	0 (51)
19p13.3/KMT2A::MLLT1	55 (0)	18 (4)	6 (14)	4 (16)	1 (19)	0 (20)
19p13	20 (0)	8 (2)	4 (5)	2 (6)	0 (8)	0 (8)
10p12/KMT2A::MLLT10	212 (0)	64 (12)	24 (49)	8 (64)	1 (71)	0 (72)
4q21/KMT2A::AFF1	12 (0)	2 (1)	1 (2)	0 (3)	0 (3)	0 (3)
6q27/KMT2A::AFDN	89 (0)	19 (5)	5 (17)	3 (19)	1 (21)	0 (22)
10p11.2/KMT2A::ABI1	24 (0)	4 (2)	1 (5)	1 (5)	0 (6)	0 (6)

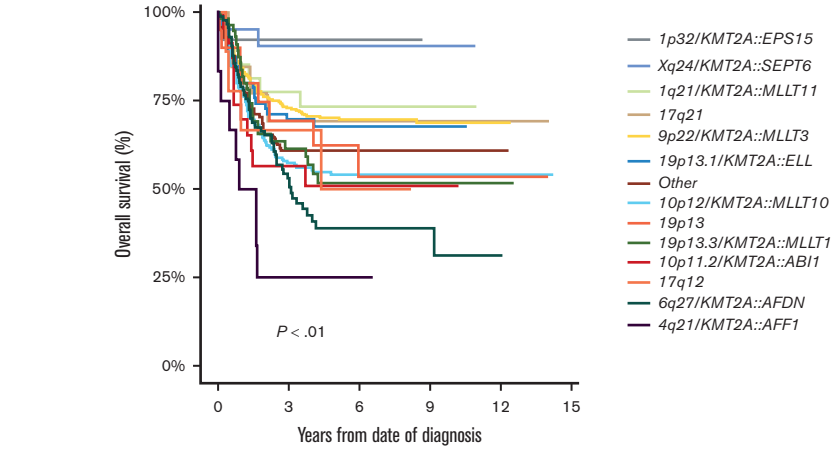
Xq24/KMT2A::SEPT6 *1p32/KMT2A::EPS15* *17q21* *17q12*
1q21/KMT2A::MLLT11 *9p22/KMT2A::MLLT3* *19p13.1/KMT2A::ELL*
Other *19p13.3/KMT2A::MLLT1* *19p13* *10p12/KMT2A::MLLT10*
4q21/KMT2A::AFF1 *6q27/KMT2A::AFDN* *10p11.2/KMT2A::ABI1*



Number at risk (number censored)

10p11.2/KMT2A::ABI1	22 (0)	4 (3)	1 (6)	1 (6)	0 (7)	0 (7)
6q27/KMT2A::AFDN	77 (0)	16 (11)	5 (22)	3 (24)	0 (27)	0 (27)
10p12/KMT2A::MLLT10	186 (0)	62 (22)	24 (58)	9 (73)	1 (81)	0 (82)
19p13.3/KMT2A::MLLT1	50 (0)	18 (5)	6 (17)	4 (19)	1 (22)	0 (23)
Other	104 (0)	45 (9)	16 (36)	6 (46)	0 (52)	0 (52)
4q21/KMT2A::AFF1	6 (0)	2 (1)	1 (2)	0 (3)	0 (3)	0 (3)
19p13	19 (0)	8 (3)	4 (7)	3 (8)	1 (10)	0 (11)
19p13.1/KMT2A::ELL	61 (0)	31 (7)	14 (22)	8 (28)	0 (36)	0 (36)
17q12	9 (0)	4 (2)	3 (3)	0 (6)	0 (6)	0 (6)
9p22/KMT2A::MLLT3	459 (0)	227 (75)	109 (189)	39 (259)	1 (297)	0 (298)
1q21/KMT2A::MLLT11	22 (0)	13 (3)	8 (8)	2 (14)	0 (16)	0 (16)
Xq24/KMT2A::SEPT6	21 (0)	11 (6)	5 (12)	4 (13)	0 (17)	0 (17)
1p32/KMT2A::EPS15	10 (0)	8 (1)	1 (8)	0 (9)	0 (9)	0 (9)
17q21	11 (0)	7 (3)	3 (7)	1 (9)	1 (9)	0 (10)

10p11.2/KMT2A::ABI1 *6q27/KMT2A::AFDN* *10p12/KMT2A::MLLT10*
19p13.3/KMT2A::MLLT1 *Other* *4q21/KMT2A::AFF1* *19p13*
19p13.1/KMT2A::ELL *17q12* *9p22/KMT2A::MLLT3*
1q21/KMT2A::MLLT11 *Xq24/KMT2A::SEPT6* *1p32/KMT2A::EPS15*
17q21



Number at risk (number censored)

1p32/KMT2A::EPS15	13 (0)	11 (1)	2 (10)	0 (12)	0 (12)	0(12)
Xq24/KMT2A::SEPT6	21 (0)	14 (5)	7 (12)	4 (15)	0 (19)	0(19)
1q21/KMT2A::MLLT11	27 (0)	19 (2)	10 (10)	2 (18)	0 (20)	0(20)
17q21	13 (0)	8 (1)	3 (6)	1 (8)	1 (8)	0(9)
9p22/KMT2A::MLLT3	522 (0)	312 (72)	143 (230)	53 (319)	2 (370)	0(372)
19p13.1/KMT2A::ELL	72 (0)	44 (7)	18 (32)	10 (40)	0 (50)	0(50)
Other	124 (0)	69 (8)	26 (51)	9 (68)	3 (74)	0(77)
10p12/KMT2A::MLLT10	214 (0)	107 (17)	52 (67)	20 (99)	2 (117)	0(119)
19p13	20 (0)	11 (3)	6 (6)	4 (8)	2 (10)	0(12)
19p13.3/KMT2A::MLLT1	55 (0)	30 (4)	10 (20)	6 (24)	1 (29)	0(30)
10p11.2/KMT2A::ABI1	24 (0)	10 (4)	6 (7)	2 (11)	0 (13)	0(13)
17q12	10 (0)	6 (1)	3 (3)	0 (6)	0 (6)	0(6)
6q27/KMT2A::AFDN	90 (0)	40 (9)	13 (27)	5 (35)	1 (38)	0 (39)
4q21/KMT2A::AFF1	12 (0)	2 (1)	1 (2)	0 (3)	0 (3)	0(3)

Figure 2.

10p11.2/*KMT2A*::*ABI1* groups were independently associated with inferior EFS ([HR, 1.7; $P < .01$], [HR, 1.8; $P < .01$], and [HR, 2.6; $P < .01$], respectively) and OS ([HR, 1.8; $P < .01$], [HR, 1.8; $P < .01$], and [HR, 2.4; $P < .01$], respectively), and higher CIR ([HR, 1.7; $P < .01$], [HR, 2.0; $P < .01$], and [HR, 3.0; $P < .01$], respectively). The 19p13.3/*KMT2A*::*MLLT1* group was independently associated with inferior EFS (HR, 1.6; $P = .01$) and higher CIR (HR, 1.8; $P < .01$). The 4q21/*KMT2A*::*AFF1* group was independently associated with inferior EFS (HR, 2.7; $P < .01$) and OS (HR, 4.5; $P < .01$). Among ACAs, trisomy 6 was independently associated with inferior EFS (HR, 1.6; $P = .01$) and OS (HR, 1.7; $P = .01$) and higher CIR (HR, 2.0; $P < .01$). Add(12p) was independently associated with inferior EFS (HR, 2.2; $P = .01$) and trisomy 16 with inferior EFS (HR, 2.5; $P < .01$) and higher CIR (HR, 4.5; $P < .01$). Monosomy 10, trisomy 1, trisomy X, and del(9q) were independently associated with inferior OS ([HR, 2.8; $P < .01$], [HR, 3.9; $P < .01$], [HR, 2.8; $P < .01$], and [HR, 2.8; $P < .01$], respectively).

The *9p22/KMT2A*::*MLLT3* group

Within this group, patients with FAB-M5 had superior EFS (65.9% [95% CI, 60.2-71.6] vs 37.9% [95% CI, 26.9-48.9]; $P < .01$) and OS (80.3% [95% CI, 75.6-85.0] vs 52.3% [95% CI, 42.0-63.5]; $P < .01$), and lower CIR (24.5% [95% CI, 19.4-29.9] vs 48.6% [95% CI, 35.9-60.1]; $P < .01$) than patients with non–FAB-M5 (supplemental Table 7). In multivariable analyses (supplemental Table 8), FAB-M5 was independently associated with superior EFS (HR, 0.5; $P < .01$) and OS (HR, 0.4; $P < .01$) and lower CIR (HR, 0.5; $P < .01$), whereas trisomy 6 was independently associated with inferior EFS (HR, 2.2; $P < .01$) and OS (HR, 2.3; $P = .01$) and higher CIR (HR, 2.7; $P < .01$). Subsequently, multivariable analyses were performed including a combination variable of FAB-type and trisomy 6, showing that, in reference to FAB-M5/no trisomy 6, the combinations of FAB-M5/trisomy 6, non–FAB-M5/no trisomy 6, or non–FAB-M5/trisomy 6 were all independently associated with inferior EFS ([HR, 3.9; $P < .01$], [HR, 2.3; $P < .01$], and [HR, 3.1; $P < .01$], respectively) and OS ([HR, 4.3; $P < .01$], HR, 2.8; $P < .01$], and [HR, 4.1; $P < .01$], respectively) and higher CIR ([HR, 3.3; $P = .02$], [HR, 2.1; $P < .01$], and [HR, 5.0; $P < .01$], respectively). The prognostic value of recurring ACAs within other *KMT2A*-r groups was explored, but none were significantly associated with EFS, CIR, or OS (data not shown).

Having previously demonstrated the independent prognostic significance of flow-MRD at EOI2 in childhood *KMT2A*-r AML (with detailed analysis described previously),[3] we explored its prognostic significance in the 9p22/*KMT2A*::*MLLT3* group within the context of FAB-type (M5 vs non-M5). It was not feasible to assess this in both the context of FAB-type and recurring ACAs because of the lack of flow-MRD at EOI2 data in 60% of patients with 9p22/*KMT2A*::*MLLT3*. Patients with EOI2 MRD negativity had superior EFS (54.2% [95% CI, 47.1-61.3] vs 35.3% [95% CI, 12.6-58.0]; $P = .02$) and OS (73.6% [95% CI, 67.3-79.9] vs 47.1% [95% CI, 23.4-70.8]; $P < .01$), but CIR was not statistically significantly different. Among patients with FAB-M5, as well as among patients with non–FAB-M5, EFS did not statistically significantly differ between patients with EOI2 MRD negativity and MRD positivity, but subgroup numbers were small (supplemental Table 7). In multivariable analyses (supplemental Table 8), FAB-M5 was independently associated with superior EFS (HR, 0.5; $P = .02$), whereas flow-MRD at EOI2 was independently associated with inferior EFS (HR, 2.4; $P = .04$) and OS (HR, 2.5; $P = .05$). The addition of the variable flow-MRD at EOI2 did not change the effect of FAB-type on survival, and vice versa, as confirmed by the nonsignificant interaction terms ($P = .52$ for EFS; $P = .63$ for OS).

Discussion

This largest study on childhood *KMT2A*-r AML confirmed the independent adverse prognostic significance of the previously defined recurring, adverse-risk *KMT2A*-r groups (ie, 4q21/*KMT2A*::*AFF1*, 6q27/*KMT2A*::*AFDN*, 10p12/*KMT2A*::*MLLT10*, 4q21/*KMT2A*::*ABI1*, and 19p13.3/*KMT2A*::*MLLT1*; together representing about 30% of pediatric *KMT2A*-r AML cases), defined and clinically characterized 3 additional, recurring *KMT2A*-r groups (ie, Xq24/*KMT2A*::*SEPT6*, 1p32/*KMT2A*::*EPS15*, and 17q12), the former 2 with good outcomes, and refined risk-group stratification of the most frequently occurring *KMT2A*-r group, 9p22/*KMT2A*::*MLLT3*, based on FAB-type and the presence/absence of trisomy 6. Flow-MRD at EOI2 was also identified as an independent adverse prognosticator in this group. Furthermore, we identified novel ACAs that were independently associated with inferior EFS (ie, add(12p) and trisomies 6 and 16), higher CIR (ie, trisomies 6 and 16), or inferior OS (ie, monosomy 10, trisomies 1, 6, and X, and del(9q)).

This and our previous studies[2,3] provide strong evidence for the inclusion of the previously defined adverse-risk *KMT2A*-r groups into the cytogenetic risk-group stratification algorithm of childhood *KMT2A*-r AML. With EFS rates <40%, patients with adverse-risk *KMT2A* fusions may benefit from high-risk–adapted treatment. However, we and others have previously shown that high-risk–adapted treatment approaches superior to allo-SCT in CR1 are urgently needed in this disease.[2-4] In this regard, studies to elucidate the biological role of *KMT2A* fusions and identify novel therapeutic targets are needed to improve survival. Ongoing phase 1/2 studies including patients with *KMT2A*-r acute leukemia have shown encouraging clinical responses with the menin inhibitors SNDX-5613 (revumenib)[25] and KO-539 (ziftomenib),[26] which target and disrupt the *KMT2A* fusion protein complex. These inhibitors constitute a novel, promising class of targeted therapeutics for this disease. However, a recent study suggests that mutations in menin are acquired with the use of SNDX-5613, thereby mediating clinical resistance.[27] Hopefully, such mutations can be avoided when menin inhibitors are combined with chemotherapy. Furthermore, the incorporation of the CD33-targeting immunoconjugate gemtuzumab ozogamicin into induction therapy in the AAML0531 trial improved EFS and reduced relapse risk in children with *KMT2A*-r AML.[4]

Figure 2. Survival curves for pediatric patients with *KMT2A*-rearranged AML, stratified by fusion-based group. Kaplan-Meier estimates of (A) EFS, (B) CIR, and (C) OS of *KMT2A* fusion-based groups. *KMT2A*::*MLLT3* refers to t(9;11)(p22;q23) (n = 544), *KMT2A*::*MLLT10* to t(10;11)(p12;q23) (n = 218), *KMT2A*::*AFDN* to t(6;11)(q27;q23) (n = 92), *KMT2A*::*ELL* to t(11;19)(q23;p13.1) (n = 75), *KMT2A*::*MLLT1* to t(11;19)(q23;p13.3) (n = 56), *KMT2A*::*MLLT11* to t(1;11)(q21;q23) (n = 28), *KMT2A*::*ABI1* to t(10;11)(p11.2;q23) (n = 24), 19p13 to t(11;19)(q23;p13) without ascertained subband (n = 23), *KMT2A*::*SEPT6* to t(X;11)(q24;q23) (n = 22), 17q21 to t(11;17)(q23;q21) (n = 13), *KMT2A*::*EPS15* to t(1;11)(p32;q23) (n = 13), *KMT2A*::*AFF1* to t(4;11)(q21;q23) (n = 12), and 17q12 to t(11;17)(q23;q12) (n = 10).

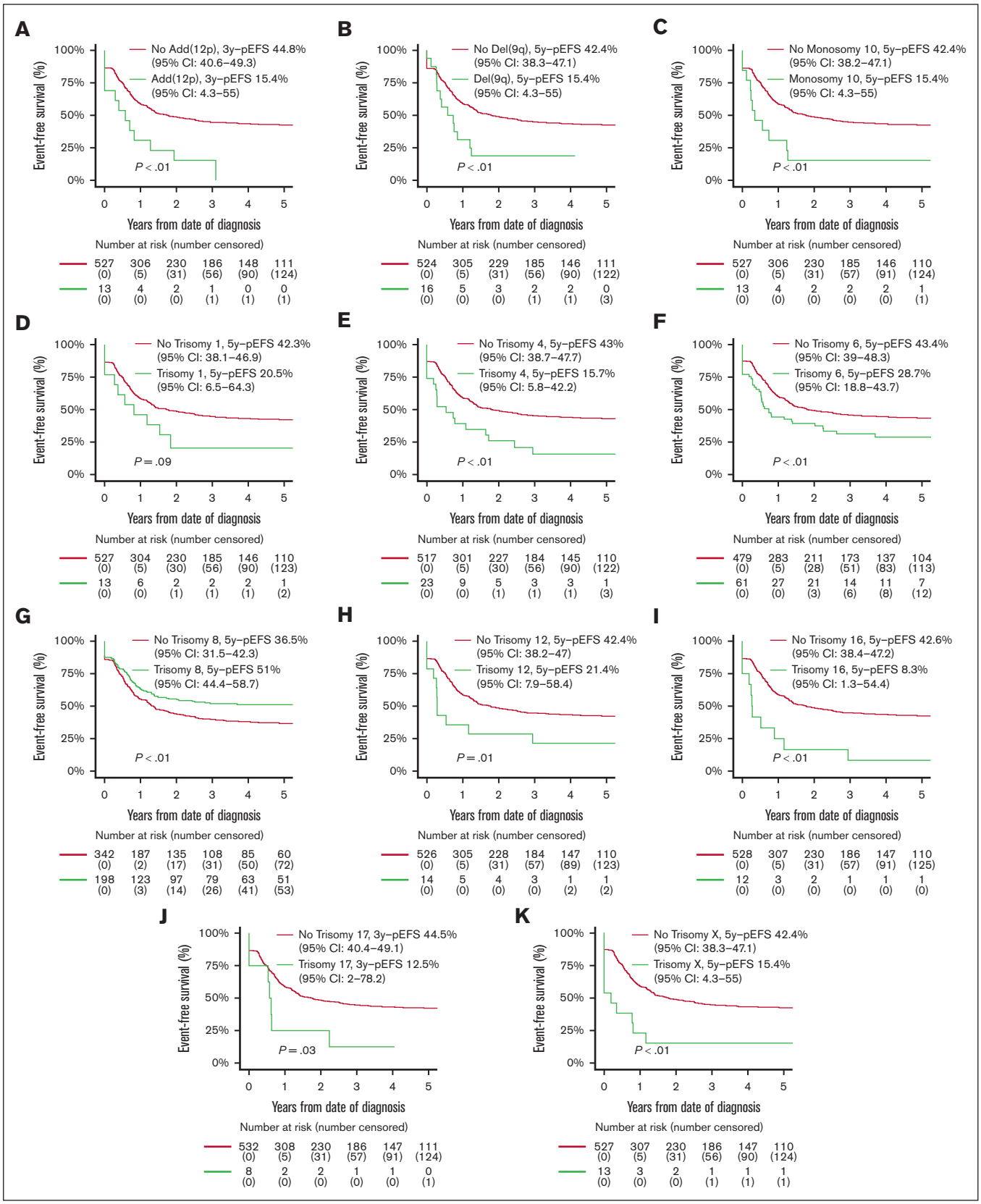


Figure 3. Survival curves for pediatric patients with KMT2A-rearranged AML with and without specific, recurring ACAs. Kaplan-Meier estimates of EFS of patients with and without (A) add (12p), (B) del(9q), (C) monosomy 10, (D) trisomy 1, (E) trisomy 4, (F) trisomy 6, (G) trisomy 8, (H) trisomy 12, (I) trisomy 16, (J) trisomy 17, and (K) trisomy X. Patients with specific ACAs are compared with patients with other ACAs.

Table 2. Multivariable analyses of EFS, CIR, and OS in childhood *KMT2A*-r AML

	pEFS				pCIR				pOS			
	No.	HR	95% CI	*P* value	No.	HR	95% CI	*P* value	No.	HR	95% CI	*P* value
Age at diagnosis, y												
≤10	837	1.0			751	1.0			845	1.0		
>10	277	1.3	1.0-1.5	.02	262	1.3	1.0-1.6	.03	279	1.8	1.4-2.2	**<.01**
WBC count, ×10^9/L												
≤100	865	1.0			NA				872	1.0		
>100	249	1.3	1.1-1.6	**<.01**	NA	NA	NA	NA	252	1.5	1.2-1.8	**<.01**
Fusion-based group												
9p22/*KMT2A*::*MLLT3*	479	1.0			440	1.0			484	1.0		
Xq24/*KMT2A*::*SEPT6*	21	0.5	0.2-1.1	.08	21	0.5	0.2-1.3	.14	21	0.3	0.1-1.4	.13
1p32/*KMT2A*::*EPS15*	12	0.5	0.2-1.5	.22	10	0.2	0.0-1.6	.13	13	0.3	0.0-1.9	.19
17q21	10	0.6	0.2-1.8	.40	10	0.2	0.0-1.5	.12	10	0.9	0.3-2.6	.84
17q12	10	0.9	0.4-2.5	.90	9	1.0	0.3-3.3	.94	10	1.3	0.5-3.6	.61
1q21/*KMT2A*::*MLLT11*	26	1.1	0.6-2.0	.78	22	0.7	0.3-1.6	.40	26	1.1	0.5-2.4	.76
19p13.1/*KMT2A*::*ELL*	67	1.3	0.9-1.9	.13	58	1.3	0.8-2.0	.24	67	1.1	0.7-1.8	.65
19p13	14	1.1	0.5-2.3	.85	19	1.3	0.6-2.6	.51	14	1.4	0.6-3.3	.38
19p13.3/*KMT2A*::*MLLT1*	52	1.6	1.1-2.3	**.01**	49	1.8	1.2-2.8	**<.01**	52	1.5	0.9-2.3	.10
10p12/*KMT2A*::*MLLT10*	198	1.7	1.3-2.1	**<.01**	178	1.7	1.3-2.2	**<.01**	200	1.8	1.4-2.4	**<.01**
4q21/*KMT2A*::*AFF1*	11	2.7	1.3-5.5	**<.01**	6	1.6	0.5-5.1	.40	11	4.5	2.2-9.4	**<.01**
6q27/*KMT2A*::*AFDN*	81	1.8	1.3-2.4	**<.01**	74	2.0	1.4-2.8	**<.01**	82	1.8	1.3-2.5	**<.01**
10p11.2/*KMT2A*::*ABI1*	22	2.6	1.6-4.4	**<.01**	22	3.0	1.7-5.2	**<.01**	22	2.4	1.3-4.5	**<.01**
Other	111	1.3	1.0-1.8	.06	95	1.5	1.1-2.1	.02	112	1.3	0.9-1.9	.11
Recurring ACAs	**Yes/no**				**Yes/no**				**Yes/no**			
Monosomy 10	13/1101	2.0	1.1-3.8	.03	10/1003	2.1	1.0-4.5	.04	13/1111	2.8	1.5-5.5	**<.01**
Trisomy 1	NA	NA	NA	NA	NA	NA	NA	NA	13/1111	3.9	2.0-7.4	**<.01**
Trisomy 4	*	*	*	*	*	*	*	*	*	*	*	*
Trisomy 6	60/1054	1.6	1.1-2.3	**.01**	47/966	2.0	1.4-3.0	**<.01**	60/1064	1.7	1.1-2.5	**.01**
Trisomy 8	194/920	0.8	0.6-1.0	.05	172/841	0.7	0.5-1.0	.03	*	*	*	*
Trisomy 12	*	*	*	*	*	*	*	*	*	*	*	*
Trisomy 16	12/1102	2.5	1.3-4.8	**<.01**	9/1004	4.5	2.1-9.5	**<.01**	NA	NA	NA	NA
Trisomy 17	8/1106	2.1	0.9-4.7	.07	*	*	*	*	8/1116	2.2	0.9-5.1	.08
Trisomy X	12/1102	2.2	1.1-4.3	.03	NA	NA	NA	NA	12/1112	2.8	1.3-5.9	**<.01**
Add(12p)	13/1101	2.2	1.2-3.9	**.01**	*	*	*	*	NA	NA	NA	NA
Del(9q)	16/1098	2.0	1.1-3.5	.03	14/999	2.2	1.1-4.5	.02	16/1108	2.8	1.5-5.1	**<.01**

Values in boldface indicate statistical significance. ACA type was excluded from multivariable analyses, as the specific ACAs and the ACA type variables are related. 9p22/*KMT2A*::*MLLT3* refers to t(9;11)(p22;q23), 10p12/*KMT2A*::*MLLT10* to t(10;11)(p12;q23), 6q27/*KMT2A*::*AFDN* to t(6;11)(q27;q23), 19p13 to t(11;19)(q23;p13) without ascertained subband, 19p13.1/*KMT2A*::*ELL* to t(11;19)(q23;p13.1), 19p13.3/*KMT2A*::*MLLT1* to t(11;19)(q23;p13.3), 1q21/*KMT2A*::*MLLT11* to t(1;11)(q21;q23), 10p11.2/*KMT2A*::*ABI1* to t(10;11)(p11.2;q23), Xq24/*KMT2A*::*SEPT6* to t(X;11)(q24;q23), 17q21 to t(11;17)(q23;q21), 4q21/*KMT2A*::*AFF1* to t(4;11)(q21;q23), 1p32/*KMT2A*::*EPS15* to t(1;11)(p32;q23), and 17q12 to t(11;17)(q23;q12).

NA, not applied (not significant variables in univariable Cox regression analyses, see supplemental Table 5); abbreviations are explained in Table 1.

*Omitted from the final multivariable model of EFS/CIR/OS because of a *P*-value > .10 in stepwise backward elimination.

The outcome of the 1q21/*KMT2A*::*MLLT11* group was not statistically significantly superior compared with that of the 9p22/*KMT2A*::*MLLT3* group, which is in contrast to Balgobind et al[2] but in agreement with Pollard et al.[4] Therefore, we recommend revision of the previous favorable-risk classification of 1q21/*KMT2A*::*MLLT11* to intermediate risk. The underlying biological function of 1q21/*KMT2A*::*MLLT11* remains unclear, although high *MLLT11* expression has been shown to be an independent adverse prognosticator in pediatric AML.[28] Another study showed that *MIR29B* directly regulates *MLLT11* expression in vitro and that low *MIR29B* expression corresponded to high *MLLT11* expression in patients with AML, resulting in poor survival.[29] In pediatric patients with 1q21/*KMT2A*::*MLLT11* AML, it remains unknown how *MLLT11* expression is regulated.

We defined and clinically characterized Xq24/*KMT2A*::*SEPT6* (n = 22) and 1p32/*KMT2A*::*EPS15* (*n* = 13) as 2 additional, recurring *KMT2A*-r groups with good outcomes, although not statistically significantly superior. Our findings need to be validated in future large cohort studies, which may include more patients with

Table 3. Evolution in risk of fusion-based groups over time and our proposed cytogenetic risk-group stratification of childhood *KMT2A*-r AML

	Balgobind et al 2009[2]			Pollard et al 2021[4]			van Weelderen et al 2024		
Fusion-based group	**No.**	**5-y pEFS (%)**	**Risk-group**	**No.**	**5-y pEFS (%)**	**Risk-group**	**No.**	**5-y pEFS (%)**	**Risk-group**
1q21/*KMT2A*::*MLLT11*	24	92	Favorable*	5	60	Intermediate	27	55	Intermediate
9p22/*KMT2A*::*MLLT3*	321	50	Intermediate	82	49	Intermediate	512	54	Intermediate
Non–FAB-M5	59	31	Adverse	ND	ND	ND	81	38	Adverse
FAB-M5	254	59	Intermediate†	ND	ND	ND	298	66	Intermediate†
FAB-M5/no trisomy 6	ND	ND	ND	ND	ND	ND	273	68	Intermediate
FAB-M5/trisomy 6	ND	ND	ND	ND	ND	ND	11	29‡	Adverse§
Non–FAB-M5/no trisomy 6	ND	ND	ND	ND	ND	ND	66	39	Adverse§
Non–FAB-M5/trisomy 6	ND	ND	ND	ND	ND	ND	10	27	Adverse§
19p13	31	49	Intermediate	ND	ND	ND	20	42	Intermediate
19p13.1/*KMT2A*::*ELL*	33	46	Intermediate	15	65	Intermediate	71	45	Intermediate
19p13.3/*KMT2A*::*MLLT1*	23	46	Intermediate	7	14	Adverse‖	55	35	Adverse*
17q21	12	42	Intermediate	ND	ND	ND	12	67	Intermediate
10p12/*KMT2A*::*MLLT10*	97	31	Adverse*	40	20	Adverse‖	212	33	Adverse*
4q21/*KMT2A*::*AFF1*	13	29	Adverse	2	0	Adverse‖	12	25	Adverse*
10p11.2/*KMT2A*::*ABI1*	12	17	Adverse*	6	17	Adverse‖	24	22	Adverse*
6q27/*KMT2A*::*AFDN*	35	11	Adverse*	15	15	Adverse‖	89	23	Adverse*
Xq24/*KMT2A*::*SEPT6*	ND	ND	ND	5	80	Intermediate	21	76	Intermediate
1p32/*KMT2A*::*EPS15*	ND	ND	ND	ND	ND	ND	12	75	Intermediate
17q12	ND	ND	ND	ND	ND	ND	10	56	Intermediate

Risk-group assignment was determined arbitrarily according to the EFS rate. Fusion-based groups with an EFS rate of <40% were classified as adverse-risk, whereas those with an EFS rate >40% were designated at intermediate risk. Furthermore, fusion-based groups with an EFS rate >75%, which demonstrated an independent association with superior EFS compared with patients with 9p22/*KMT2A*::*MLLT3*, were considered favorable risk. 9p22/*KMT2A*::*MLLT3* refers to t(9;11)(p22;q23), 10p12/*KMT2A*::*MLLT10* to t(10;11)(p12;q23), 6q27/*KMT2A*::*AFDN* to t(6;11)(q27;q23), 19p13.1/*KMT2A*::*ELL* to t(11;19)(q23;p13.1), 19p13.3/*KMT2A*::*MLLT1* to t(11;19)(q23;p13.3), 1q21/*KMT2A*::*MLLT11* to t(1;11)(q21;q23), 10p11.2/*KMT2A*::*ABI1* to t(10;11)(p11.2;q23), 19p13 to t(11;19)(q23;p13) without ascertained subband, Xq24/*KMT2A*::*SEPT6* to t(X;11)(q24;q23), 17q21 to t(11;17)(q23;q21), 1p32/*KMT2A*::*EPS15* to t(1;11)(p32;q23), 4q21/*KMT2A*::*AFF1* to t(4;11)(q21;q23), and 17q12 to t(11;17)(q23;q12).

*Independently associated with superior/inferior EFS compared with patients with 9p22/*KMT2A*::*MLLT3*.

†Independently associated with superior EFS compared with patients with 9p22/*KMT2A*::*MLLT3* with non–FAB-M5 morphology.

‡For patients with FAB-M5 morphology with trisomy 6, the 3-year pEFS is shown because this estimate could not be extrapolated to 5 years.

§Independently associated with inferior EFS compared with patients with 9p22/*KMT2A*::*MLLT3* with FAB-M5 morphology and without trisomy 6.

‖In the study by Pollard et al,[4] these 5 fusion-based groups were clustered into a high-risk cohort, which was independently associated with inferior EFS compared with the non–high-risk cohort.

these fusions as screening methods have improved over the years. For now, it seems justified to consider these fusions as intermediate risk.

Our study confirms the independent favorable prognostic significance of FAB-M5 in the most common *KMT2A*-r group, 9p22/*KMT2A*::*MLLT3*, which is a notable repeated finding.[2,5] It remains to be determined how FAB-M5 is associated with favorable outcomes in these children. Potentially, high sensitivity to chemotherapy,[30] or overexpression of specific genes, such as *IGSF4*, may be related to differences in outcome. *IGSF4* has been identified as a discriminative, epigenetically, upregulated gene in children with 9p22/*KMT2A*::*MLLT3* AML with FAB-M5 morphology.[31] We propose to consider patients who are non–FAB-M5 as adverse risk, as their EFS rate was <40% (supplemental Table 7). Although the use of FAB morphology has dwindled in clinical pediatric AML practice, the determination of FAB-type in these patients thus remains relevant. Furthermore, although the number of cases in specific subgroups may be limited, we propose to consider children with 9p22/*KMT2A*::*MLLT3* AML with FAB-M5/no trisomy 6 as intermediate risk and those with FAB-M5/trisomy 6, non–FAB-M5/no trisomy 6, or non–FAB-M5/trisomy 6 as adverse risk, as their EFS rates were <40% and on par with those of adverse-risk *KMT2A* fusions (supplemental Table 7).

Compared with Coenen et al (supplemental Table 9),[5] our study identified different recurring ACAs to have a prognostic impact. This may be explained by the larger number of patients, allowing us to identify ACAs of greater independent prognostic significance, conduction of our study over a different period with the application of different treatment protocols, the co-occurrence of ACAs, or concurrent gene mutation profiles. Trisomy 8 has been previously reported to be an independent prognosticator for improved survival among children with *KMT2A*-r AML.[5] In our study, trisomy 8 was significantly associated with a superior outcome in univariable analyses only. Regarding structural ACAs in general, they have been previously reported as independent adverse prognostic indicators of EFS in childhood *KMT2A*-r AML.[5] To our knowledge, we are the first to specifically identify add(12p) and del(9q) to be independently associated with inferior EFS and OS, respectively. Abnormalities of 12p have also been associated with an adverse outcome in pediatric AML in general,[32-34] and del(9q) has been previously reported to be associated with lower CR rates among children with t(8;21)(q22;q22)/*RUNX1*::*RUNX1T1* AML.[35]

Regarding numerical ACAs, an independent association of trisomy 6 with higher CIR was found in our study, whereas in the study of Coenen et al,[5] it was associated with inferior OS in univariable analysis only. Furthermore, independent associations of monosomy 10 and trisomies 1, 16, and X with inferior outcomes were found, whereas the former 3 ACAs had not been previously described as recurring ACAs in pediatric AML. To date, biological indicators of the prognostic relevance of the ACAs identified in our study remain to be elucidated.

Limitations of our study include its retrospective nature, the diverse treatment regimens used across SGs/countries, although with similar chemotherapeutic backbones, and no inclusion of data on allo-SCT in CR1 and flow-MRD response at EOI2 in the entire cohort analysis. Inclusion of the latter was precluded because subgroups became too small because of the large number of *KMT2A*-r groups and the low number of patients with specific ACAs, as well as the overall low transplantation rate and lack of flow-MRD data, which was also discussed in our previous study analyzing the impact of flow-MRD and use of allo-SCT in CR1 on outcome in this disease.[3] Furthermore, 10% of the cohort were assigned to the *KMT2A*-other group, and molecular genetic data were not available to analyze the mutational landscape. With the increasing use of flow-MRD assays, quantitative polymerase chain reaction, and next-generation sequencing, future studies will likely allow for accurate detection of MRD in all patients and identification of all (cryptic) fusion genes, as well as gene mutations, which may affect the prognosis of this disease.

In conclusion, from this study, we can propose an optimized cytogenetic risk-group stratification of *KMT2A*-r pediatric AML in the pre-menin inhibitor era. Table 3 highlights how the risk of fusion-based groups has evolved over time and shows our proposal. Children with *KMT2A*-r AML may be stratified into an intermediate-risk or adverse-risk group based on cytogenetics, or both cytogenetics and FAB morphology in 9p22/*KMT2A*::*MLLT3* cases. Regarding the 3 additional, recurring *KMT2A*-r groups and newly identified ACAs, future studies should validate the associations found in this study. In addition, once a large cohort becomes available with more flow-MRD data, it would be of great interest to evaluate whether individual *KMT2A*-r groups and ACAs retain their independent prognostic value if flow-MRD response is considered in multivariable analyses. Moreover, future studies should validate the role of allo-SCT in CR1, especially among the adverse-risk *KMT2A*-r groups, elucidate the mutational landscape, and further unravel the underlying biological pathogenesis of *KMT2A* fusions and ACAs. Together with ongoing discoveries and encouraging results from new targeted therapeutics, it will likely lead to improved risk-group stratification and risk-adapted treatment, as well as enhanced survival of childhood *KMT2A*-r AML.

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Authorship

Contribution: R.E.v.W., K.K., and G.J.L.K. conceptualized and designed the study; G.J.L.K. provided financial support; C.J.H., J.A., T.A., R.A., N.A.-C., E.B.-D., B.D.M., M.N.D., J.M.F.N., A.G., R.B.G., E.G., S.-Y.H., H.H., C.K., H.L., F.L., S.P., J.E.R., J.S., D.T., C.M.Z., and G.J.L.K. provided study materials or patients; R.E.v.W., K.K., C.J.H., J.A., T.A., R.A., N.A.-C., E.B.-D., B.B., B.D.M., M.N.D., S.E., J.M.F.N., A.G., R.B.G., H.A.d.G.-K., E.G., S.-Y.H., H.H., C.K., H.L., G.L., F.L., U.N.-N., S.P., M.R., J.E.R., J.S., A.T., and D.T. collected and assembled data; R.E.v.W., K.K., C.J.H., Y.J., B.F.G., E.G., H.H., F.L., J.E.R., J.S., C.M.Z., and G.J.L.K. analyzed and interpreted the data; and all authors wrote the manuscript and approved and were accountable for all aspects of the work.

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