haematologica
Journal of the Ferrata Storti Foundation

Outcome of infants with acute lymphoblastic leukemia treated with the Chinese Children's Cancer Group Acute Lymphoblastic Leukemia 2015 study protocol

by Alex W.K. Leung, Jiaoyang Cai, Zhi Wan, Jiefen Qin, Yongjun Fang, Lirong Sun, Jiashi Zhu, Shaoyan Hu, Ningling Wang, Pan Gao, Xin Tian, Xiaofan Zhu, Fen Zhou, Xuedong Wu, Xiuli Ju, Xiaowen Zhai, Hua Jiang, Qun Hu, Changda Liang, Liangchun Yang, Hui Zhang, Jingyan Tang, Ju Gao, Ching-Hon Pui, and Chi-kong Li

Received: January 31, 2024.
Accepted: April 10, 2024.

Citation: Alex W.K. Leung, Jiaoyang Cai, Zhi Wan, Jiefen Qin, Yongjun Fang, Lirong Sun, Jiashi Zhu, Shaoyan Hu, Ningling Wang, Pan Gao, Xin Tian, Xiaofan Zhu, Fen Zhou, Xuedong Wu, Xiuli Ju, Xiaowen Zhai, Hua Jiang, Qun Hu, Changda Liang, Liangchun Yang, Hui Zhang, Jingyan Tang, Ju Gao, Ching-Hon Pui, and Chi-kong Li. Outcome of infants with acute lymphoblastic leukemia treated with the Chinese Children's Cancer Group Acute Lymphoblastic Leukemia 2015 study protocol. Haematologica. 2024 Apr 18. doi: 10.3324/haematol.2024.285201 [Epub ahead of print]

Outcome of infants with acute lymphoblastic leukemia treated with the Chinese Children's Cancer Group Acute Lymphoblastic Leukemia 2015 study protocol

Running heads: Outcome of Infants with ALL in CCCG ALL- 2015 protocol

*Alex WK Leung[1]; *Jiaoyang Cai[2]; *Zhi Wan[3]; Jiefen Qin[4]; Yongjun Fang[5]; Lirong Sun[6]; Jiashi Zhu[7]; Shaoyan Hu[8]; Ningling Wang[9]; Pan Gao[10]; Xin Tian[11]; Xiaofan Zhu[12]; Fen Zhou[13]; Xuedong Wu[14]; Xiuli Ju[15]; Xiaowen Zhai[16]; Hua Jiang[17]; Qun Hu[18]; Changda Liang[19]; Liangchun Yang[20]; Hui Zhang[2]; Jingyan Tang[2]; #Ju Gao[3]; #Ching-Hon Pui[21]; #Chi-kong Li[1]

* A.-W.L, J.C., and Z.W. contributed equally as co-first authors.

† JG, C.-H.P., and C.-K.L. contributed equally to this article as principal investigators.

Correspondence: C-K Li, MD., Department of Pediatrics, Hong Kong Children's Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China. 852-35051019; e-mail: ckli@cuhk.edu.hk.

Author Affiliations:

[1]Department of Pediatrics, Hong Kong Children's Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China

[2]Department of Hematology/Oncology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Key Laboratory of Pediatric Hematology & Oncology of China Ministry of Health, and National Children's Medical Center, Shanghai, China

[3]Department of Pediatrics, West China Second University Hospital, Sichuan University, Key Laboratory of Birth Defects and Related Disease of Women and Children, Ministry of Education, Chengdu, China

[4]Department of Hematology/Oncology, Chongqing Medical University Affiliated Children's Hospital, Chongqing, China

[5]Department of Hematology/Oncology, Children's Hospital of Nanjing Medical University, Nanjing, China

[6]Department of Pediatrics, Affiliated Hospital of Qingdao University, Qingdao, China

[7]Department of Hematology/Oncology, Shanghai Children's Hospital, Shanghai, China

[8]Department of Hematology/Oncology, Children's Hospital of Soochow University, Suzhou, China

[9]Department of Pediatrics, Anhui Medical University Second Affiliated Hospital, Anhui, China

[10]Department of Hematology/Oncology, Xi 'an Northwest Women's and Children's Hospital, Xi 'an, China

[11]Department of Hematology/Oncology, KunMing Children's Hospital, Kunming, China

[12]Department of Pediatrics, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

[13]Department of Pediatrics, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[14]Department of Pediatrics, Nanfang Hospital, Southern Medical University, Guangzhou, China

[15]Department of Pediatrics, Qilu Hospital of Shandong University, Jinan, China

[16]Department of Hematology/Oncology, Children's Hospital of Fudan University, Shanghai, China

[17]Department of Hematology/Oncology, Guangzhou Women and Children's Medical Center, Guangzhou, China

[18]Department of Pediatrics, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[19]Department of Hematology/Oncology, Jiangxi Provincial Children's Hospital, Nanchang, China

[20]Department of Pediatrics, Xiangya Hospital Central South University, Changsha, China

[21]Departments of Oncology, Pathology, and Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee, USA.

Acknowledgment: This study was supported by the VIVA China Children's Cancer Foundation, and the American Lebanese and Syrian Associated Charities (to C.-H.P.).

Authorship contributions: C.-K.L., C.-H.P., and J.G. conceived and performed the research, discussed data and wrote the paper; A.W.L., J.C., and Z.W. collated data and provided statistical analysis; and all authors contributed to the manuscript and interpretation of the data and approved the final version of the manuscript.

Data-sharing statement: the original data and protocols are available to other investigators on reasonable request to corresponding author.

The authors declare no competing financial interests.

Word counts: 1500

Tables 2, Figures 1

Clinical trial registration: ChiCTR-IPR-14005706

Infants diagnosed with acute lymphoblastic leukemia (ALL) constitutes a subgroup of patients notorious for their inferior outcome, high risk of treatment failure and susceptibility to treatment-related toxicities when compared to older children with ALL. This subgroup accounts for less than 5% of all paediatric ALL cases, with overall event-free survival (EFS) reported in the range of 40-50%.[1] The presence of *KM2TA*-rearrangement (*KMT2A*-r) is a well-defined prognostic factor for infants with ALL. Despite various multi-centre studies aimed at testing new treatment strategies to enhance outcomes, success has proven elusive.[2-5] The Chinese Children's Cancer Group ALL-2015 (CCCG-ALL-2015) study, a multicenter collaboration in China for the treatment of pediatric ALL, has published its results elsewhere.[6,7] In this report, we present the treatment outcomes of the infant patients enrolled in this study and analyze the factors influencing treatment outcomes.

Patients were enrolled between January 2015 and December 2019. Written informed consent was obtained from patient's parents or legal guardian. All infants were categorized into intermediate-risk (IR) or high-risk (HR) group. Infants aged < 6 months and *KMT2A*-r and a presenting white cell count (WCC) ≥ $300x10^9$/L, or those experiencing induction failure defined by the presence of ≥ 5% blast on morphology assessment of the day 46 bone marrow aspirate or minimal residual disease (MRD) ≥ 1%, were stratified to HR group. Dose adjustments based on age were not implemented in this study.

EFS was computed from diagnosis to the first adverse event, including induction failure, relapse, death from any cause, development of a second malignant neoplasm, withdrawal upon parental request, or off-protocol by the decision of the treating physician. Overall survival (OS) was defined as the duration from diagnosis to death due to any cause. Outcome data were updated on December 2022. The cumulative incidence of relapse (CIR) and treatment-related fatal infections were estimated by Kalbfleisch and Prentice and compared with Grey's test. The Kaplan–Meier method was used to estimate EFS and OS. The Cox hazards model was used for univariate or multivariate analyses. Statistical analyses were performed using R software, version 3.6.3 and SPSS 25.0. A 2-tailed p value of <0.05 was considered statistically significant.

Among the 134 enrolled infant ALL, the median age was 254 days (range 46–364 days) (Supplementary Table S1). The median WCC was 62.7 (1.3–$777x10^9$/L), with 11.2% having a WCC≥$300x10^9$/L. There were 71 (53.0%) having *KMT2A-r* ALL (median age 7.4 months) and 63 had *KMT2A*-g ALL (median age 9.4 months). Among the 71 *KMT2A*-r, 60 had fusion partners identified, 32 (53.3%) had *KMT2A::AFF1* fusion, 10 (16.7%) had *KMT2A::MLLT1*, 15 (25%) had *KMT2A::MLLT3*, and 3 (5%) had *KMT2A::MLLT10*. In the *KMT2A*-r patients, 20 (27.8%) were age <6 months at diagnosis and 12 (16.9%) had a presenting WCC≥$300x10^9$/L, with 5 being both < 6 months and WCC ≥$300x10^9$/L, thus classified as HR. WCC >$300x10^9$/L was less commonly encountered in the *KMT2A*-g patients, occurring in 3 (4.8%).

As of December 2022, with a median follow up of 4.2 years (range, 0.08 - 7.2 years), 45 patients had deceased. Eighteen subjects (13.4%) experienced discontinuation of protocol specified treatment, 10 were withdrawn upon parental request. (Supplementary Figure S1) For the entire cohort, the 5-year EFS was 52.1% (95%CI 44.2-61.4%) and the 5-year OS was 66.1 (95%CI 58.4-74.8%). The 5-year EFS and OS for *KMT2A*-g versus *KMT2A*-r were 69.8 (95% CI 59.3-82.1%) versus 35.6% (95%CI 25.7-49.4%) (p < 0.001), and 74.6% (95%CI 64.5-86.1%) versus 58.1% (95%CI 47.2-71.5%) (p = 0.02), respectively. (Figure 1A and B) The complete remission (CR) rate for the entire group was 89.6% (120/134). The CR rate was 81.6% (58/71) for *KMT2A-r* ALL and 98.4% (62/63) for *KMT2A-g* ALL. On day 5 of induction therapy (i.e.

after 4 days of oral dexamethasone), 86 patients had peripheral blood blast count available, with 63 showing blast count dropped to below $1x10^9$/L, considered as good responders. There was no statistically significant difference in the EFS and OS between the dexamethasone good responder and poor responder.

For the entire group, MRD negativity on day 19 and day 46, IR group, and *KMT2A-g* had superior EFS on univariate analysis, and the MRD negativity on day 19, IR group and *KMT2A-g* remained significant on multivariate analysis. (Table 1) Among *KMT2A*-r patients, factors associated with an inferior EFS were < 3 months and day 19 and day 49 MRD positive (Table 2). *KMT2A*-r subtypes had no prognostic value for EFS and OS (Figure 1C and D). For *KMT2A*-r subgroup, multivariate analysis of EFS only showed day 19 with MRD >0.01% as a significant factor (p=0.008). Presenting WCC over $100x10^9$/L was of prognostic significance in the *KMT2A-g* group, with inferior OS (55% vs 83.7%, p=0.01) and EFS (50% vs 79%, p=0.01). Dexamethasone poor response was associated with a poorer EFS among *KMT2A*-g subgroup (p=0.009). (Supplementary Table S2)

The infection rates for sepsis, severe pneumonia and invasive fungal infection were 44.8% (60/134), 17.9% (24/134) and 9.0% (12/134). There were 18 deaths in remission, including 8 severe pneumonia (44.4%), 7 septic shock (38.9%), 2 invasive fungal infections (11.1%) and 1 third-degree atrioventricular block (5.6%). The cumulative incidence of fatal infection during the entire treatment was 13.5% (95% CI 7.7-19.3%). Twenty-nine recurrence (21.6%) occurred at a median of 15.7 months (range 1.6 month to 39.2 months); five patients relapsed more than 2 years post-diagnosis. Among these, 23 (17.2%) relapses manifested in the bone marrow, two (3% in male patients) were isolated testicular relapse, three (2.2%) were isolated CNS recurrences and one (0.7%) involved combined bone marrow and CNS relapse. The 5-year CIR for the entire group was 23.0% (15.7-30.3%). The 5-year CIR was 30.2% (95% CI, 18.8-41.6%) in the *KMT2A*-r subgroup and 15.9% (95% CI, 6.8-25.0%) in the *KMT2A*-g subgroup (p = 0.05).

Seven subjects underwent HSCT without chimeric antigen receptor T-cell therapy (CAR-T therapy), all of whom had *KMT2A-r*. HSCT timing ranged from 4.2 - 33.8 months post-diagnosis. Among transplant recipients, three subjects died of progressive and refractory disease, one succumbed to an accident, and the remaining three subjects were alive with a duration follow up of 37.5 to 51.1 months. Six patients received CAR-T therapy, 2 received CD19 and 4 received CD19/CD22. Five patients received HSCT after CAR-T, with a mean interval of 71 days from CAR-T and they remained in remission. Notably, the subject with *KMT2A-g* who did not receive HSCT post CAR-T experienced a second relapse six months post-CAR-T therapy, and succumbed to progressive disease ten months later.

This cohort of infants with ALL is part of the CCCG-ALL-2015 study which had enrolled 7640 subjects. The infant cohort, constituting approximately 1.7% of the entire CCCG-ALL-2015 protocol, was notably lower than the anticipated 3-4% based on comparisons with other studies. Within our cohort, the percentage of infants under 6 months of age at diagnosis was 18.4%, significantly lower than the 50-68% reported in previous studies.[3,8] Moreover, Infants with *KMT2A-r* was observed in 53.0% of the enrolled subjects, a figure also below the 74-83% reported in other studies.[3,8] It is noteworthy that high-risk subjects appeared to be under-represented in our enrolled patients. Additionally, only 11% of our subject had WCC > $300x10^9$/L, significantly lower than that in the Interfant 06 and JPLSG MLL10 studies, which reported 29% and 30% respectively.[3,8] (supplementary Table S3)

In our study, first lumbar puncture (LP) and CNS assessment was deferred to day 5 of induction and demonstrated a lower CNS involvement after 4 days of dexamethasone prophase. The isolated CNS relapse rate was 2.2% and combined BM and CNS relapse was 0.7%, contrasting with isolated CNS relapse rate of 11.9% in the Interfant 06 study.[3] Performing LP when the blast count in peripheral blood was reduced after the pre-phase treatment might be a safer approach. Notably, CNS relapse rate remained low despite a relatively high rate of traumatic LP (~10%) in our cohort.

The early treatment related mortality was high in our cohort, with 10 fatal infections (7.5%) occurring in induction period; this rate surpasses that reported in the Interfant-99 protocol (3.8%).[2] Recognizing the critical role of supportive care in the early phase of therapy, particular in developing countries, is essential for enhancing outcomes. Implementing dose modification during the induction could also contribute to reducing early mortality.[9] To mitigate treatment-related mortality during the early intensive phase, we developed a dedicated Infant ALL study with age-adjusted dose approach and blinatumomab.

Blinatumomab, recently investigated in a pilot study based on the Interfant regimen, demonstrated remarkable early results.[10] CAR-T therapy, performed in patients with relapsed or refractory ALL, raises concerns about lineage switch, particularly in patients with mixed-phenotype acute leukemia, where the B-lineage is the target.[11,12] Instances of myeloid leukaemia have been reported in infants after achieved remission with ALL treatment post-blinatumomab therapy or CAR-T therapy.[13-15] Consolidative HSCT after CAR-T therapy has shown success in our cohorts. In conclusion, the CCCG-2015-Study had a low percentage of patients being infants as well as *KMT2A-r*. Despite, high treatment-related mortality, the relapse rate was not excessively high. Dexamethasone prophase may offer protection against CNS relapse in infants. CAR-T therapy followed by allogeneic HSCT should be explored in future studies.

Reference

1. Hilden JM, Dinndorf PA, Meerbaum SO, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. Blood. 2006;108(2):441-451.
2. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet. 2007;370(9583):240-250.
3. Pieters R, De Lorenzo P, Ancliffe P, et al. Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study. J Clin Oncol. 2019;37(25):2246-2256.
4. Dreyer ZE, Hilden JM, Jones TL, et al. Intensified chemotherapy without SCT in infant ALL: results from COG P9407 (Cohort 3). Pediatr Blood Cancer. 2015;62(3):419-426.
5. Brown PA, Kairalla JA, Hilden JM, et al. FLT3 inhibitor lestaurtinib plus chemotherapy for newly diagnosed *KMT2A*-rearranged infant acute lymphoblastic leukemia: Children's Oncology Group trial AALL0631. Leukemia. 2021;35(5):1279-1290.
6. Yang W, Cai J, Shen S, et al. Pulse therapy with vincristine and dexamethasone for childhood acute lymphoblastic leukaemia (CCCG-ALL-2015): an open-label, multicentre, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2021;22(9):1322-1332 .
7. Tang J, Yu J, Cai J, et al. Prognostic factors for CNS control in children with acute lymphoblastic leukemia treated without cranial irradiation. Blood. 2021;138(4):331-343.
8. Tomizawa D, Miyamura T, Imamura T, et al. A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial. Blood. 2020;136(16):1813-1823.
9. Salzer WL, Jones TL, Devidas M, et al. Decreased induction morbidity and mortality following modification to induction therapy in infants with acute lymphoblastic leukemia enrolled on AALL0631: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2015;62(3):414-418.
10. van der Sluis IM, de Lorenzo P, Kotecha RS, et al. Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia. N Engl J Med. 2023;388(17):1572-1581.
11. Stasik C, Ganguly S, Cunningham MT, Hagemeister S, Persons DL. Infant acute lymphoblastic leukemia with t(11;16)(q23;p13.3) and lineage switch into acute monoblastic leukemia. Cancer Genet Cytogenet. 2006;168(2):146-149.
12. Jacoby E, Nguyen AM, Fountaine TJ. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. Nat Commun. 2016,7:12320.
13. Du J, Chisholm KM, Tsuchiya K, et al. Lineage Switch in an Infant B-Lymphoblastic Leukemia With t(1;11)(p32;q23); KMT2A/EPS15, Following Blinatumomab Therapy. Pediatr Dev Pathol. 2021;24(4):378-382.
14. Rayes A, McMasters RL, O'Brien MM. Lineage Switch in MLL-Rearranged Infant Leukemia Following CD19-Directed Therapy. Pediatr Blood Cancer. 2016;63(6):1113-1115.
15. Leahy AB, Devine A, Li Y, et al. Impact of high-risk cytogenetics on outcomes for children and young adults receiving CD19-directed CAR T-cell therapy. Blood. 2022;139(14):2173-2185

Table 1. Risk analysis of Event-free Survial in infants Acute Lymphoblastic Leukemia.

		Univariate analysis		Multivariate analysis	
	N(%)	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
KMT2A status					
KMT2Ag	63(47.0)	1		1	
KMT2Ar	71(53.0)	3.1(1.8-5.3)	<0.001	2.8 (1.4-5.8)	0.005
Age					
>=3 months	131(97.8)	1			
<3 months	3 (2.2)	2.2(0.5-9.0)	0.27		
>= 6 months	109(81.3)	1			
< 6 months	25(18.7)	1.3(0.7-2.4)	0.39		
>=9 months	55(41.0)	1			
< 9months	79(59.0)	1.5(0.9-2.4)	0.15		
Final risk group					
IR*	126(94.7)	1		1	
HR*	7(5.3)	3.8(1.6-9.0)	0.002	3.5(1.1-11.4)	0.04
Sex					
Female	69(51.5)	1			
Male	65(48.5)	1.1(0.7-1.9)	0.62		
CNS status					
CNS1	112(83.6)	1			
CNS2	5(3.7)	0.9(0.2-3.5)	0.84		
CNS3	2(1.5)	1.0(0.1-7.4)	0.98		
Traumatic	15(11.2)	1.5(0.8-3.1)	0.23		
WBC x (10^9/L)					
<100	78(58.2)	1			
>=100	56(41.8)	1.7(1.0-2.7)	0.09		
<300	119(88.8)	1			
>=300	15(11.2)	1.8(0.9-3.7)	0.10		
Day5 blast (Dexamethasone response x10^9/L)					
Good response (blast <1)	63(73.3)	1			
Poor response (blast >=1)	23(26.7)	1.8(0.9-3.4)	0.09		
Day19 MRD					
Day 19MRD<0.01%	67(57.3)	1		1	
Day 19MRD>=0.01%	50(42.7)	2.4(1.4-4.3)	0.002	3.8(1.8-8.2)	<0.001
Day 46 MRD					
Day 46MRD<0.01%	88(87.1)	1		1	
Day 46MRD>=0.01%	13(12.9)	3.0(1.4-6.7)	0.006	1.3(0.5-3.3)	0.59

IR*: Intermediate Risk, HR*: High Risk, MRD: Minimal residual disease

Table 2. Treatment outcome according to selected clinical and biological characteristics in infants with *KMT2A*-r ALL

	N(%)	5-year Event-free survival (95%CI)	P-value	5-year Overall Survival (95%CI)	P-value
KMT2A subtype			0.4		0.3
AFF1+ *MLLT1*	42(59.2)	34.4(22.5-52.7)		56.1(42.8-73.6)	
MLLT3 + *MLLT10* + others	29(40.8)	38.3(23.6-62.2)		60.6(43.6-84.0)	
			0.9		0.9
AFF1	32(45.1)	35.9(22.4-57.5)		59.4(44.6-79.1)	
MLLT1+ *MLLT3* + *MLLT10* + others	39(54.9)	35.6(22.7-55.6)		56.7(41.8-76.8)	
Age			0.02		<0.001
<3 months	2(2.8)	0		0	
>=3 months	69(97.2)	36.7(26.5-50.8)		59.8(48.8-73.3)	
			0.9		0.4
< 6 months	19(26.8)	36.8(20.4-66.4)		50.0(31.5-79.4)	
>= 6 months	52(73.2)	35.6(24.2-52.2)		61.2(48.7-76.8)	
			0.3		0.4
< 9months	54(76.1)	35.3(24.4-51.0)		57.4(45.3-72.6)	
>=9 months	17(23.9)	39.2(21.1-72.8)		62.3(42.2-92.0)	
Final risk group			0.06		0.01
IR	64(90.1)	37.9(27.3-52.8)		61.4(50.0-75.4)	
HR	7(9.9)	14.3(2.3-87.7)		28.6(8.9-92.2)	
Sex			0.8		0.8
Male	33(46.5)	36.7(22.8-58.9)		57.9(42.6-78.7)	
Female	38(53.5)	35.1(22.6-54.6)		58.9(44.9-77.3)	
CNS status			0.3		0.02
CNS1	57(80.3)	37.3(26.1-53.4)		62.7(50.7-77.5)	
CNS2	4(5.6)	50.0(18.8-100)		75.0(42.6-100)	
CNS3	1(1.4)	0		0	
Traumatic	9(12.7)	11.1(1.8-70.5)		11.7(2.0-78.2)	
WBC ($x10^9$/L)			0.9		0.8
>=100	36(50.7)	37.5(24.2-58.1)		59.0(44.6-78.1)	
<100	35(49.3)	33.5(20.6-54.5)		56.0(40.4-77.6)	
			0.3		0.02
>=300	12(16.9)	33.3(15.0-74.2)		38.1(17.9-81.1)	
<300	59(83.1)	35.8(24.9-51.1)		62.0(50.1-76.6)	
Day5 blast (Dexamethasone response, $x10^9$/L)			0.3		0.7
Good response (blast <1)	30(78.9)	33.0(19.7-55.2)		55.6(40.1-76.9)	
Poor response (blast	8(21.1)	25.0(7.5-83.0)		50.0(25.0-100)	

>=1)					
Day 19MRD			0.001		0.07
Day 19MRD<0.01%	34(54.8)	59.3(44.0-79.9)		75.8(62.5-91.9)	
Day 19MRD>=0.01%	28(45.2)	15.2(6.2-37.3)		50.8(34.9-74.1)	
Day 46MRD			<0.001		0.001
Day 46MRD<0.01%	39(83.0)	58.9(44.6-77.8)		87.0(76.9-98.3)	
Day 46MRD>=0.01%	8(17.0)			37.5(15.3-91.7)	

IR: Intermediate risk, HR: High risk, MRD: Minimal residual disease

Figure Legends

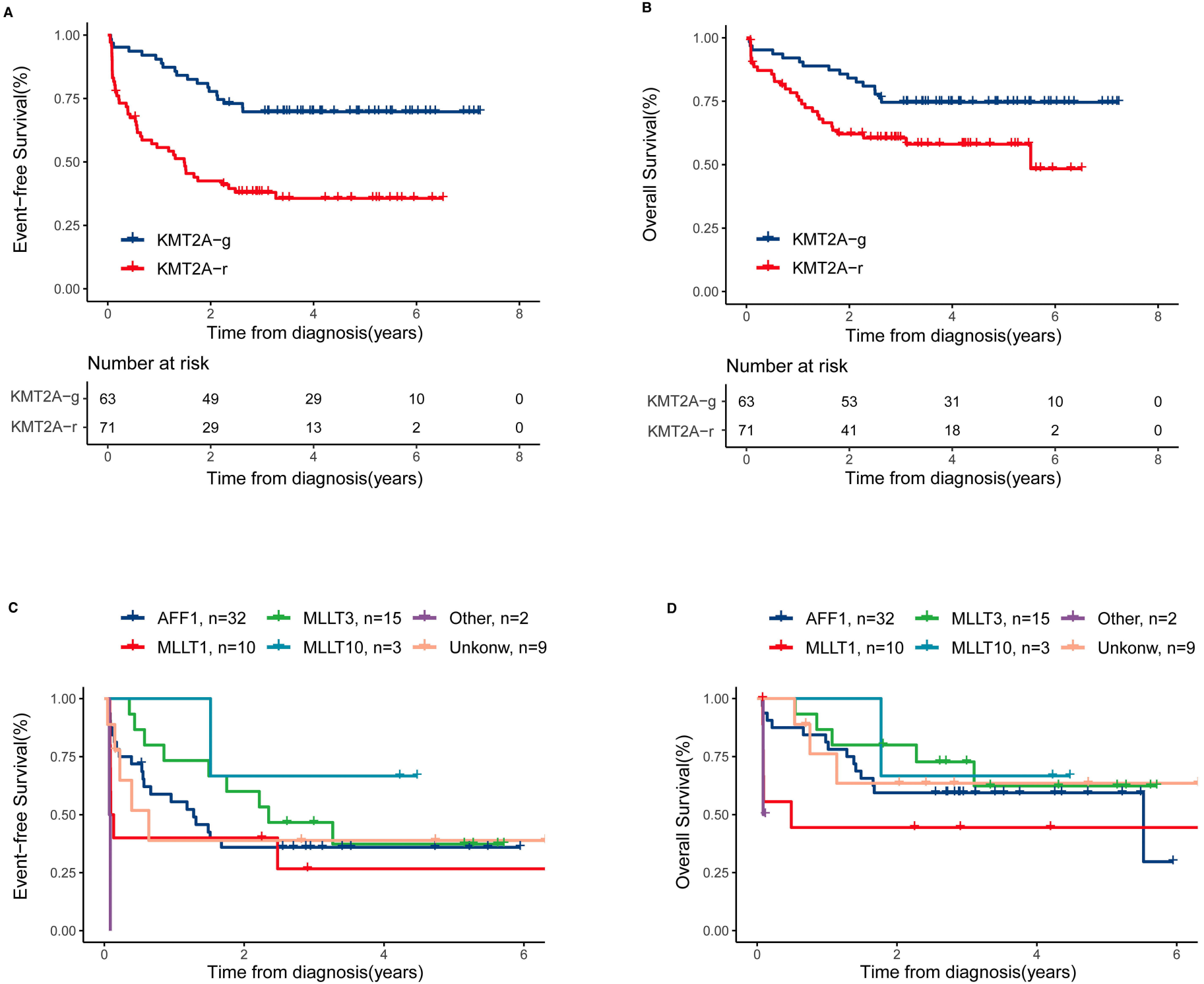
Figure 1: 5-year Event-free survival and Overall Survival of Infant ALL according to genetic subtypes.

A: 5-year EFS of KMT2A-r group compared with KMT2A-g group, EFS 69.8 (95% CI 59.3-82.1%) versus 35.6%(95%CI 25.7-49.4%) ($p < 0.001$)

B: 5-year OS of KMT2A-r group compared with KMT2A-g group, 74.6% (95%CI 64.5-86.1%) versus 58.1% (95%CI 47.2-71.5%) ($p = 0.02$)

C: The EFS of the various KMT2A-r subtypes

D: The OS of the various KMT2A-r subtypes


A
Event−free Survival(%)
1.00
0.75
0.50
0.25
0.00
KMT2A−g
KMT2A−r
0
2
4
6
8
Time from diagnosis(years)
Number at risk
KMT2A−g 63 49 29 10 0
KMT2A−r 71 29 13 2 0
Time from diagnosis(years)
B
Overall Survival(%)
KMT2A−g
KMT2A−r
Time from diagnosis(years)
Number at risk
KMT2A−g 63 53 31 10 0
KMT2A−r 71 41 18 2 0
Time from diagnosis(years)
C
AFF1, n=32
MLLT3, n=15
Other, n=2
MLLT1, n=10
MLLT10, n=3
Unkonw, n=9
Event−free Survival(%)
Time from diagnosis(years)
D
AFF1, n=32
MLLT3, n=15
Other, n=2
MLLT1, n=10
MLLT10, n=3
Unkonw, n=9
Overall Survival(%)
Time from diagnosis(years)

Supplementary Table S1 Characteristics of infants ALL.

Characteristic	All	*KMT2A-g*	*KMT2A-r*	P value
Age	No. (%)	No. (%)	No. (%)	0.99
<3 months	3 (2.2)	1(1.6)	2(2.8)	
>=3 months	131(97.8)	62(98.4)	69(97.2)	
				0.01
< 6 months	25(18.7)	6(9.5)	19(26.8)	
>= 6 months	109(81.3)	57(90.5)	52(73.2)	
				<0.001
< 9months	79(59.0)	25(39.7)	54(76.1)	
>=9months	55(41.0)	38(60.3)	17(23.9)	
Final risk group				0.01
IR	126(94.7)	63(100)	64(90.1)	
HR	7(5.3)	0(0)	7(9.9)	
Sex				0.73
Male	65(48.5)	32(50.8)	33(46.5)	
Female	69(51.5)	31(49.2)	38(53.5)	
CNS status				0.64
CNS1	112(83.6)	55(87.3)	57(80.3)	
CNS2	5(3.7)	1(1.6)	4(5.6)	
CNS3	2(1.5)	1(1.6)	1(1.4)	
Traumatic	15(11.2)	6(9.5)	9(12.7)	
WCC				0.04
>=100	56(41.8)	20(31.7)	36(50.7)	
<100	78(58.2)	43(68.3)	35(49.3)	
				0.03
>=300	15(11.2)	3(4.8)	12(16.9)	
<300	119(88.8)	60(95.2)	59(83.1)	
Day5 blast (Dexamethasone response, $x10^9$/L)				0.33
Good response (blast <1)	63(73.3)	33(68.7)	30(78.9)	
Poor response (blast >=1)	23(26.7)	15(31.3)	8(21.1)	
Day19MRD				0.58
Day19MRD <0.01%	67(57.3)	33(60.0)	34(54.8)	
Day19MRD >=0.01%	50(42.7)	22(40.0)	28(45.2)	
Day46MRD				0.37
Day46MRD <0.01%	88(87.1)	49(90.7)	39(83.0)	
Day46MRD >=0.01%	13(12.9)	5(9.3)	8(17.0)	

Supplementary Table S2 Treatment outcome according to selected clinical and biological characteristics in infants with *KMT2A*-g ALL

	N(%)	5-year Overall Survival (95%CI)	P-value	5-year Event-free survival (95%CI)	P-value
Age			0.6		0.5
<3 months	1(1.6)	100		100	
>=3 months	62(98.4)	74.2(64.0-85.9)		69.3(58.7-81.8)	
			0.7		0.5
< 6 months	6(9.5)	83.3(58.3-100)		83.3(58.3-100)	
>= 6 months	57(90.5)	73.6(63.0-86.0)		68.3(57.2-81.6)	
			0.4		0.3
< 9months	25(39.7)	79.8(65.4-97.3)		76.0(61.0-94.7)	
>=9 months	38(60.3)	71.1(58.0-87.0)		65.8(52.3-82.7)	
Sex			0.2		0.2
Male	32(50.8)	68.8(54.4-86.8)		62.3(47.6-81.7)	
Female	31(49.2)	80.6(67.9-95.8)		77.4(64.0-93.6)	
CNS status			0.2		0.1
CNS1	55(87.3)	74.5(63.8-87.0)		69.1(57.9-82.4)	
CNS2	1(1.6)	100		100	
CNS3	1(1.6)	0		0	
Traumatic	6(9.5)	83.3(58.3-100)		83.3(58.3-100)	
WCC			0.01		0.01
>=100	20(31.7)	55.0(37.0-81.8)		50.0(32.3-77.5)	
<100	43(68.3)	83.7(73.4-95.5)		79.0(67.7-92.2)	
			0.8		0.99
>=300	3(4.8)	66.7(30.0-100)		66.7(30.0-100)	
<300	60(95.2)	75.0(64.8-86.8)		69.9(59.2-82.6)	
Day5 blast (Dex response)			0.07		0.009
Good response (blast <1)	33(68.7)	81.7(69.5-96.1)		78.8(66.0-94.0)	
Poor response (blast >=1)	15(31.3)	60.0(39.7-90.7)		46.7(27.2-80.2)	
Day19MRD			0.3		0.4
Day19MRD<0.01	33(60.0)	84.8(73.5-98.0)		78.8(66.0-94.0)	
Day19MRD>=0.01	22(40.0)	72.7(56.3-93.9)		68.2(51.3-90.7)	
Day46MRD			0.9		0.9
Day46MRD<0.01	49(90.7)	81.6(71.5-93.2)		75.5(64.3-88.5)	
Day46MRD>=0.01	5(9.3)	80.0(51.6-100)		80.0(51.6-100)	

Supplementary Table S3: Comparison of Infant ALL studies

	CCCG 2015	Interfant 99	Interfant 06	Japan MLL-10	COG AALL0631
No. of patients (total ALL)	134 (7640, =1.7%)	482	651	90	210
Age					
<3 months	2.2% (3)	23%	21.1%	24%	Germline median 281 Day, Rearranged median 169 Day.
3-<6 months	16.4% (22)	25%	29%	41%	
6-<9 months	40.3% (54)	25%	26.9%	34% (>6 month)	
9-<12 months	42% (55)	26%	23%		
WCC x(10^9/L)					
<100	58.2%	44%	47%	49%	Germline 38
100-300	30.6%	29%	23.7%	31%	Rearranged 160
>300	11.2%	27%	29%	30%	
CNS disease	1.5%	9%	12.7%	11%	10%
Yes	88% (4.5%CNS2)	76%	65.6%	88% (CNS1 or2)	83.8% (CNS2 35.2%)
No		15%	21.7%		
unknown	10.4% Traumatic			1%	
***KMT2A* status**					
Unknown		86 (18%)	8 (1.2%)		
Germline	63 (47%)	82 (17%)	167 (25.7%)	15 (17%)	64 (30.4%)
Rearranged	71 (53%)	314 (65%)	476 (73.1%)	75 (83%)	146 (69.5%)
AFF1	45%	53%	43.9%	52%	
MLLT3	21%	11%	10.9%	8%	

MLLT1 *MLLT10* others	14% 4.2% 15.5%	20% 16%	21.7% 23.5%	20% 20%	
Induction remission (germline vs rearranged)	89.6% (98.4% -g, 81.6% -r)	93.7% (97% SR, 88% HR)	92.9% (93% NHR, 87.2% HR)	91% (100% -g, 89.3% -r)	(89% for germline)
Deaths in induction	7.5%	3.8%	3.7%	0	(0 for germline)
Resistant disease	0.7%	2.5%	3.4%	5.5%	
Death in CR	4.4%	5.2%	7.1%	2.2%	(0 for germline)
Overall survival (germline vs rearranged)	67.1% (75.4% vs 54.3%)	55%	58.2% (87.2% vs 48%)	85% (82%)	(93.6% germline)
Event-free Survival (germline vs rearranged)	65.4% (69.8% vs 38%)	47% (74.5% vs 36.4%)	46.1% (73.9% vs 36.4%)	70.9% (93.3% vs 66.2%)	(87.3% germline)

CCCG: Chinese Children's Cancer Group, COG: Children's Oncology Group, CR: complete remission

Supplementary Figure S1: Clinical outcome of 134 enrolled patients under CCCG ALL 2015 Study