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Age-specific mutation profiles and their prognostic implications in pediatric *KMT2A*-rearranged acute myeloid leukemia

Running Title: Age-Specific Mutations in pediatric *KMT2A*-r AML

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KS, KY, and HMatsuo analyzed the clinical and sequencing data; SI, MI, MT, MNobe, NSaito, and YShino assisted with the analysis; KY, YN, GY, ST, NShiba, and YH performed sequencing; YShiozawa, YShiraishi, KC, AO, HT, and SM developed the sequence data processing pipelines; YK, HG, KT, EI, NK, DT, TT, HMoritake, AT, JT, and SA collected the clinical samples; KY, MNishikori, SA, SO, and HMatsuo supervised the project. KS, KY, and HMatsuo wrote the manuscript.

Data-sharing statement

The datasets used in this study are available from the corresponding author upon reasonable request.

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Competing interests

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Abstract

Driver mutations in *KMT2A*-rearranged (*KMT2A*-r) have been identified in acute myeloid leukemia (AML); however, age-related differences in their frequency and prognostic factors remain unclear. In this study, we report age-specific mutation profiles and outcomes in pediatric patients with *KMT2A*-r AML. In 239 cases of *KMT2A*-r AML, infants (<1 year, n = 59) showed a significantly higher event-free survival (EFS) and overall survival (OS) compared with children (≥1 year, n = 180). Conversely, in 538 cases of non-*KMT2A*-r AML, infants exhibited a significantly lower EFS and OS than children. *KMT2A*::*MLLT4* was only detected in children with *KMT2A*-r AML and was associated with a poor prognosis. In *KMT2A*-r AML, mutations in signaling pathway genes, such as *KRAS*, were frequently detected in infants and children. However, the frequency of non-signaling pathway mutations was significantly higher in children. Moreover, non-signaling pathway mutations had no significant effect on the prognosis in infants and children, whereas *KRAS* mutations were associated with poor prognosis in both groups. Multivariate analysis identified older age, a high white blood cell count, *KMT2A::MLLT4*, and *KRAS* mutations as independent adverse prognostic factors for both EFS and OS. These age-specific mutation profiles suggest distinct disease mechanisms across age groups and may help refine risk stratification and treatment strategies for pediatric *KMT2A*-r AML.

Introduction

Acute myeloid leukemia (AML) is a relatively rare but aggressive pediatric leukemia characterized by the clonal expansion of immature myeloid precursors[1]. The genetic and molecular features of AML have been revealed by advances in next-generation sequencing technology[2,3]. The accumulation of data on patient clinical outcomes associated with genetic abnormalities has enabled the risk stratification and appropriate treatment of AML[4,5]. However, relapses remain common, and patients with relapsed AML have a poor prognosis[6]. Therefore, further research is required to understand the detailed mechanisms of AML and provide better risk stratification.

One of the hallmark genetic abnormalities in AML is *KMT2A* rearrangement, where chromosomal translocations occur between the *KMT2A* gene (located at 11q23, formerly referred to as *MLL*) and various partner genes[7]. More than 100 partner genes associated with *KMT2A* rearrangements have been identified, and the prognosis varies depending on the specific rearrangement pattern[7–9]. For example, t(9;11)(p22;q23)/*KMT2A*::*MLLT3*, the most common fusion pattern, is associated with intermediate risk, whereas t(6;11)(q27;q23)/*KMT2A*::*MLLT4* is associated with high risk. Therefore, some of the fusion patterns are currently used for the risk stratification of AML treatment[10–12]. *KMT2A*-rearranged (*KMT2A*-r) AML is known to have fewer coexisting mutations compared to other AML subtypes[2,3]. Among the coexisting mutations in *KMT2A*-r AML, RAS pathway genes are frequently mutated[13–16]. Our recent study identified mutations in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene as poor prognostic factors in *KMT2A*-r AML[17]. In particular, *KRAS* codon 12 (G12) mutations were associated with a poorer prognosis when compared with other *KRAS* mutations[18].

Differences in recurrent chromosomal and genetic abnormalities between adult and pediatric AML have been previously elucidated[3,19,20]. *KMT2A*-r AML is frequently observed in pediatric AML, with a prevalence of approximately 40% in infants (aged <1 year) and 15% in children (aged 1≥ year)[3,21]. Several reports have shown that patients with infant AML have a more favorable prognosis compared to patients with childhood AML[22–24]; however, whether the results are applicable to all AML subtypes as well as the underlying molecular mechanisms is unclear. In this study, we focused on pediatric *KMT2A*-r AML and compared the mutation profiles and prognosis between infants and children. As several differences were identified between infants and children in terms of genetic abnormalities and prognosis, this study may lead to better risk stratification and *KMT2A*-r AML treatment outcomes.

Methods

Patients

The AML99, AML-05, and AML-12 studies were nationwide, multicenter clinical trials that were conducted in Japan by the Japan Children's Cancer Group (JCCG) in children (<18 years) with *de novo* AML. The treatment schedules and regimens have been previously described[25–27]. In this study, we included 11 cases of pediatric *KMT2A*-r AML from the AML99 trial, 58 cases from the AML-05 trial, and 58 cases from the AML-12 trial. In addition, 112 cases of *KMT2A*-r AML and 538 cases of non-*KMT2A*-r AML were sourced from the TARGET cohort, with the clinical data obtained from the TARGET Data Matrix[3].

In accordance with previous studies[7,22,23,27,28], infants were defined as <1 year of age, and children were defined as ≥1 year of age. However, as several studies have defined the threshold between infants and children as 3 years of age[3,24], analyses were also performed where differentiation was established at 3 years of age.

All procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki and were reviewed and approved by the ethics committees of all participating institutions, including the Kyoto University Medical Ethics Committee and the JCCG Research Review Committee (approval numbers: G0361 and 106). Written informed consent was obtained from all patients and/or their parents/guardians.

Targeted sequencing

Targeted sequencing was performed, targeting 338 genes in the *KMT2A*-r AML patients' samples from the AML99 and AML-05 studies. Sample preparation, sequencing, and data analyses were conducted as described previously[16]. AML-12 samples underwent targeted sequencing of 507 genes selected for their relevance to myeloid malignancies and therapeutic potential. Target capture was performed using a SureSelect custom kit (Agilent), and sequencing was conducted on a HiSeq 2000/2500 (Illumina). Detailed information regarding mutation calling is provided in the Supplemental Methods.

Mutation data for samples from 650 TARGET cohort patients were collected as previously described[3].

Statistical analysis

In this study, survival analysis was performed using the Kaplan–Meier method, and log-rank tests were performed to compare the survival distributions between groups. Categorical variables were compared using Fisher's exact test. The Mann–Whitney U test was performed to compare the data distributions between two independent groups. In addition, multivariate analysis was performed on patients with *KMT2A*-r AML. All statistical analyses were performed using R software with $P < 0.05$ considered statistically significant.

Results

Age distribution and prognosis of *KMT2A*-r AML and non-*KMT2A*-r AML

The distribution of the infant and child cases for *KMT2A*-r AML and non-*KMT2A*-r AML was visualized in Figures 1A and B, respectively. The age distribution of pediatric patients with *KMT2A*-r AML showed that, among a total of 239 cases, 59 patients (24.7%) were infants and 180 (75.3%) were children. In contrast, among the 538 cases of pediatric AML without *KMT2A* rearrangements, 13 patients (2.4%) were infants and 525 (97.6%) were children. The proportion of infant cases was significantly higher in *KMT2A*-r AML compared to non-*KMT2A*-r AML ($P < 0.001$). Furthermore, the patients were categorized into either infant or children groups, and Kaplan–Meier curves for event-free survival (EFS) and overall survival (OS) were generated and compared (Figures 1C, D). In *KMT2A*-r AML, infant cases showed a significantly better prognosis compared to that of children (EFS: $P = 0.049$, OS: $P = 0.032$). In contrast, in non-*KMT2A*-r AML, infant cases exhibited a significantly worse prognosis compared to that of children (EFS: $P < 0.001$, OS: $P = 0.015$).

We also performed the same analysis by categorizing patients into age groups using a threshold of 3 years (Supplementary Figures 1A–D). The proportion of patients under the age of 3 years was significantly higher in the *KMT2A*-r AML group than in the non-*KMT2A*-r AML group ($P < 0.001$). Among *KMT2A*-r AML patients, those younger than 3 years had a significantly better OS ($P = 0.0032$), although the EFS difference was not statistically significant ($P = 0.062$). In contrast, the prognostic difference nearly disappeared in the non-*KMT2A*-r AML group (EFS: $P = 0.67$, OS: $P = 0.96$).

We also conducted a similar analysis using 0.5 years as the cutoff (Supplementary Figures 2A–D). Patients younger than 0.5 years were significantly more common in *KMT2A*-r AML than non-*KMT2A*-r AML ($P < 0.001$). When stratified into three age groups (<0.5 years, 0.5 to <1 year, and ≥1 year), no significant differences in EFS or OS were observed between the <0.5 years and 0.5 to <1 year groups for *KMT2A*-r AML (EFS: $P = 0.057$, OS: $P = 0.39$) or non-*KMT2A*-r AML (EFS: $P = 0.94$, OS: $P = 0.92$).

These findings indicate that the most notable prognostic differences occur when patients are stratified using 1 year of age as the cutoff. In this study, infants accounted for a larger proportion of *KMT2A*-r AML cases, and the prognostic impact of age differs significantly between *KMT2A*-r and non-*KMT2A*-r AML.

Differences in patient characteristics between infants and children

To integrate patient characteristics across cohorts, we summarized the clinical features of the AML99, AML-05, AML-12, and TARGET AML cohorts (Supplementary Table 1). No major differences in baseline characteristics were observed among the cohorts, and the proportions of infants and children were nearly identical. Prognostic comparisons within each cohort consistently demonstrated better outcomes in infants than in children (Supplementary Figures 3A–E). These findings indicated that there were no substantial biases in patient characteristics or prognosis between infants and children across cohorts, and the influence of treatment protocols on prognosis appeared limited. Therefore, subsequent analyses were conducted using the integrated cohort.

The characteristics of infants and children with *KMT2A*-r AML and non-*KMT2A*-r AML at diagnosis are summarized in Supplementary Tables 2 and 3. In *KMT2A*-r AML, there were no significant differences between infants and children with regard to gender, white blood cell (WBC) count, or French-American-British (FAB) classification (Supplementary Table 2). To examine the relationship between age and *KMT2A* rearrangement subtypes, we assessed both the age distribution for each subtype and their frequencies by age group (infants vs. children) (Figures 2A, B; Supplementary Table 2). *KMT2A::MLLT4* was associated with a higher age distribution, whereas other minor *KMT2A* fusion subtypes were predominantly observed in younger patients (Figure 2A). When stratified by age, both *KMT2A*::*MLLT3* and *KMT2A*::*MLLT4* were significantly more frequent in children than in infants (*P* = 0.031 and 0.0085, respectively; Figure 2B, Supplementary Table 2), while *KMT2A*::*MLLT10*, *KMT2A*::*ELL*, and *KMT2A*::*MLLT1* showed no significant age-related differences. In contrast, other *KMT2A* fusions were significantly more common in infants than in children (*P* < 0.001).

In non-*KMT2A*-r AML, there was no significant difference between infants and children in terms of gender (Supplementary Table 3). The WBC level at diagnosis was significantly higher in infants compared to children (*P* = 0.019). The percentage of FAB M0 was significantly higher in infants compared to children (*P* = 0.0035), whereas the percentage of FAB M2 was significantly higher in children than in infants (*P* = 0.024). To investigate the mechanism of underlying poor prognosis in infant non-*KMT2A*-r AML, we further characterized these 13 cases (Supplementary Figure 4). Among them, four harbored the

CBFB::*MYH11* fusion, and all survived. In contrast, among the nine cases without *CBFB*::*MYH11*, seven deaths occurred. One case each harbored *KAT6A*::*EP300* and *CBFA2T3*::*GLIS2* fusions. Fatal cases also showed mutations unrelated to activated signaling pathways—such as *WT1* mutations—and chromosomal abnormalities, including del(7q).

These results suggest that there are significant differences in patient characteristics between infants and children in both *KMT2A*-r AML and non-*KMT2A*-r AML. The most notable difference was the absence of *KMT2A*::*MLLT4* rearrangements in infant *KMT2A*-r AML cases.

Genetic mutation patterns between infants and children

The genetic mutation landscape of infants and children with *KMT2A*-r AML is depicted in Figure 3A. To investigate the distribution of genetic variants, genes were categorized into the following pathways: activated signaling pathway (*FLT3, KRAS, NRAS, PTPN11, CBL*, and *BRAF*), epigenetic regulators (*SETD2, ASXL1, ASXL2, BCOR, CREBBP, EP300*, and *KDM6A*), transcription factors (*WT1, SPI1, GATA2*, and *RUNX1*), cohesion complex (*STAG2* and *SMC3*), and other pathways (*CCND3, U2AF1, TET2,* and trisomy 8). A comparison of the number of mutated genes between infants and children revealed that the average number of mutated genes was 0.92 (range: 0–3) in infants and 1.36 (range: 0–7) in children, with significantly more mutations identified in children (P = 0.0061) (Supplementary Figure 5). The number of patients with at least one mutation was counted and plotted in each pathway, relative to the total number of patients (Figures 3B, C). Mutations in the activated signaling pathway were common in both infants and children, with no significant difference. In contrast, non-signaling pathway mutations were significantly more frequent in children than infants (infants: 15.3% vs. children: 43.9%, P < 0.001; Figure 3B). Among non-signaling mutations, a significant difference was observed in epigenetic regulation (infants: 3.4% vs. children: 17.8%, P = 0.0046). While no significant differences were found in transcription factors, cohesin complex, or other pathways, these mutations were frequent in children. At the individual gene level, *NRAS* mutations were more frequent in infants than in children (infants: 27.1% vs. children:16.1%), though not statistically significant (*P* = 0.083). In contrast, *SETD2* mutations were significantly more common in children than infants (infants: 0% vs. children 11.1%, *P* = 0.0050) (Figure 3A). Similarly, a comparison was made for non-*KMT2A*-r cases categorized by pathways, but no significant differences were observed (Supplementary Figures 6A, B).

These results suggest that there are significant differences in mutation patterns between infants and children in *KMT2A*-r AML, where the frequency of non-signaling mutations is significantly higher in children with *KMT2A*-r AML.

Prognostic impact of *KMT2A* fusion subtypes and co-occurring non-signaling mutations in *KMT2A*-r AML

KMT2A rearrangement patterns are known prognostic indicators. In our cohort, differences in prognosis were observed among the various *KMT2A* rearrangement subtypes (Supplementary Figure 7). Notably, the *KMT2A*::*MLLT4* subtype was associated with a particularly poor prognosis.

Based on the observed differences in genetic abnormalities between infants and children, we hypothesized that *KMT2A*::*MLLT4* and non-signaling mutations contribute to the poor prognosis of children with *KMT2A*-r AML compared with infants. First, we divided the patients into two groups based on the presence or absence of *KMT2A*::*MLLT4*, which was exclusively detected in cases of children with AML, and compared their prognosis (Figures 4A). As a result, children with *KMT2A*::*MLLT4* had a significantly poorer prognosis than children without *KMT2A*::*MLLT4* (EFS: *P* < 0.001, OS: *P* < 0.001). When the prognosis of children without *KMT2A*::*MLLT4* was compared with that of infants, no significant differences were detected (EFS: *P* = 0.14, OS: *P* = 0.10). Next, we examined the prognostic impact of non-signaling mutations; however, no significant differences were detected in the prognosis between patients with and without non-signaling mutations (Figures 4B). These results suggest that *KMT2A*::*MLLT4* is associated with a poor prognosis in childhood *KMT2A*-r AML, while non-signaling mutations have no prognostic impact.

We then evaluated prognosis in patient groups stratified by age—infants (<1 year) and children (≥1 year)—for each *KMT2A* rearrangement subtype (Supplementary Figures 8A–E). In the more common subtypes, *KMT2A*::*MLLT3* and *KMT2A*::*MLLT10*, infants had a better prognosis than children, although the differences were not statistically significant. We also conducted similar analyses dividing patients into three age groups: <1 year, 1 to <3 years, and ≥3 years (Supplementary Figure 9A–F). In the most common subtype, *KMT2A*::*MLLT3*, younger age groups appeared to have better prognosis; however, these differences did not reach statistical significance. In the remaining *KMT2A* fusion subtypes, the prognostic ranking of the age groups varied, and none showed statistically significant differences.

Prognostic impact of *KRAS* mutations in *KMT2A*-r AML

In addition, we investigated the prognostic impact of *KRAS* mutations stratified in *KMT2A*-r AML. In infants, 12 patients (20.3%) were *KRAS* mutation-positive, and despite these cases having poorer outcomes, the differences were not statistically significant (EFS: $P = 0.090$, OS: $P = 0.082$) (Figure 5A). In children, 47 patients (26.1%) were *KRAS* mutation-positive, and these cases had significantly worse outcomes in terms of EFS but not OS (EFS: $P = 0.0037$, OS: $P = 0.061$) (Figure 4B).

The prognostic impact of *KRAS* mutations according to each codon was also examined because we previously showed that *KRAS* G12 mutations are particularly associated with adverse prognostic factors in pediatric *KMT2A*-r AML[18] (Supplementary Figures 10A–F). *KRAS* G12 mutations were observed in 3.4% of infants and 9.4% of children, *KRAS* G13 mutations in 10.2% of infants and 10.6% of children, and other *KRAS* mutations in 6.8% of infants and 6.7% of children (Supplementary Table 2). Children with *KRAS* G12 mutations had significantly poorer outcomes (EFS: $P < 0.001$, OS: $P < 0.001$); however, no significant differences were detected in infants. Infants with *KRAS* G13 mutations also had poor outcomes, but the differences were not statistically significant (EFS: $P = 0.062$, OS: $P = 0.075$). These results suggest that *KRAS* mutations are associated with a poor prognosis in childhood *KMT2A*-r AML.

Multivariate analysis

To comprehensively assess the prognostic impact of each variable, we performed a multivariate analysis including the following factors: age (+1 year), WBC count (+10□/μL), *KMT2A*::*MLLT3*, *KMT2A*::*MLLT10*, *KMT2A*::*ELL*, *KMT2A*::*MLLT4*, *KMT2A*::*MLLT1*, other *KMT2A* fusions, non-signaling mutations, *KRAS* mutations, and *FLT3*-ITD (Table 1). Both EFS and OS analyses identified age (+1 year), WBC count (+10□/μL), *KMT2A*::*MLLT4*, and *KRAS* mutations as independent adverse prognostic factors.

We further subdivided *KRAS* mutations into *KRAS* G12, *KRAS* G13, and other *KRAS* mutations (Supplementary Table 4). The results were consistent with the overall analysis; however, only *KRAS* G12 mutations emerged as independent adverse prognostic factors.

These findings suggest that in *KMT2A*-r AML, older age, elevated WBC count, *KMT2A*::*MLLT4* and *KRAS* mutations independently predict poor prognosis.

Discussion

In this study, we examined mutation profiles and their prognostic implications in *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML (n = 538) and compared these between infants (<1 year) and children (≥1 year). To our knowledge, this is one of the largest studies to date focusing on age-specific mutation profiles and their prognostic implications in pediatric AML.

The proportion of infants was high in the *KMT2A*-r AML group, which is consistent with previous studies[3,21]. Interestingly, infants exhibited a better prognosis in *KMT2A*-r AML and a worse prognosis in non-*KMT2A*-r AML compared with that of children. The present study may be the first to uncover data on the reversal of prognosis between infants and children according to AML subtype.

To explore the reasons for these prognostic differences in *KMT2A*-r AML, we compared *KMT2A* fusion patterns between the two age groups and evaluated their impact on outcomes. *KMT2A*::*MLLT4* was detected exclusively in children and was associated with poor prognosis. This finding aligns with previous reports showing that *KMT2A*::*MLLT4* is more frequent in older patients with *KMT2A*-r AML and is linked to inferior survival[8,9,29]. *KMT2A*::*MLLT3* was also significantly more frequent in children, whereas other minor *KMT2A* fusions predominated in infants. As these age-related differences are rarely reported, validation in independent cohorts and further investigation are warranted.

We also assessed prognostic differences by *KMT2A* fusion subtypes other than *KMT2A*::*MLLT4*; no significant associations were observed. However, small subgroup sizes limit these analyses, and larger cohorts will be needed. Multivariate analysis confirmed that both older age and *KMT2A*::*MLLT4* were independent adverse prognostic factors, indicating that the poorer prognosis in children relative to infants is attributable to both. Given prior evidence of age-related differences in gene expression and DNA methylation in AML[3,30,31], elucidating the age-dependent mechanisms driving poor outcomes in *KMT2A*-r AML may reveal novel therapeutic targets and improve survival.

We also compared genetic abnormalities between infants and children within the *KMT2A*-r AML cohort. Mutations in activated signaling pathways were detected in over 60% of patients in both groups. These mutations were also reported to promote the development of *KMT2A*-r AML in a mouse model[32], which suggests that signaling mutations are important in the development of *KMT2A*-r AML, regardless of age. In contrast, non-signaling mutations were less frequent in infants (<20%) and more frequent in children (>40%). Generally, hematopoietic cells are known to accumulate mutations with increasing age, and cells from the founding clone can acquire additional cooperative mutations, yielding subclones that can contribute to leukemogenesis[33]. The higher frequency of non-signaling mutations in children likely reflects this age-related accumulation; however, their prognostic impact appeared limited.

We have previously demonstrated that *KRAS* mutations are adverse prognostic factors in *KMT2A*-r AML[17,18]; therefore, we examined their prognostic significance in this study. Multivariate analysis confirmed *KRAS* mutations as independent adverse prognostic factors for both EFS and OS. Unlike *KMT2A*::*MLLT4*, which was confirmed to the children group, *KRAS* mutations were present in both infants and children, suggesting that *KRAS* may represent a broadly relevant adverse prognostic factor. This finding aligns with recent studies that have also identified *KRAS* mutations as predictors of poor prognosis in *KMT2A*-r AML[34–37]. It would be valuable to determine whether this adverse effect persists across age groups in other cohorts.

In stark contrast, the non-*KMT2A*-r AML cohort showed the opposite age-related trend, with infants exhibiting significantly poorer outcomes than children. Notably, all infant patients harboring *CBFB*::*MYH11* in this cohort survived, consistent with its well-established role as a favorable prognostic marker[11]. Thus, infants with *CBFB::MYH11* can be considered to have a favorable prognosis even within non-*KMT2A*-r AML. Fatal infant cases included chromosomal translocations such as *KAT6A*::*EP300* and *CBFA2T3*::*GLIS2*, mutations not related to activated signaling pathways such as *WT1*, and chromosomal abnormalities including del(7q), all of which have been associated with adverse outcomes[38–43]. However, some fatal cases lacked identifiable high-risk genetic lesions, highlighting the need for larger cohort and comprehensive approaches such as multi-omics analyses to clarify the underlying mechanisms.

In conclusion, this study clarified prognostic differences between infants and children with *KMT2A*-r and non-*KMT2A*-r AML in a large cohort, highlighting the prognostic relevance of age, *KMT2A* fusion patterns, and gene mutations, as well as their interrelationships. These findings may advance understanding of subtype-specific AML characteristics, support the development of improved treatment stratification strategies, and help elucidate age-specific pathogenic mechanisms in *KMT2A*-r AML with potential therapeutic implications.

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Table 1. Results of multivariate analysis for event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML

	EFS			OS		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Age (+1 year)	1.04	1.00 – 1.08	0.032 *	1.07	1.03 – 1.12	< 0.001 ***
WBC (+10□/μL)	1.02	1.00 – 1.03	0.035 *	1.02	1.00 – 1.04	0.032 *
KMT2A::*MLLT3*	0.77	0.41 – 1.45	0.42	1.01	0.43 – 2.38	0.99
KMT2A::*MLLT10*	1.63	0.85 – 3.11	0.14	1.92	0.80 – 4.62	0.14
KMT2A::*ELL*	1.14	0.53 – 2.46	0.73	1.80	0.67 – 4.83	0.24
KMT2A::*MLLT4*	2.48	1.12 – 5.46	0.025 *	2.85	1.07 – 7.62	0.037 *
KMT2A::*MLLT1*	1.19	0.48 – 2.90	0.71	0.78	0.22 – 2.73	0.70
Other *KMT2A* fusions	1.47	0.82 – 2.63	0.20	2.64	1.26 – 5.51	0.0097 **
Non-signaling mutations	0.89	0.54 – 1.48	0.66	0.59	0.30 – 1.18	0.14
KRAS mutations	1.74	1.17 – 2.59	0.0062 **	1.75	1.07 – 2.87	0.027 *
FLT3-ITD	1.82	0.70 – 4.76	0.22	2.60	0.85 – 7.94	0.095

Abbreviations: CI, confidence interval; WBC, white blood cells; *FLT3*-ITD, *FLT3* internal tandem duplications.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Figure Legends

Figure 1. Comparison of *KMT2A*-r and non-*KMT2A*-r AML cases

(A, B) Age distribution of *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML cases (n = 538). Infants are defined as <1 year old, and children are defined as ≥1 year old. **(C)** Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the age group (infants and children). **(D)** EFS and OS in non-*KMT2A*-r AML based on the age group (infants and children).

$^*P < 0.05$; $^{***}P < 0.001$

Figure 2. Comparison of *KMT2A* rearrangement patterns in infants and children with *KMT2A*-r AML

(A) Scatter and box plots showing the age distribution for each *KMT2A* rearrangement pattern. **(B)** Pie charts showing the proportions of *KMT2A* rearrangement patterns in infants, children, and the combined cohort, along with mean age and standard deviation. The legend is shared across all panels.

Figure 3. Comparison of gene mutations in infants and children with *KMT2A*-r AML

(A) Gene mutation landscape, *KMT2A* rearrangement patterns, age, event status, and death status in infants and children with AML. The cohort (n = 239) is ranked by age, with the youngest (rank 1) shown in red, the oldest (rank 239) shown in blue, and the median (rank 120) shown in green. Events and deaths that occurred within 100 days are color-coded differently from those that occurred later. The color legend for *KMT2A* fusion patterns corresponds to Figure 2. The bar graph on the right summarizes the proportions of each category. **(B, C)** Comparison of the positive rates of gene mutations classified by function between infants and children with *KMT2A*-r AML.

$^{**}P < 0.01$; $^{***}P < 0.001$.

Figure 4. Impact of *KMT2A*::*MLLT4* and non-signaling mutations on prognosis

(A) Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the *KMT2A::MLLT4* and age group (infants and children). **(B)** EFS and OS in *KMT2A*-r AML based on the non-signaling mutation and age group (infants and children).

***P < 0.001

Figure 5. Impact of *KRAS* mutations on prognosis

(A) Event-free survival (EFS) and overall survival (OS) in infants with *KMT2A*-r AML based on the *KRAS* mutations. **(B)** EFS and OS in children with *KMT2A*-r AML based on the *KRAS* mutations.

**P < 0.01.

Figure 1

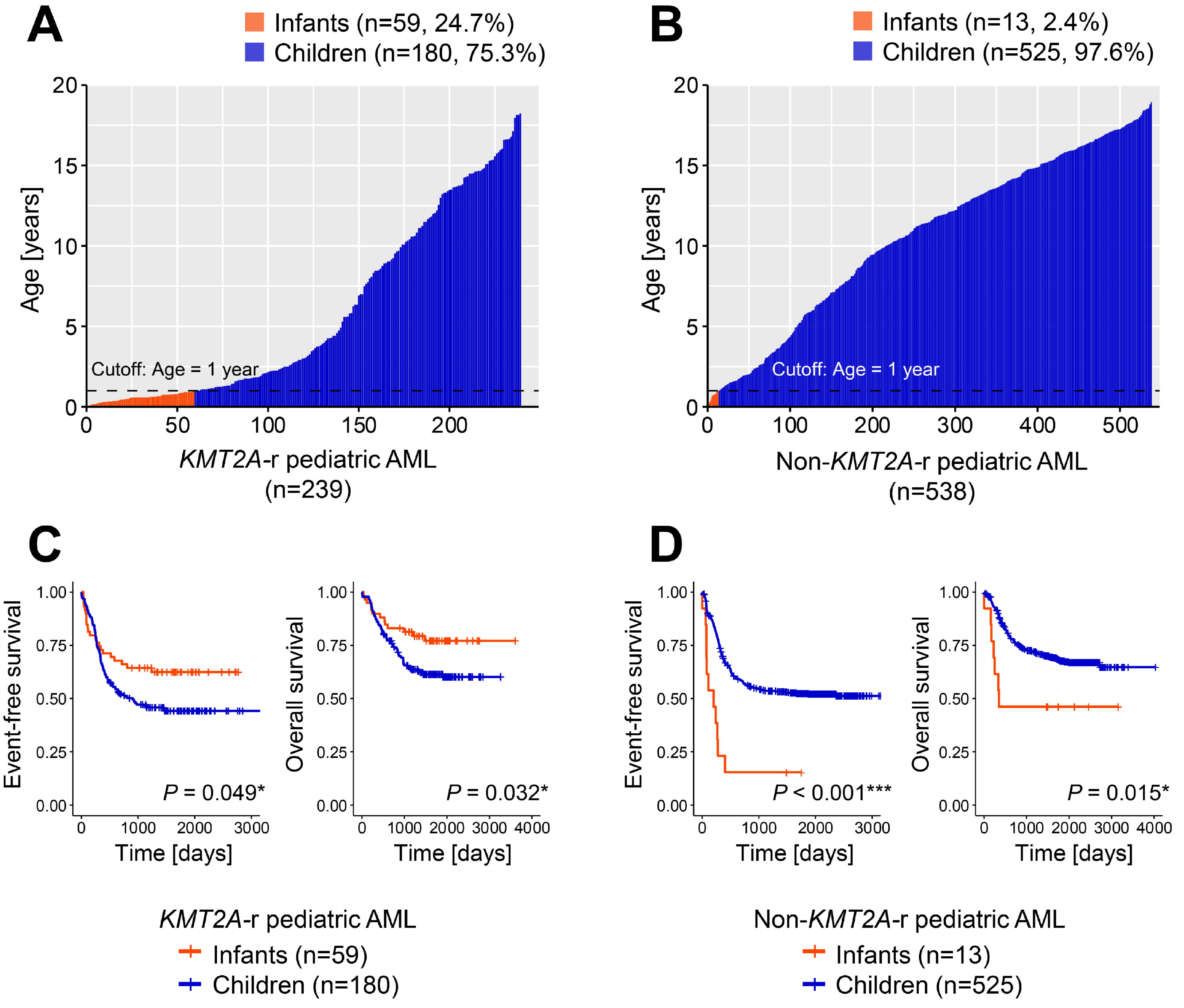

A
Infants (n=59, 24.7%)
Children (n=180, 75.3%)
Age [years]
20
15
10
5
0
Cutoff: Age = 1 year
0
50
100
150
200
KMT2A-r pediatric AML
(n=239)
B
Infants (n=13, 2.4%)
Children (n=525, 97.6%)
Age [years]
20
15
10
5
0
Cutoff: Age = 1 year
0
100
200
300
400
500
Non-KMT2A-r pediatric AML
(n=538)
C
Event-free survival
1.00
0.75
0.50
0.25
0.00
P = 0.049*
0
1000
2000
3000
Time [days]
Overall survival
1.00
0.75
0.50
0.25
0.00
P = 0.032*
0
1000
2000
3000
4000
Time [days]
D
Event-free survival
1.00
0.75
0.50
0.25
0.00
P < 0.001***
0
1000
2000
3000
Time [days]
Overall survival
1.00
0.75
0.50
0.25
0.00
P = 0.015*
0
1000
2000
3000
4000
Time [days]
KMT2A-r pediatric AML
Infants (n=59)
Children (n=180)
Non-KMT2A-r pediatric AML
Infants (n=13)
Children (n=525)

Figure 2

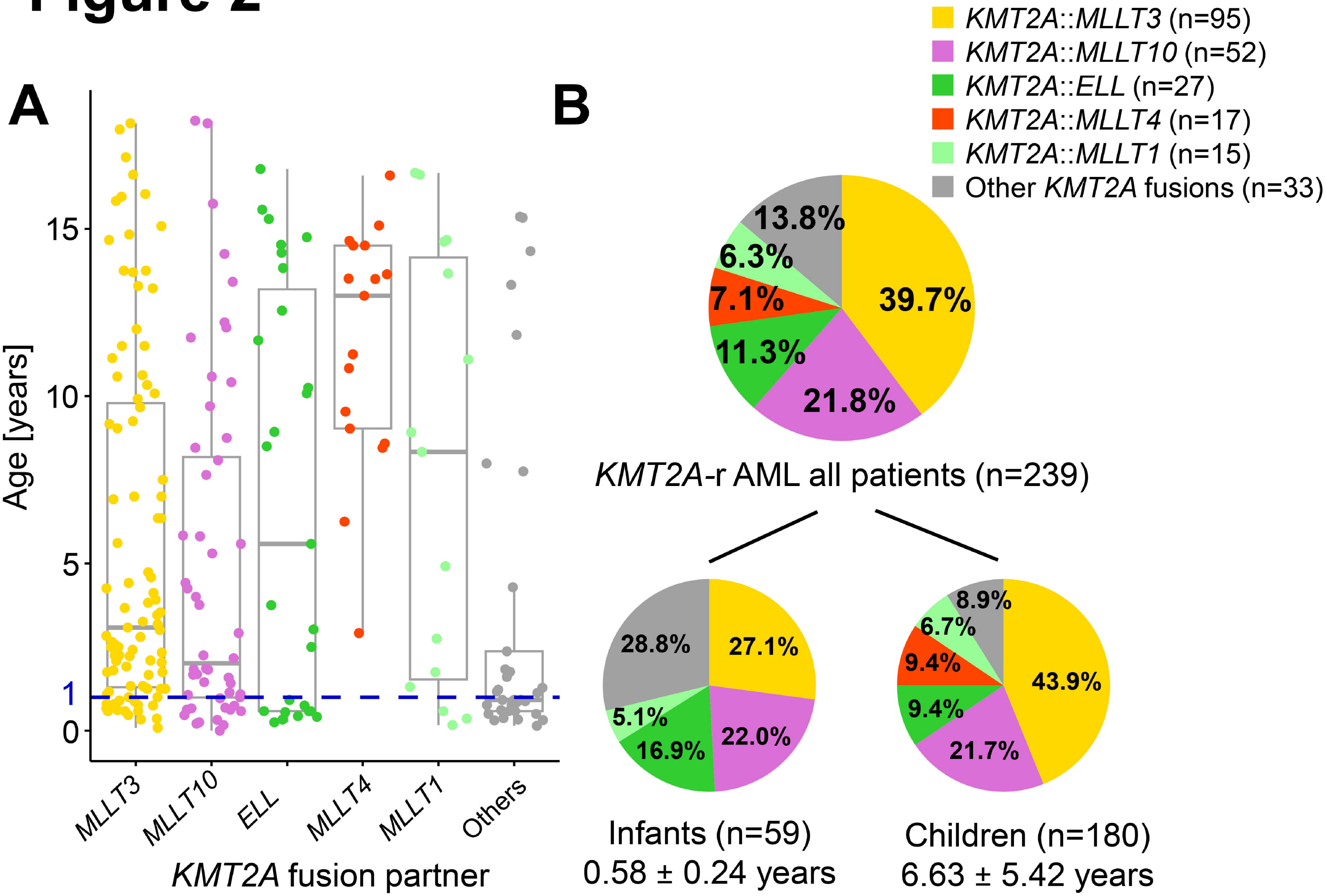

A
Age [years]
0
1
5
10
15
MLLT3
MLLT10
ELL
MLLT4
MLLT1
Others
KMT2A fusion partner
B
KMT2A::MLLT3 (n=95)
KMT2A::MLLT10 (n=52)
KMT2A::ELL (n=27)
KMT2A::MLLT4 (n=17)
KMT2A::MLLT1 (n=15)
Other KMT2A fusions (n=33)
13.8%
6.3%
7.1%
39.7%
11.3%
21.8%
KMT2A-r AML all patients (n=239)
28.8%
27.1%
5.1%
22.0%
16.9%
8.9%
6.7%
9.4%
43.9%
9.4%
21.7%
Infants (n=59)
0.58 ± 0.24 years
Children (n=180)
6.63 ± 5.42 years

Figure 3

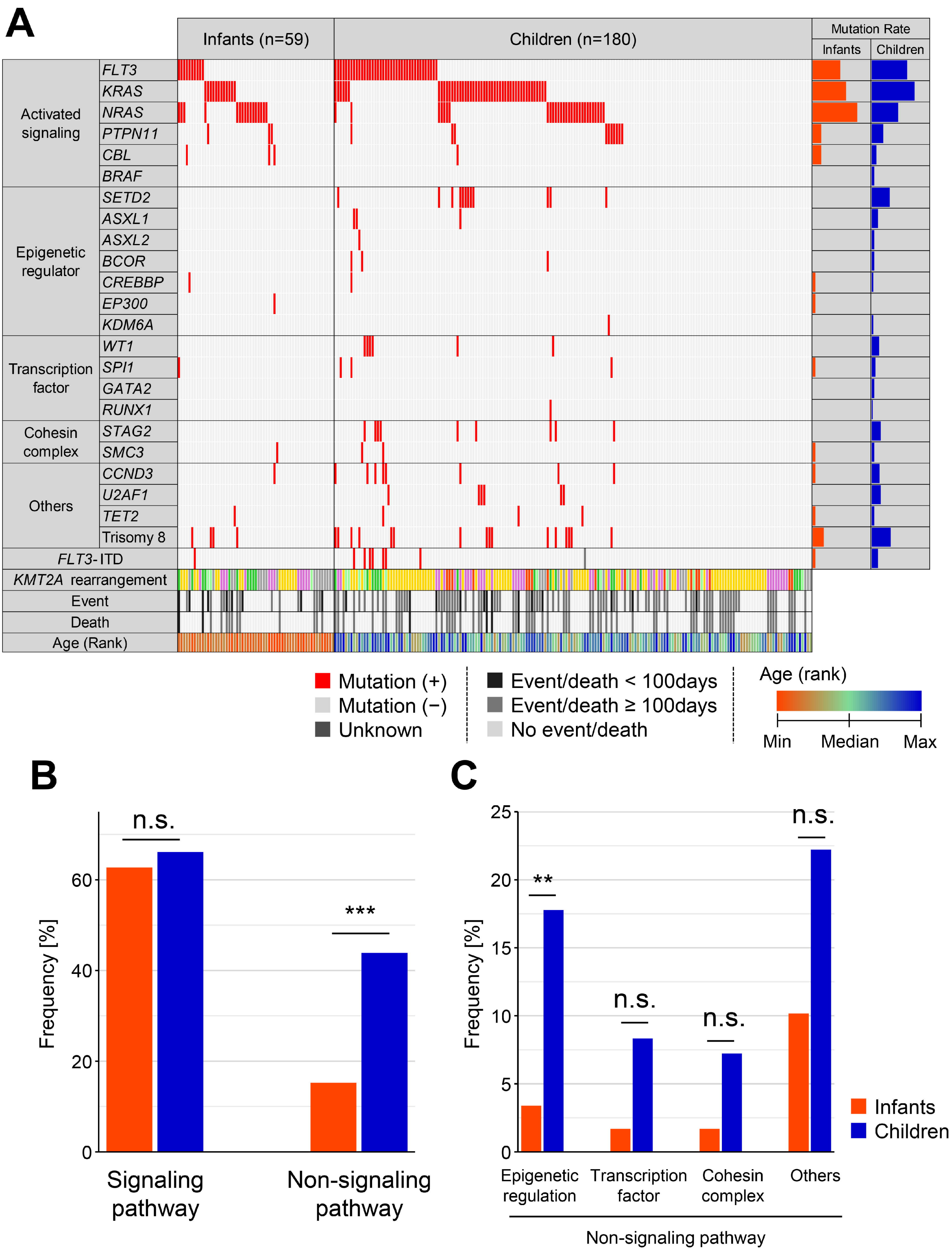

A
Infants (n=59)
Children (n=180)
Mutation Rate
Infants
Children
Activated signaling
FLT3
KRAS
NRAS
PTPN11
CBL
BRAF
Epigenetic regulator
SETD2
ASXL1
ASXL2
BCOR
CREBBP
EP300
KDM6A
Transcription factor
WT1
SPI1
GATA2
RUNX1
Cohesin complex
STAG2
SMC3
Others
CCND3
U2AF1
TET2
Trisomy 8
FLT3-ITD
KMT2A rearrangement
Event
Death
Age (Rank)
Mutation (+)
Mutation (−)
Unknown
Event/death < 100days
Event/death ≥ 100days
No event/death
Age (rank)
Min
Median
Max
B
Frequency [%]
0
20
40
60
n.s.
***
Signaling pathway
Non-signaling pathway
C
Frequency [%]
0
5
10
15
20
25
**
n.s.
n.s.
n.s.
Epigenetic regulation
Transcription factor
Cohesin complex
Others
Non-signaling pathway
Infants
Children

Figure 4

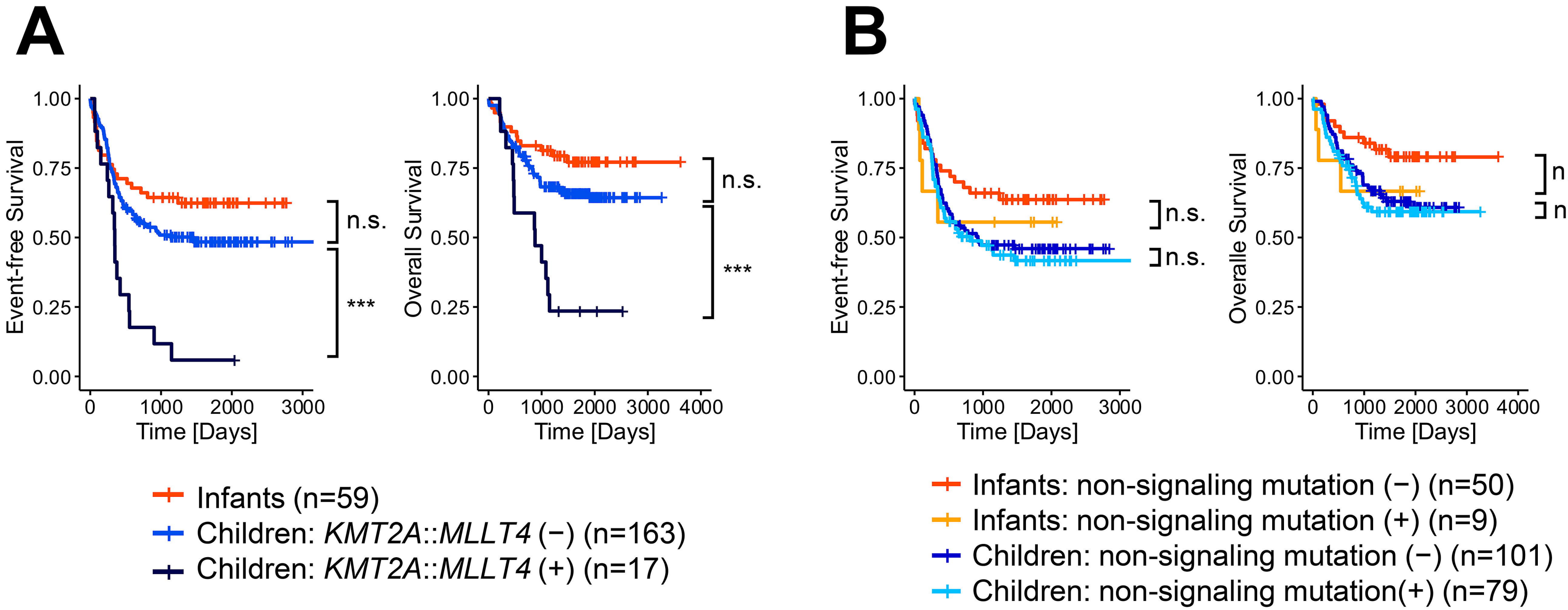
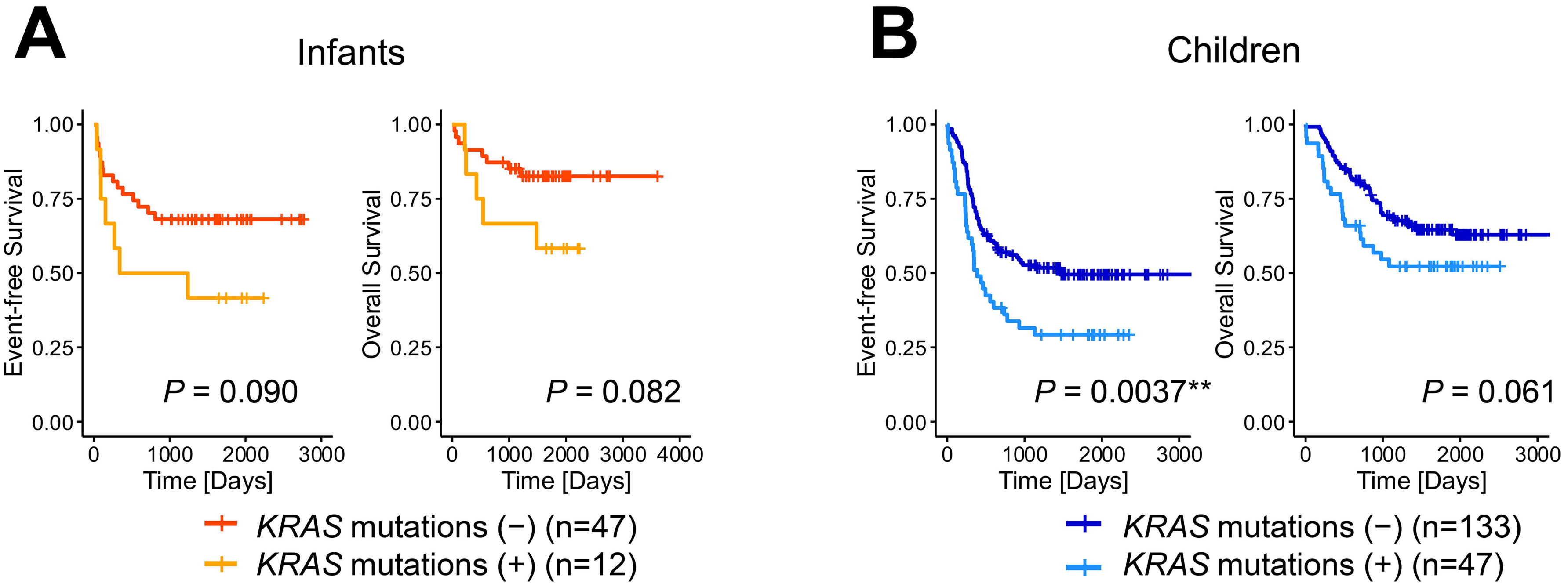

A
B
Event-free Survival
Overall Survival
Overalle Survival
1.00
0.75
0.50
0.25
0.00
Time [Days]
0
1000
2000
3000
4000
n.s.
***
Infants (n=59)
Children: *KMT2A*::*MLLT4* (−) (n=163)
Children: *KMT2A*::*MLLT4* (+) (n=17)
Infants: non-signaling mutation (−) (n=50)
Infants: non-signaling mutation (+) (n=9)
Children: non-signaling mutation (−) (n=101)
Children: non-signaling mutation(+) (n=79)

Figure 5


A
Infants
Event-free Survival
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time [Days]
P = 0.090
Overall Survival
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
4000
Time [Days]
P = 0.082
KRAS mutations (−) (n=47)
KRAS mutations (+) (n=12)
B
Children
Event-free Survival
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time [Days]
P = 0.0037**
Overall Survival
1.00
0.75
0.50
0.25
0.00
0
1000
2000
3000
Time [Days]
P = 0.061
KRAS mutations (−) (n=133)
KRAS mutations (+) (n=47)

Age-specific mutation profiles and their prognostic implications in pediatric *KMT2A*-rearranged acute myeloid leukemia

Supplementary Information

Supplementary Methods

Targeted sequencing

Samples from the AML-12 study were subjected to targeted sequencing of 507 genes. The target genes were selected based on the following criteria: (1) established driver genes in myeloid malignancies and other malignant neoplasms; (2) relevance to myeloid malignancies; (3) previously detected mutations in whole-exome sequencing studies; and (4) potential therapeutic targets.

Target enrichment was conducted using a SureSelect custom kit (Agilent, Santa Clara, CA, USA) designed to capture all coding exons of the 507 genes. Massively parallel sequencing of the captured targets was conducted on a HiSeq 2000/2500 system (Illumina, San Diego, CA, USA) with paired-end 126-133 bp reads, following the manufacturer's instructions.

Sequencing reads were aligned to the human genome (hg19) using Burrows-Wheeler Aligner (BWA)-mem version 0.5.8 with default parameters. BWA v0.7.12-r1039 (with default parameters and a -mem option; https://github.com/lh3/bwa) and VarScan2 [1] v2.3 (with default parameters and -min-var-freq 0.05 -min-coverage 5 -min-reads2 5 -min-avg-qual 15 -p-value 0.01) were used to detect single-nucleotide variants (SNVs) and small indels.

Variants were retained if they met all of the following criteria: (i) mapping quality score ≥ 40; (ii) base quality score ≥ 20; (iii) < 5 SNVs on the same read; (iv) < 2 indels on the same read; (v) total read count ≥ 10; (vi) variant read count ≥ 5; and (vii) variant allele frequency (VAF) ≥ 0.05. Variants were excluded if they were: (i) synonymous or annotated as "unknown" by ANNOVAR; (ii) listed in dbSNP138, ESP6500, or the 1000 Genomes Project (as of October 2014); (iii) present only in unidirectional reads; (iv) detected in 12 unrelated germline samples with mean VAF <0.01; or (v) missense SNVs with a VAF of 0.4-0.6 unless recorded as somatic mutations in hematopoietic or lymphoid tissue in the Catalogue of Somatic Mutations in Cancer (v90). Finally, an in-house pipeline retained only gene variants associated with hematologic malignancies, and potential sequencing or mapping artifacts were manually reviewed using Integrative Genome Viewer.

[1] Koboldt DC, Zhang Q, Larson DE, et al. VarScan 2: somatic mutation and copy number alteration discovery in cancer by exome sequencing. Genome Res. 2012;22(3):568–576.

Supplementary Table 1. Clinical characteristics of *KMT2A*-r AML in each cohort

	JCCG (Japan Children's Cancer Group)												TARGET AML cohort			
	AML99				AML-05				AML-12							
Description	**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**	
Number	1		10		14		44		15		43		29		83	
Percentage	9.1%		90.9%		24.1%		75.9%		25.9%		74.1%		25.9%		74.1%	
Sex																
Male	1	(100.0%)	9	(90.0%)	6	(42.9%)	19	(43.2%)	10	(66.7%)	16	(37.2%)	13	(44.8%)	40	(48.2%)
Female	0	(0.0%)	1	(10.0%)	8	(57.1%)	25	(56.8%)	5	(33.3%)	27	(62.8%)	16	(55.2%)	43	(51.8%)
Age (year)																
Median	0.47		2.7		0.58		6.4		0.58		4.4		0.63		8.5	
Range			1.0 – 13.5		0.00 – 0.92		1.0 – 15.1		0.17 – 0.92		1.0 – 15.8		0.15 – 0.97		1.1 – 18.2	
WBC (×10⁹/L)																
Median	11.5		30.6		33.4		22.5		49.5		9.0		32.7		33.5	
Range			2.1 – 224		5.4 – 152		1.1 – 459		1.5 – 726		1.2 – 376		3.4 – 519		1.3 – 610	
FAB																
M0	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.4%)	2	(2.4%)
M1	0	(0.0%)	1	(10.0%)	0	(0.0%)	4	(9.1%)	0	(0.0%)	3	(7.0%)	0	(0.0%)	3	(3.6%)
M2	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	1	(6.7%)	3	(7.0%)	0	(0.0%)	2	(2.4%)
M3	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
M4	0	(0.0%)	2	(20.0%)	3	(21.4%)	11	(25.0%)	2	(13.3%)	2	(4.7%)	4	(13.8%)	12	(14.5%)
M5	1	(100.0%)	7	(70.0%)	9	(64.3%)	25	(56.8%)	12	(80.0%)	31	(72.1%)	22	(75.9%)	50	(60.2%)
M6	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
M7	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.7%)	0	(0.0%)	1	(1.2%)
NOS	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.4%)
RAEB-T	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Unknown	0	(0.0%)	0	(0.0%)	2	(14.3%)	1	(2.3%)	0	(0.0%)	2	(4.7%)	2	(6.9%)	11	(13.3%)
***KMT2A* rearrangement**																
KMT2A::*MLLT3*	1	(100.0%)	5	(50.0%)	4	(28.6%)	23	(52.3%)	4	(26.7%)	20	(46.5%)	7	(24.1%)	31	(37.3%)
KMT2A::*MLLT10*	0	(0.0%)	1	(10.0%)	3	(21.4%)	8	(18.2%)	2	(13.3%)	12	(27.9%)	8	(27.6%)	18	(21.7%)
KMT2A::*ELL*	0	(0.0%)	1	(10.0%)	5	(35.7%)	5	(11.4%)	2	(13.3%)	1	(2.3%)	3	(10.3%)	10	(12.0%)
KMT2A::*MLLT4*	0	(0.0%)	2	(20.0%)	0	(0.0%)	3	(6.8%)	0	(0.0%)	3	(7.0%)	0	(0.0%)	9	(10.8%)
KMT2A::*MLLT1*	0	(0.0%)	0	(0.0%)	1	(7.1%)	4	(9.1%)	1	(6.7%)	3	(7.0%)	1	(3.4%)	5	(6.0%)
Other *KMT2A* fusions	0	(0.0%)	1	(10.0%)	1	(7.1%)	1	(2.3%)	6	(40.0%)	4	(9.3%)	10	(34.5%)	10	(12.0%)
***FLT3*-ITD**	1	(100.0%)	0	(0.0%)	0	(0.0%)	3	(6.8%)	0	(0.0%)	1	(2.3%)	0	(0.0%)	3	(3.6%)
***KRAS* mutations**	0	(0.0%)	5	(50.0%)	2	(14.3%)	8	(18.2%)	1	(6.7%)	9	(20.9%)	9	(31.0%)	25	(30.1%)
KRAS G12 mutaions	0	(0.0%)	2	(20.0%)	1	(7.1%)	5	(11.4%)	0	(0.0%)	1	(2.3%)	1	(3.4%)	8	(9.6%)
KRAS G13 mutaions	0	(0.0%)	3	(30.0%)	1	(7.1%)	2	(4.5%)	0	(0.0%)	6	(14.0%)	5	(17.2%)	7	(8.4%)
KRAS G12&G13 mutations	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	0	(0.0%)	0	(0.0%)
Other *KRAS* mutations	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	1	(6.7%)	1	(2.3%)	3	(10.3%)	10	(12.0%)

Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.

Supplementary Table 2. Clinical characteristics of *KMT2A*-r AML

Description	**Infants (<1 year)**		**Children (≥1 year)**		***P* value**
Number	59		180		
Percentage	24.7%		75.3%		
Sex					
Male	30	(50.8%)	84	(46.7%)	0.65
Female	29	(49.2%)	96	(53.3%)	
Age (year)					
Median	0.58		6.6		
Range	0.0 – 0.97		1.0 – 18.2		
WBC ($\times 10^9$/L)					
Median	38.1		24.9		0.058
Range	1.5 – 726		1.1 – 610		
FAB					
M0	1	(1.7%)	2	(1.1%)	0.57
M1	0	(0.0%)	11	(6.1%)	0.070
M2	1	(1.7%)	6	(3.3%)	1.00
M3	0	(0.0%)	0	(0.0%)	1.00
M4	9	(15.3%)	27	(15.0%)	1.00
M5	44	(74.6%)	113	(62.8%)	0.11
M6	0	(0.0%)	0	(0.0%)	1.00
M7	0	(0.0%)	3	(1.7%)	1.00
NOS	0	(0.0%)	2	(1.1%)	1.00
RAEB-T	0	(0.0%)	2	(1.1%)	1.00
Unknown	4	(6.8%)	14	(7.8%)	1.00
***KMT2A* rearrangement**					
KMT2A::*MLLT3*	16	(27.1%)	79	(43.9%)	0.031 *
KMT2A::*MLLT10*	13	(22.0%)	39	(21.7%)	1.00
KMT2A::*ELL*	10	(16.9%)	17	(9.4%)	0.15
KMT2A::*MLLT4*	0	(0.0%)	17	(9.4%)	0.0085 **
KMT2A::*MLLT1*	3	(5.1%)	12	(6.7%)	1.00
Other *KMT2A* fusions	17	(28.8%)	16	(8.9%)	< 0.001 ***
***FLT3*-ITD**	1	(1.7%)	7	(3.9%)	0.68
***KRAS* mutations**	12	(20.3%)	47	(26.1%)	0.49
KRAS G12 mutations	2	(3.4%)	16	(8.9%)	0.25
KRAS G13 mutations	6	(10.2%)	18	(10.0%)	1.00
KRAS G12&G13 mutations	0	(0.0%)	1	(0.6%)	1.00
Other *KRAS* mutations	4	(6.8%)	12	(6.7%)	1.00

Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.
**P* < 0.05; ***P* < 0.01; ****P* < 0.001

Supplementary Table 3. Clinical characteristics of non-*KMT2A*-r AML

Description	**Infants (<1 year)**		**Children (≥1 year)**		***P* value**
Number	13		525		
Percentage	2.4%		97.6%		
Sex					
Male	8	(61.5%)	272	(51.8%)	0.58
Female	5	(38.5%)	253	(48.2%)	
Age (year)					
Median	0.73		11.8		
Range	0.21 – 0.98		1.0 – 19.0		
WBC ($\times 10^9$/L)					
Median	115		34.2		0.019 *
Range	10.8 – 310		0.2 – 473		
FAB					
M0	3	(23.1%)	11	(2.1%)	0.0035 **
M1	0	(0.0%)	73	(13.9%)	0.23
M2	0	(0.0%)	148	(28.2%)	0.024 *
M3	0	(0.0%)	2	(0.4%)	1.00
M4	3	(23.1%)	131	(25.0%)	1.00
M5	2	(15.4%)	43	(8.2%)	0.30
M6	0	(0.0%)	8	(1.5%)	1.00
M7	1	(7.7%)	13	(2.5%)	0.29
NOS	0	(0.0%)	29	(5.5%)	1.00
RAEB-T	0	(0.0%)	0	(0.0%)	1.00
Unknown	4	(30.8%)	67	(12.8%)	0.079
Cytogenetic Abnormalities					
CBFB::*MYH11*	4	(30.8%)	88	(16.8%)	0.25
RUNX1::*RUNXT1*	0	(0.0%)	100	(19.0%)	0.14
Normal Karyotype	4	(30.8%)	155	(29.5%)	1.00
Other Cytogenetics	5	(38.5%)	182	(34.7%)	0.77
***FLT3*-ITD**	0	(0.0%)	119	(22.7%)	0.082

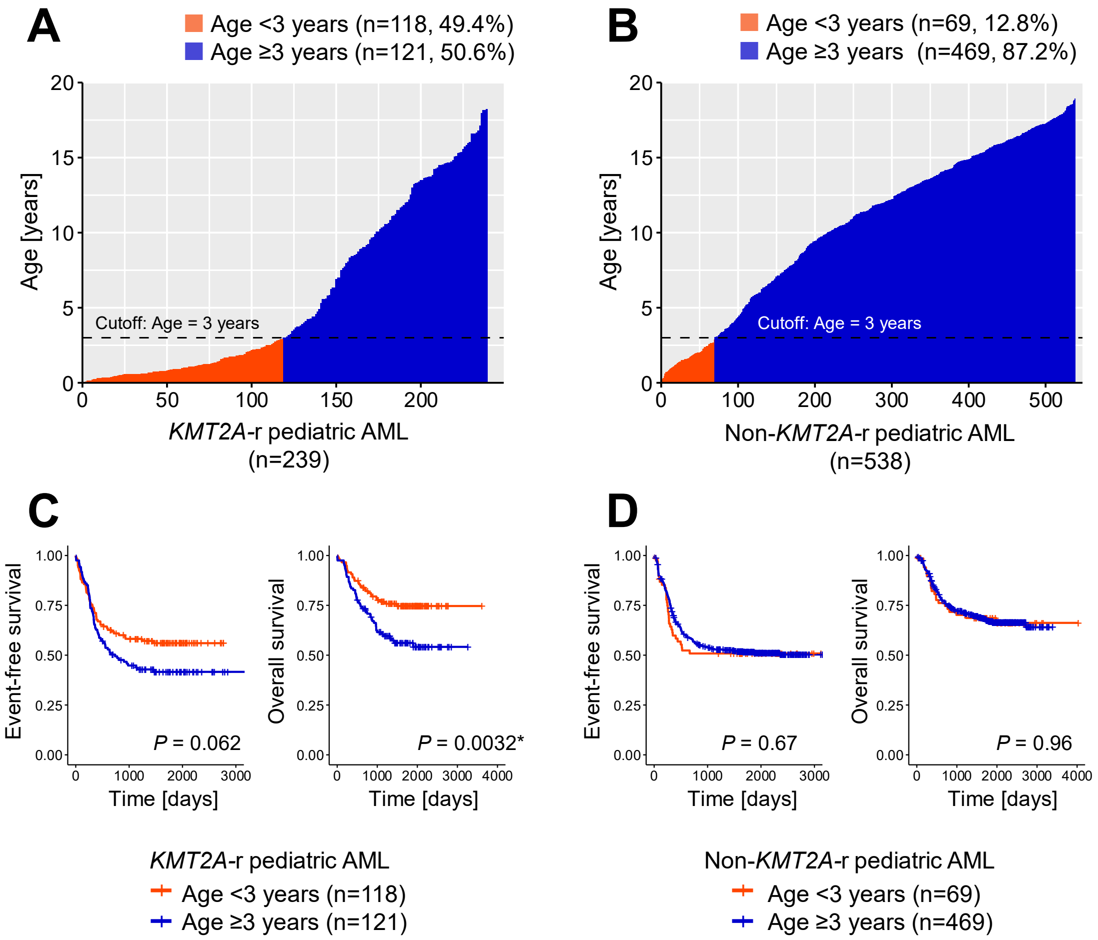
Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.
**P* < 0.05; ***P* < 0.01

Supplementary Table 4. Results of multivariate analysis for event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML

	EFS			OS		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Age (+1 year)	1.04	1.00 – 1.08	0.044 *	1.07	1.03 – 1.12	0.0013 **
WBC (+10^4/μL)	1.02	1.00 – 1.03	0.049 *	1.02	1.00 – 1.04	0.030 *
KMT2A::*MLLT3*	0.75	0.40 – 1.43	0.39	0.95	0.40 – 2.25	0.91
KMT2A::*MLLT10*	1.55	0.80 – 2.98	0.19	2.01	0.83 – 4.88	0.12
KMT2A::*ELL*	1.01	0.46 – 2.21	0.98	1.62	0.60 – 4.39	0.34
KMT2A::*MLLT4*	2.30	1.02 – 5.17	0.044 *	2.57	0.95 – 6.93	0.062
KMT2A::*MLLT1*	1.19	0.48 – 2.93	0.71	0.75	0.21 – 2.64	0.65
Other *KMT2A* fusions	1.44	0.80 – 2.59	0.23	2.51	1.19 – 5.29	0.015 *
Non-signaling mutations	0.89	0.53 – 1.47	0.64	0.62	0.31 – 1.24	0.18
KRAS G12 mutations	2.23	1.29 – 3.86	0.0043 **	2.17	1.15 – 4.11	0.017 *
KRAS G13 mutations	1.18	0.65 – 2.14	0.58	1.66	0.83 – 3.32	0.15
Other *KRAS* mutations	1.51	0.74 – 3.06	0.26	0.80	0.27 – 2.35	0.69
FLT3-ITD	1.76	0.67 – 4.60	0.25	2.56	0.84 – 7.86	0.10

Abbreviations: CI, confidence interval; WBC, white blood cells; *FLT3*-ITD, *FLT3* internal tandem duplications.
*$P < 0.05$; **$P < 0.01$

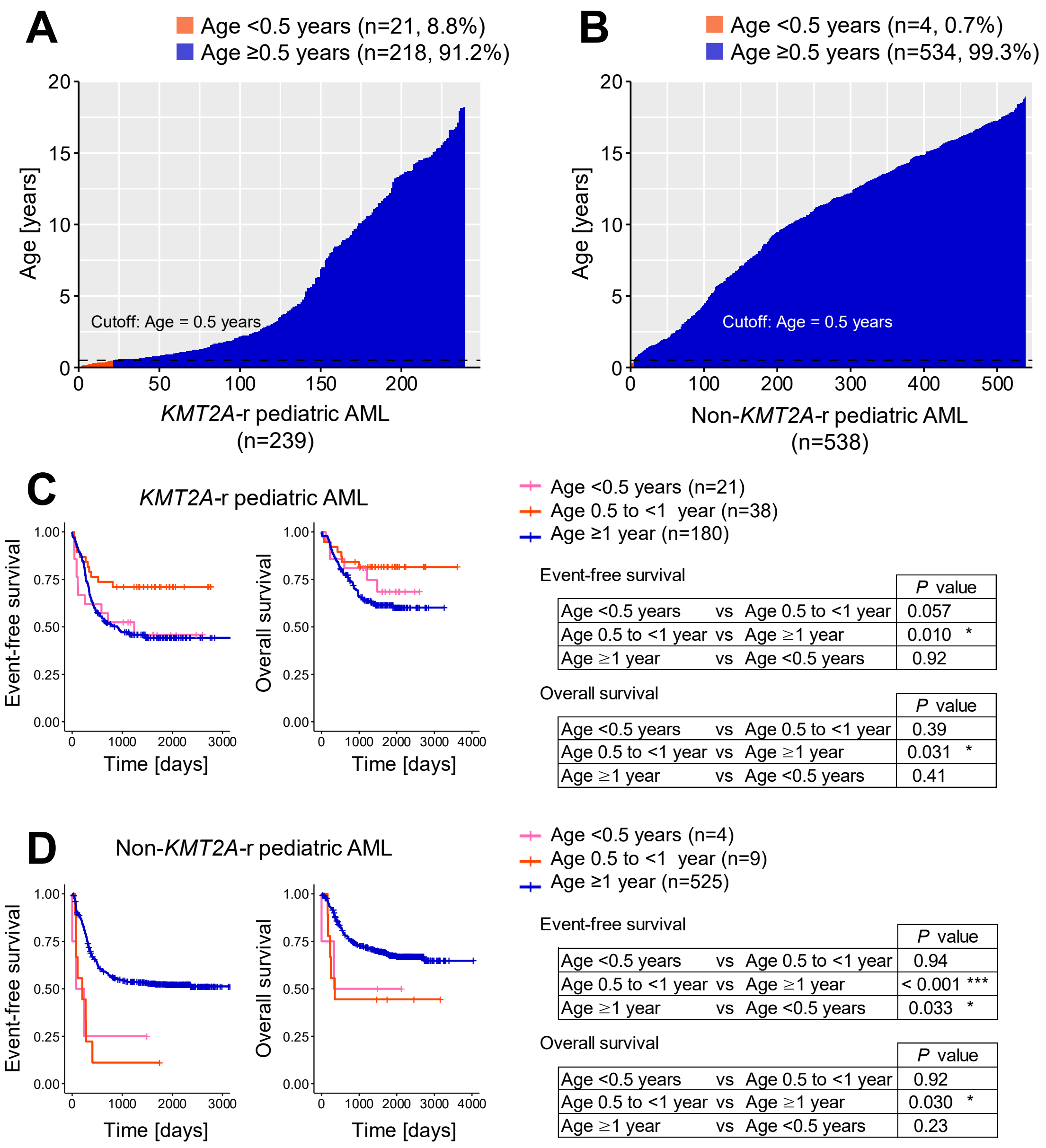
Supplementary Figure 1. Comparison of *KMT2A*-r and non-*KMT2A*-r AML cases (Cutoff: Age = 3 years)



(A, B) Age distribution of *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML cases (n = 538). Patients divided by age groups using a cutoff at 3 years (<3 years vs. ≥3 years). **(C)** Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the age group (<3 years vs. ≥3 years). **(D)** EFS and OS in non-*KMT2A*-r AML based on the age group (<3 years vs. ≥3 years).

**P < 0.01

Supplementary Figure 2. Comparison of *KMT2A*-r and non-*KMT2A*-r AML cases (Cutoff: Age = 0.5 years)



C *KMT2A*-r pediatric AML

Event-free survival

			P value
Age <0.5 years	vs	Age 0.5 to <1 year	0.057
Age 0.5 to <1 year	vs	Age ≥1 year	0.010 *
Age ≥1 year	vs	Age <0.5 years	0.92

Overall survival

			P value
Age <0.5 years	vs	Age 0.5 to <1 year	0.39
Age 0.5 to <1 year	vs	Age ≥1 year	0.031 *
Age ≥1 year	vs	Age <0.5 years	0.41

D Non-*KMT2A*-r pediatric AML

Event-free survival

			P value
Age <0.5 years	vs	Age 0.5 to <1 year	0.94
Age 0.5 to <1 year	vs	Age ≥1 year	< 0.001 ***
Age ≥1 year	vs	Age <0.5 years	0.033 *

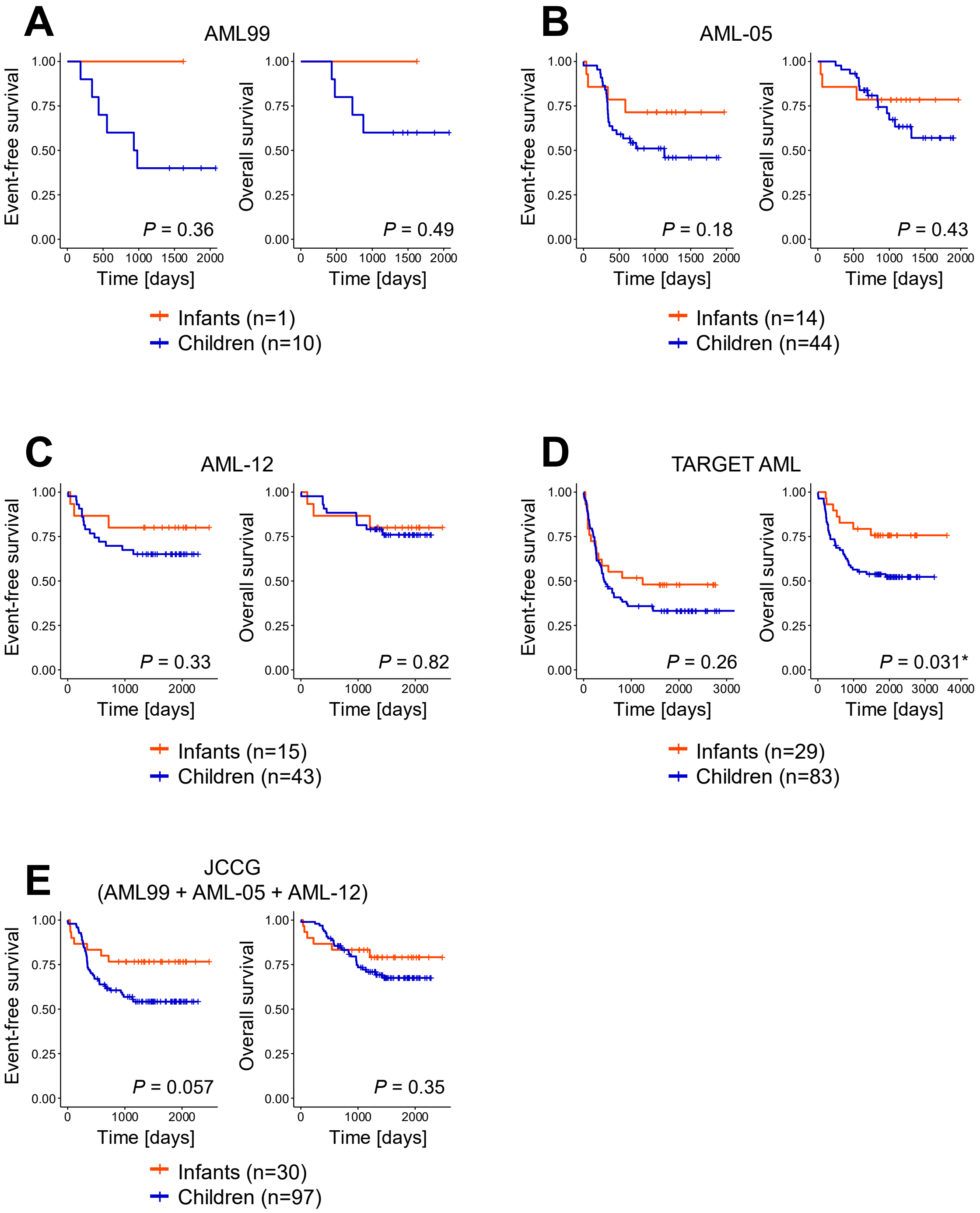
Overall survival

			P value
Age <0.5 years	vs	Age 0.5 to <1 year	0.92
Age 0.5 to <1 year	vs	Age ≥1 year	0.030 *
Age ≥1 year	vs	Age <0.5 years	0.23

(A, B) Age distribution of *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML cases (n = 538). Patients divided by age groups using a cutoff at 0.5 years (<0.5 years vs. ≥0.5 years). **(C)** Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the age group (<0.5 years, 0.5 to <1 year and ≥1 year). **(D)** EFS and OS in non-*KMT2A*-r AML based on the age group (<0.5 years, 0.5 to <1 year and ≥1 year). Pairwise log-rank test results are shown in both C and D.

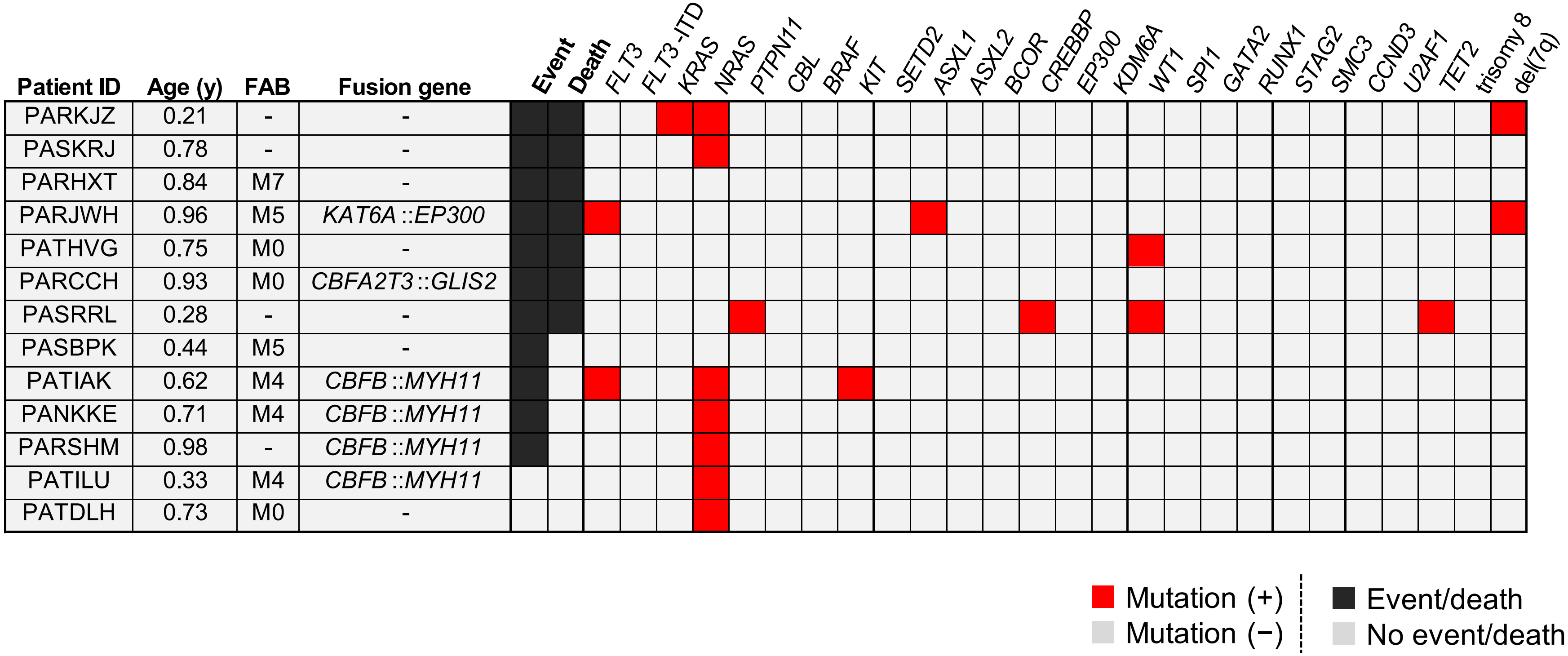
**P* < 0.05; ****P* < 0.001

Supplementary Figure 3. Comparison of prognosis between infants and children in each cohort



Event-free survival (EFS) and overall survival (OS) between infants and children in *KMT2A*-r AML, stratified by cohorts. Analyses were conducted in the following order: **(A)** AML99, **(B)** AML-05, **(C)** AML-12, **(D)** TARGET AML cohort, and **(E)** Japan Children's Cancer Group (JCCG; AML99 + AML-05 + AML-12).
**P* < 0.05

Supplementary Figure 4. Clinical and genetic characteristics of infants with non-*KMT2A*-rearranged AML

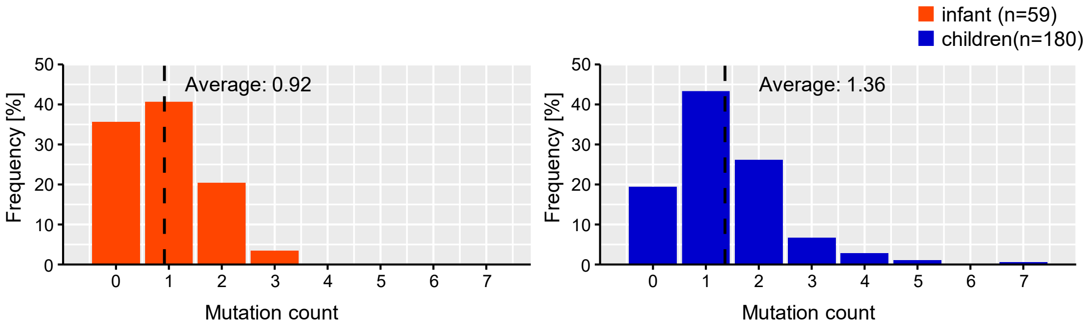


Patient ID	Age (y)	FAB	Fusion gene	Event	Death	*FLT3*	*FLT3*-ITD	*KRAS*	*NRAS*	*PTPN11*	*CBL*	*BRAF*	*KIT*	*SETD2*	*ASXL1*	*ASXL2*	*BCOR*	*CREBBP*	*EP300*	*KDM6A*	*WT1*	*SPI1*	*GATA2*	*RUNX1*	*STAG2*	*SMC3*	*CCND3*	*U2AF1*	*TET2*	trisomy 8	del(7q)
PARKJZ	0.21	-	-	⬛	⬛	⬜	⬜	🟥	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥
PASKRJ	0.78	-	-	⬛	⬛	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PARHXT	0.84	M7	-	⬛	⬛	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PARJWH	0.96	M5	*KAT6A*::*EP300*	⬛	⬛	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥
PATHVG	0.75	M0	-	⬛	⬛	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PARCCH	0.93	M0	*CBFA2T3*::*GLIS2*	⬛	⬛	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PASRRL	0.28	-	-	⬛	⬛	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜
PASBPK	0.44	M5	-	⬛	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PATIAK	0.62	M4	*CBFB*::*MYH11*	⬛	⬜	🟥	⬜	⬜	🟥	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PANKKE	0.71	M4	*CBFB*::*MYH11*	⬛	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PARSHM	0.98	-	*CBFB*::*MYH11*	⬛	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PATILU	0.33	M4	*CBFB*::*MYH11*	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜
PATDLH	0.73	M0	-	⬜	⬜	⬜	⬜	⬜	🟥	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜	⬜

🟥 Mutation (+)
⬜ Mutation (−)
⬛ Event/death
⬜ No event/death

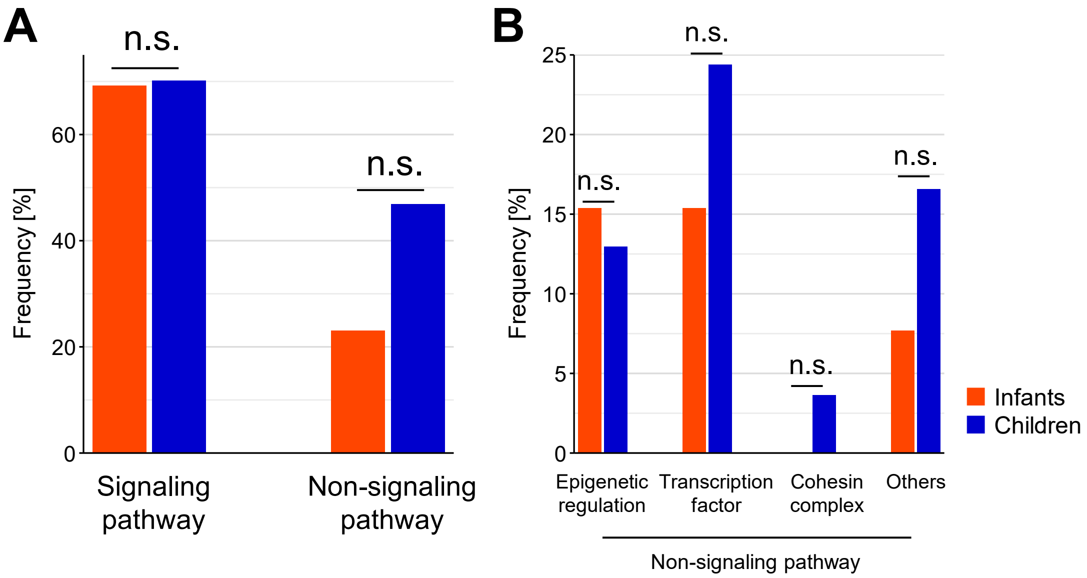
Overview of the patient characteristics and gene mutation landscape in infants and children with non-*KMT2A*-r AML. Abbreviations: FAB, French-American-British classification; *FLT3*-ITD, *FLT3* internal tandem duplications.

Supplementary Figure 5. Comparison of mutation counts between infants and children with *KMT2A*-r AML



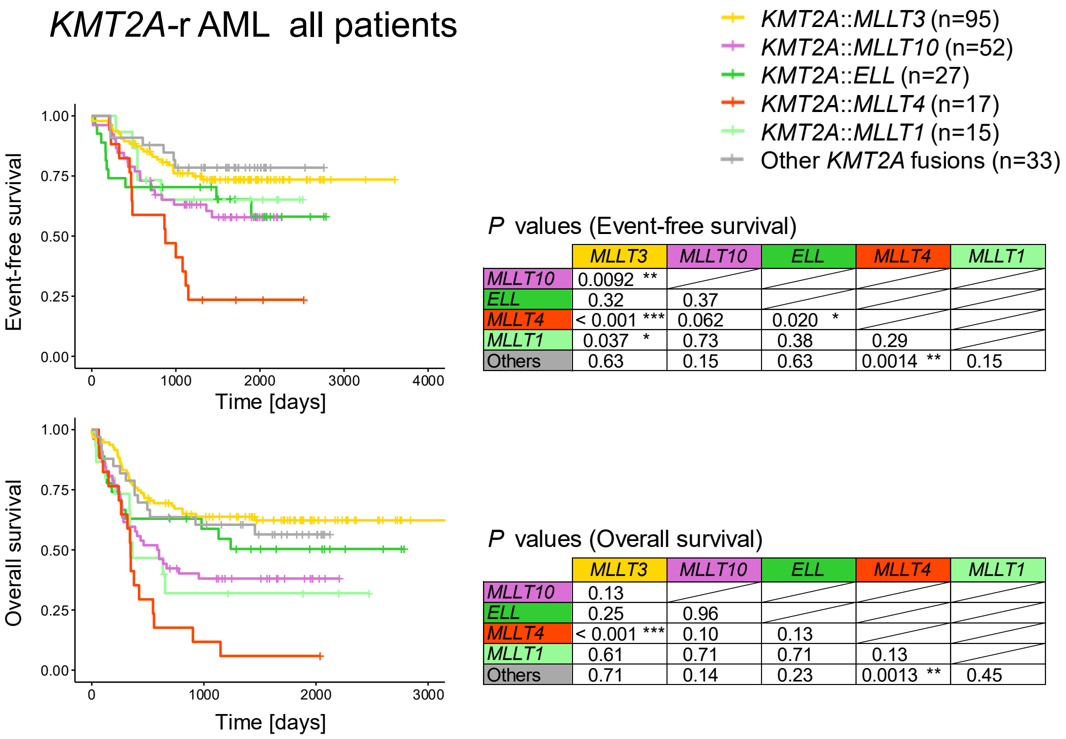
Number of mutated genes between infants and children were compared. Genes with at least one detected mutation are mutation-positive genes, and the number of mutation-positive genes is used as the x-axis. The number of mutation-positive genes per patient was calculated, and the relative frequency was visualized for infants and children, and the dashed line represents the mean value.

Supplementary Figure 6. Comparison of gene mutations in infants and children with non-*KMT2A*-r AML



Comparison of positive mutation rates classified by function between infants and children with non-*KMT2A*-r AML.

Supplementary Figure 7. Comparison of prognosis according to *KMT2A* rearrangement patterns



P values (Event-free survival)

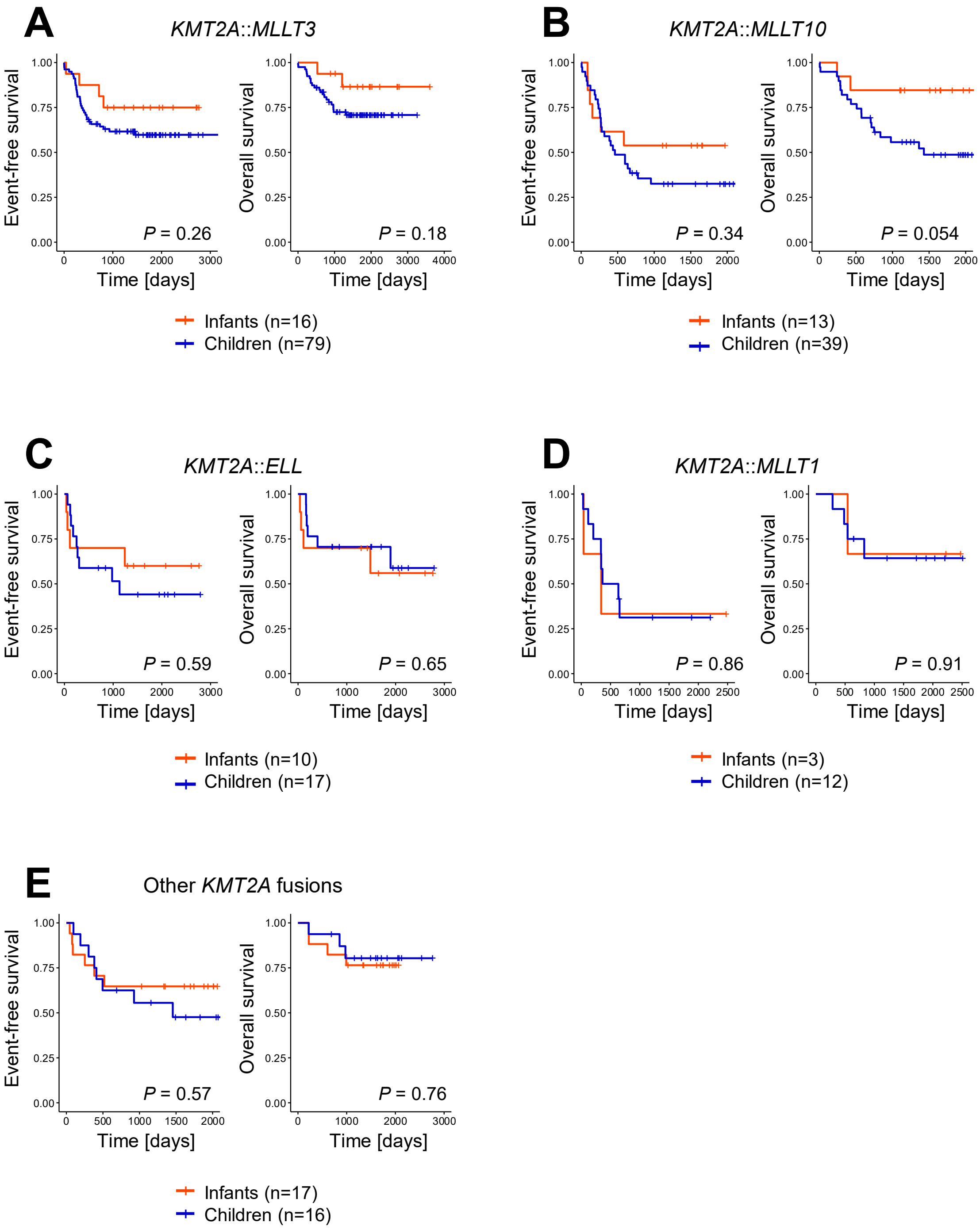
	MLLT3	*MLLT10*	*ELL*	*MLLT4*	*MLLT1*
MLLT10	0.0092 **				
ELL	0.32	0.37			
MLLT4	< 0.001 ***	0.062	0.020 *		
MLLT1	0.037 *	0.73	0.38	0.29	
Others	0.63	0.15	0.63	0.0014 **	0.15

P values (Overall survival)

	MLLT3	*MLLT10*	*ELL*	*MLLT4*	*MLLT1*
MLLT10	0.13				
ELL	0.25	0.96			
MLLT4	< 0.001 ***	0.10	0.13		
MLLT1	0.61	0.71	0.71	0.13	
Others	0.71	0.14	0.23	0.0013 **	0.45

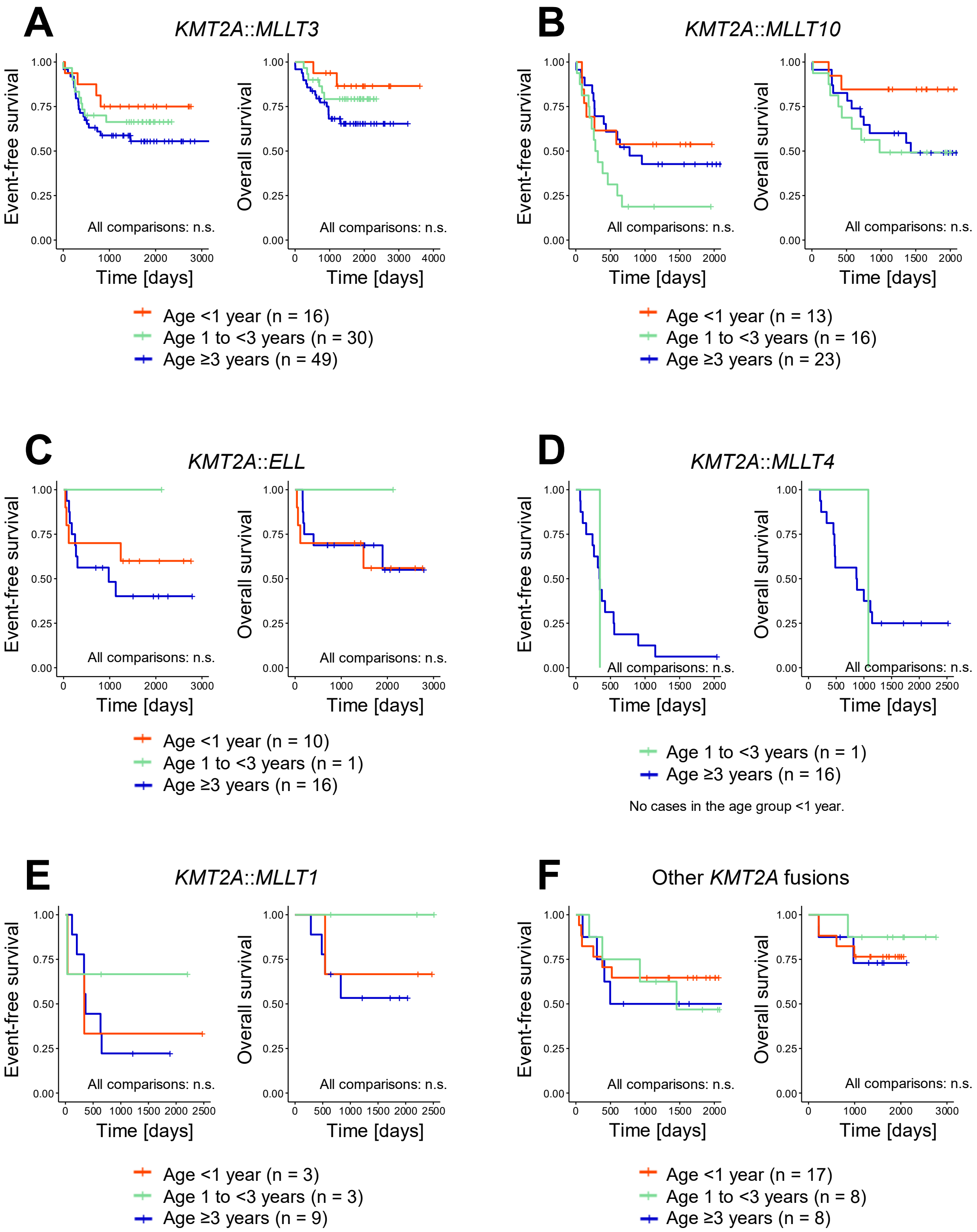
Event-free survival (EFS) and overall survival (OS) according to *KMT2A* rearrangement patterns in patients with *KMT2A*-r AML. The result of pair wised log-rank test is also presented.
**P* < 0.05; ***P* < 0.01; ****P* < 0.001.

Supplementary Figure 8. Comparison of the impact of the *KMT2A* fusion pattern on prognosis in infants and children with AML



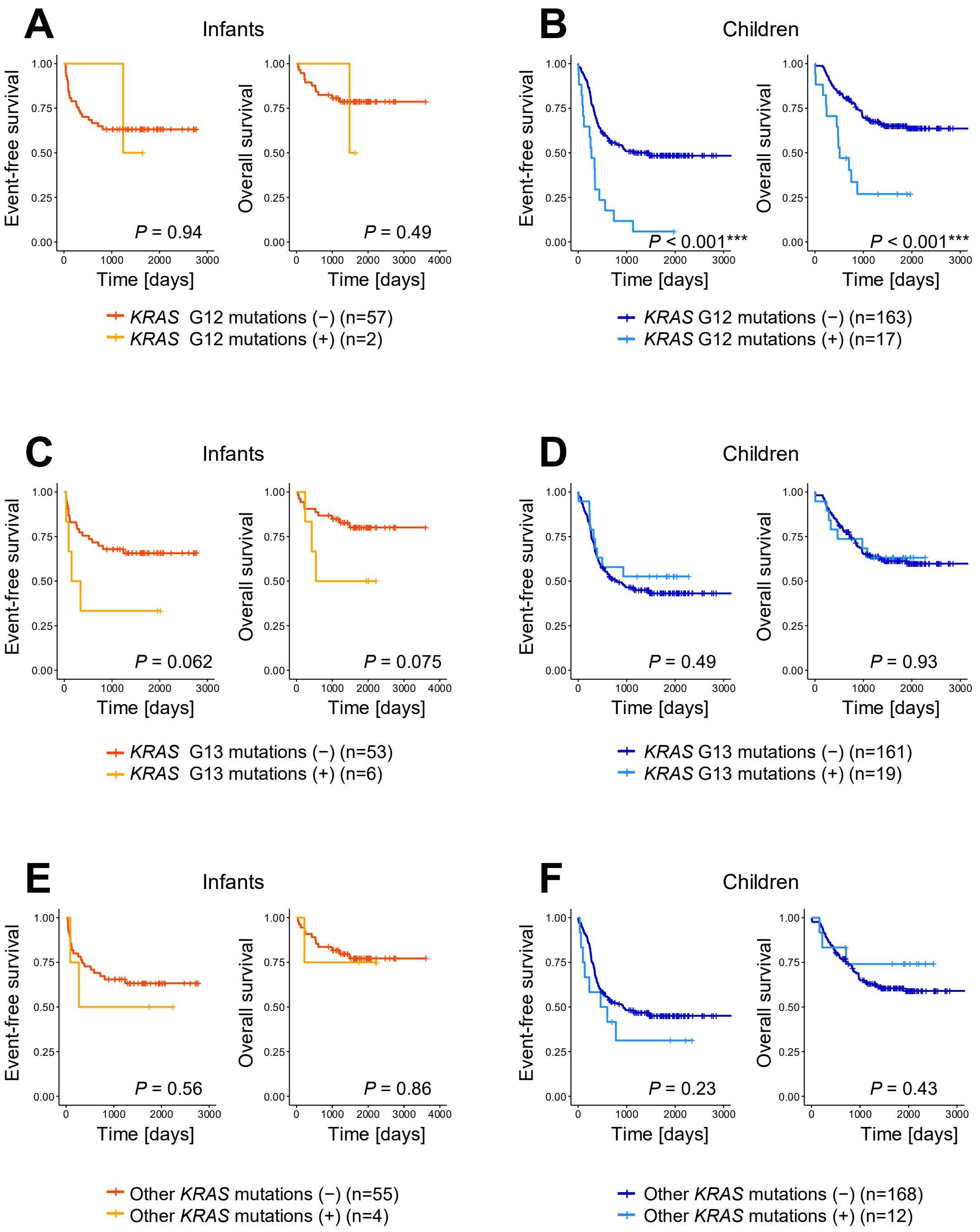
Event-free survival (EFS) and overall survival (OS) between infants and children, stratified by *KMT2A* rearrangement subtype. Analyses were conducted in the following order: **(A)** *KMT2A*::*MLLT3*, **(B)** *KMT2A*::*MLLT10*, **(C)** *KMT2A*::*ELL*, **(D)** *KMT2A*::*MLLT1*, and **(E)** other *KMT2A* fusions.

Supplementary Figure 9. Comparison of the impact of *KMT2A* fusion patterns on prognosis in AML patients stratified by age groups: <1 year, 1 to <3 years, and ≥3 years



Event-free survival (EFS) and overall survival (OS) by three age group (<1 year, 1 to <3 years, and ≥3 years), stratified by *KMT2A* rearrangement subtype. Analyses were conducted in the following order: **(A)** *KMT2A*::*MLLT3*, **(B)** *KMT2A*::*MLLT10*, **(C)** *KMT2A*::*ELL*, **(D)** *KMT2A*::*MLLT4*, **(E)** *KMT2A*::*MLLT1*, and **(F)** other *KMT2A* fusions.

Supplementary Figure 10. Impact of codon-specific *KRAS* mutations on prognosis



(A) Event-free survival (EFS) and overall survival (OS) in infants with *KMT2A*-r AML based on the presence of the *KRAS* G12 mutations. **(B)** EFS and OS in children with *KMT2A*-r AML based on the presence of the *KRAS* G12 mutations. **(C)** EFS and overall survival OS in infants with *KMT2A*-r AML based on the presence of the *KRAS* G13 mutations. **(D)** EFS and OS in children with *KMT2A*-r AML based on the presence of the *KRAS* G13 mutations. **(E)** EFS and OS in infants with *KMT2A*-r AML based on the presence of the other *KRAS* mutations. **(F)** EFS and OS in children with *KMT2A*-r AML based on the presence of the other *KRAS* mutations.
***$P < 0.001$