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Superior survival with allogeneic hematopoietic stem cell transplantation *versus* chemotherapy for high-risk adult acute lymphoblastic leukemia in a PDT-ALL-2016 pediatric-inspired cohort

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Authors' contribution

Hongsheng Zhou and Junjie Chen contributed to the conception of the study. Jieping Lin, Zhixiang Wang, Jiawang Ou, Xiuli Xu, Bingqing Tang, Chenhao Ding, Jia Li, Ren Lin, Ting Zhang, Li Xuan contributed to the provision of study materials and acquisition of the clinical data. Junjie Chen, Zihong Cai, Zicong Huang, Jieping Lin, Zhixiang Wang performed the statistical analyses. Junjie Chen, Zihong Cai, Zicong

Huang drafted the manuscript. Hongsheng Zhou and Qifa Liu revised the final manuscript. All authors reviewed the final manuscript and consented to submission. Junjie Chen, Zihong Cai, Zicong Huang contributed equally to this work.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest statement

The authors declare no conflict of interest.

The role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has undergone gradual changes in adult acute lymphoblastic leukemia (ALL). In the era of conventional adult chemotherapy regimen, MRC UKALLXII/ E2993 study have demonstrated that allo-HSCT is superior to consolidation chemotherapy in adult ALL patients in first complete remission (CR1)[1]. This supports the critical role of allo-HSCT as a post-remission treatment for adult ALL, including standard risk (SR) and high risk (HR) ALL. As pediatric-inspired regimen remarkably improved the survival of adolescents and young adult ALL (AYA ALL)[2], allo-HSCT was less pronounced as post-remission therapy. Several studies compared outcomes between pediatric-like regimen and allo-HSCT in adult ALL, revealing that allo-HSCT does not exhibit superiority over pediatric-inspired regimen[3, 4]. However, these studies did not provide a clear conclusion regarding the benefit of allo-HSCT in HR-ALL. PETHEMA ALL-HR-11 study showed that avoiding allo-HSCT did not hamper the outcomes of HR-ALL patients[5]. GRAALL 2003/2005 study found that allo-HSCT could improve the survival in the minimal residual disease (MRD)-positive subgroup, but not in the MRD-negative population[6].

In present study, we designed a PDT-ALL-2016 pediatric-inspired protocol, in which allo-HSCT was allocated post-consolidation, instead of post-remission, as a total-therapy regimen. Herein, we demonstrated that allo-HSCT post-consolidation exhibited superior survival versus chemotherapy for HR-ALL regardless of MRD

status, in the PDT-ALL-2016 pediatric-inspired cohort.

We analyzed 245 consecutive adults with HR-ALL diagnosed at Nanfang Hospital from January 2016 to December 2021, with outcomes updated in January 2023. Patients in this study were enrolled from PDT-ALL-2016 pediatric-inspired cohort, a GRAALL-2003 backbone, PEG-asparaginase-intensified, pediatric-inspired regimen[7, 8]. The study was approved by the Institutional Review Board of the Nanfang Hospital. Inclusion criteria for this study encompassed patients with any high-risk features, all of whom achieved complete remission (CR) and received allo-HSCT at CR1[6, 9]. High risk features included:(1) white blood cell count (WBC) count $\geq 30\times10^9$/L for B-ALL or 100×10^9/L for T-ALL; (2) presence of t(9;22), t(1;19), t(4;11) or any other 11q23 rearrangements; (3) complex karyotype, hypodiploid, or near-triploid; (4) pro-B or early T-cell precursor (ETP) immunophenotype; (5) Philadelphia chromosome-like (Ph-like) or IKZF1-deleted (IKZF1del) subtype.

Patients were assigned to either the chemotherapy cohort or the transplant cohort after consolidation therapy, according to the donor availability and their individual preferences and decisions[10-12] (the haploidentical related donor (HID) donor should younger than 45 years). MRD evaluation took place after induction (day 45), and the methods and definition of MRD response was reported previously[8]. For patients in allo-HSCT cohorts, 4 cycles of consolidation chemotherapy pre-transplantation was mandatory. These patients received allo-HSCT from human leukocyte antigen

(HLA)-matched sibling donor (MSD), unrelated-donor (MUD) or HID. Donor selection was based on patients' biological characteristics and patients or guardians consent. Conditioning regimens consist of BuCy (busulfan and cyclophosphamide) and TBI/Cy (total body irradiation, cyclophosphamide).

Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. Event-free survival (EFS) was measured from the date of CR1 to the date of event occurred or at the last follow-up. Relapse or death by any cause were considered as events in the EFS analysis. Cumulative incidence of relapse (CIR) was calculated from the date of CR1 to the date of relapse, considering non-relapse mortality (NRM) as a competing event. This analysis aimed to compare the outcomes between transplantation and chemotherapy, to avoid bias from other therapies, patients who received immunotherapy when they relapsed, such as chimeric antigen receptor T-Cell (CAR-T) therapy or CD3/CD19 bispecific T cell engager (Blinatumomab), were censored at the time of starting immunotherapy. The left-truncated Kaplan-Meier method was used to compare survival between the allo-HSCT and chemotherapy cohorts, as previous reported[4]. Probabilities of NRM and CIR were generated using cumulative incidence estimates to account for competing risks and compared by Gray’s test. To adjust for differences in baseline characteristics, left-truncated Cox proportional hazards regression was used to compare the two cohorts. The data that support the findings of this study are available from the corresponding author (hanson_tcm@126.com) upon reasonable request.

A total of 245 patients were enrolled in this analysis, characteristics of patients in the allo-HSCT cohort and patients in the chemotherapy cohort were summarized in Table1, which showed comparable baseline characteristics. With a median follow-up time of 43.6 (3.5-82.5) months, the 3-yr OS and EFS were significantly superior in allo-HSCT cohort compared to the chemotherapy cohort. The estimated 3-yr OS was 77.4% (71.0-84.5%) and 53.3% (43.4-65.5%) in allo-HSCT and chemotherapy cohorts (Figure 1A), respectively. The 3-year EFS in the allo-HSCT cohort (71.0%, 64.1-78.7%) was also superior to the chemotherapy cohort (38.0%, 28.8-50.1%, Figure 1B). The 3-yr CIR was 13.0% (8.2-18.8%) in the allo-HSCT cohort and 54.2% (42.6-64.3%) in the chemotherapy cohort. Meanwhile, the 3-yr NRM in allo-HSCT cohort was 11.1% (6.7-16.6%).

To further address the role of transplantation in different MRD statuses, particularly for MRD-negative subset, subgroup analysis were conducted. In the post-induction MRD-positive subset (allo-HSCT, N=65; chemotherapy, N=36), patients who received allo-HSCT exhibited longer EFS and OS along with lower CIR, compared to the chemotherapy cohort (3-yr OS, 70.0% vs. 36.6%, $P < 0.001$; 3-yr EFS, 63.7% vs. 18.9%, $P < 0.001$; 3-yr CIR, 15.7% vs. 72.4%, $P < 0.001$; Fig 2A). Notably, patients who achieved MRD-negative also benefit from transplantation. In the post-induction MRD-negative subset (allo-HSCT, n=94; CT, n=50), the allo-HSCT cohort exhibited longer EFS, OS, and lower CIR, compared with chemotherapy cohort (3-yr OS,

82.5% vs. 65.6%, P=0.030; 3-yr EFS, 76.1% vs. 51.1%, P=0.010; 3-yr CIR, 11.1% vs. 42.6%, P < 0.001; Fig 2B). Furthermore, for patients with positive post-induction MRD and turning negative after consolidation therapy, allo-HSCT showed tendency of better survival (Fig 2C).

In multivariate analysis for entire cohort (Table S1), allo-HSCT was a protective factors for OS (HR=0.31, 0.19-0.51, P<0.001), EFS (HR=0.32, 0.20-0.50, P<0.001) and CIR (HR=0.12, 0.07-0.22, P<0.001), and negatively affected NRM (HR=4.04, 1.23-13.3, P<0.001). Meanwhile, in MRD-negative or positive subsets, allo-HSCT also led to superior OS and EFS in the multivariate analysis (Table S2).

As the HR features included Ph-positive ALL in PDT-ALL-2016 protocol, we repeated our analysis in Ph-negative HR-ALL (N=175). For these patients, allo-HSCT showed better survival compared with chemotherapy in both entire cohort, MRD positive and negative cohort (Figure S1).

Emerging evidence indicates that the survival for HR-ALL patients may not be further improved by allo-HSCT when receiving a pediatric-inspired chemotherapy, particularly in the MRD-negative subset. In present study, our data showed that post-consolidation transplantation exhibited superior survival compared to chemotherapy for HR-ALL in the PDT-ALL-2016 pediatric-inspired cohort. In this study, we included very high risk subtype, such as IKZF1 deletion and Ph-like ALL

and more patients had detective MRD at 45 days, even though, the survival of the entire cohort and chemotherapy cohort was comparable with other reports[5, 6]. These findings suggested that the integrated pediatric-inspired chemotherapy and post-consolidation allo-HSCT may be the optimal therapy for adult HR-ALL. Of note, this study showed the advantage of post-consolidation allo-HSCT for HR-ALL patients in the context of pediatric-inspired regimen, even for patients achieved negative MRD.

The efficacy of allo-HSCT has been debated since using pediatric-inspired regimen in adult ALL. This controversy arises from several aspects, firstly, the survival rate of AYA ALL patients has been significantly improved by pediatric-inspired regimen. Secondly, it's well-established that a weaker graft-versus-leukemia (GVL) effect was yielded post-allo-HSCT in ALL compared to myeloid neoplasms. Another unresolved question pertains to bridging the gap between the time required for immune reconstitution for GVL, and early relapse after allo-HSCT. In present protocol, we speculated that treatment with pediatric-inspired regimen could induce durable remission to avoid early relapse, and subsequently spare enough time to reconstitute the immune system to exert GVL effect. Our previous study, the PASS-ALL study, illustrated that this integrated total-therapy yielded durable or deeper MRD response (d/d MRD) in HR-ALL. We found that, as pre-transplantation chemotherapy, pediatric-inspired regimen resulted in significant longer time-to-positive MRD than adult protocol[8].

For HR-ALL, the chemotherapy alone may be insufficient to maintain the remission status, even for patients who achieved MRD-negative status, for these patients, more sensitive techniques, such as next-generation sequencing-based MRD, may detect residual leukemic cells[13]. These surviving leukemic cells, which are resistant to prior chemotherapy, increase the risk of relapse, necessitating more intensive interventions such as allo-HSCT. A limitation associated with allo-HSCT is the high NRM. Allo-HSCT' s ability to reduce the relapse rate may offset by the excessively high NRM of transplantation. In present study, the 3-year NRM was 11.8% (9.5-20.5%), a relatively low rate compared with other reports[3, 14, 15], which might benefit from experienced management of allo-HSCT in our center.

Limitations in our study included that this is a single-center analysis. In conclusion, we demonstrated that allo-HSCT still had an irreplaceable role in adult HR-ALL post-remission therapy in the pediatric-inspired regimen era. We highlighted the importance of total therapy for adult HR-ALL, and the post-consolidation allo-HSCT should be considered for patients who achieved MRD-negative.

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Table 1. Patients Characteristics

Total=245	Allo-HSCT (N=159)	Chemotherapy (N=86)	p
Age (range)	29.1 (18.0-60.2)	28.1 (18.0-68.7)	.435
Sex, No. (%)			
Male	68 (42.8%)	37 (43%)	.999
Female	91 (57.2%)	49 (57%)	
Immuno-type, No. (%)			
T-ALL	41 (25.8%)	20 (23.3%)	.967
ETP	30 (18.1%)	14 (16.2%)	.546
B-ALL	118 (74.2%)	66 (76.7%)	.845
Pro-B	24 (15.0%)	14 (116.2%)	.540
Clinical features, No. (%)			
CNSL at presentation	8 (5.0%)	7 (8.1%)	.491
High WBC [a]	62 (39.0%)	41 (47.7%)	.239
> 30×10^9 for B-ALL	53 (33.3%)	33 (38.3%)	
> 100×10^9 for T-ALL	9 (5.7%)	8 (9.4%)	
Cytogenetic features, No. (%)			
Non/ other	66 (41.5%)	41 (47.6%)	.888
MLLr	7 (4.4%)	3 (3.4%)	
E2Ar	3 (1.8%)	4 (4.6%)	
IGHdel	9 (5.6%)	5 (5.8%)	
Ph+	44 (27.6%)	26 (30.2%)	
CK	20 (12.5%)	4 (4.6%)	
Missing	10 (6.2%)	3 (3.4%)	
Ph-like, No. (%)			
No	137 (86.2%)	75 (87.2%)	.974
Yes	22 (13.8%)	11 (12.8%)	
IKZF1 deletion, No. (%)			
No	132 (83%)	73 (84.9%)	.845
Yes	27 (17%)	13 (15.1%)	
MRD at day 45, No. (%)			

Negative	94 (59.1%)	50 (58.1%)	.990
Positive	65 (40.9%)	36 (41.9%)	
Donor type, No. (%)			
HID	93 (58.49%)		
MSD/MUD	66 (41.51%)		
Reconstitution, No. (%)			
Neutrophil	12.54 ± 2.25		
Platelet	14.29 ± 4.28		
GVHD prophylaxis, No. (%)			
CSA+MTX	93 (58.49%)		
CSA+MMF+MTX+ATG	12 (7.55%)		
CSA+MMF+MTX+ATG+PT-CY	54 (33.96%)		
Donor sex, No. (%)			
F-M	23 (14.47%)		
Other	136 (85.53%)		
Stem cell source, No. (%)			
PB	87 (54.7%)		
PB+BM	72 (45.3%)		
Conditioning regimen, No. (%)			
Non-TBI based	66 (41.51%)		
TBI based	93 (58.49%)		

Abbreviations: CNSL, central nervous system leukemia; WBC, white blood cell; Ph+, Philadelphia chromosome positive; MLLr, MLL rearrangement; E2Ar, E2A rearrangement; CK, complex karyotype; a, For B-ALL, WBC > 30×10^9/L; for T-ALL, WBC > 100×10^9/L; MRD, minimal residual disease; HID, haploidentical related donor; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated-donor; GVHD, graft versus-host disease; F-M, female to male; P, peripheral blood stem cells; M, marrow stem cells; BF, busulfan + fludarabine; BuCy, busulfan + cyclophosphamide; TBI+Cy+VP16, total body irradiation + cyclophosphamide + etoposide;

Legend to figures

Figure 1: Survival outcomes. (A) Event-free survival (EFS) for entire cohort according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method. (B) Overall survival (OS) for entire cohort according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method.

Figure 2: Survival outcomes. (A) Event-free survival (EFS) and overall survival (OS) for patients who had positive minimal residual disease (MRD) at day 45 (post-induction) according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method. (B) Event-free survival (EFS) and overall survival (OS) for patients who had negative MRD at post-induction according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method. (C) Event-free survival (EFS) and overall survival (OS) for patients who had positive post-induction MRD and turning negative post-consolidation, according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method.

Figure 1

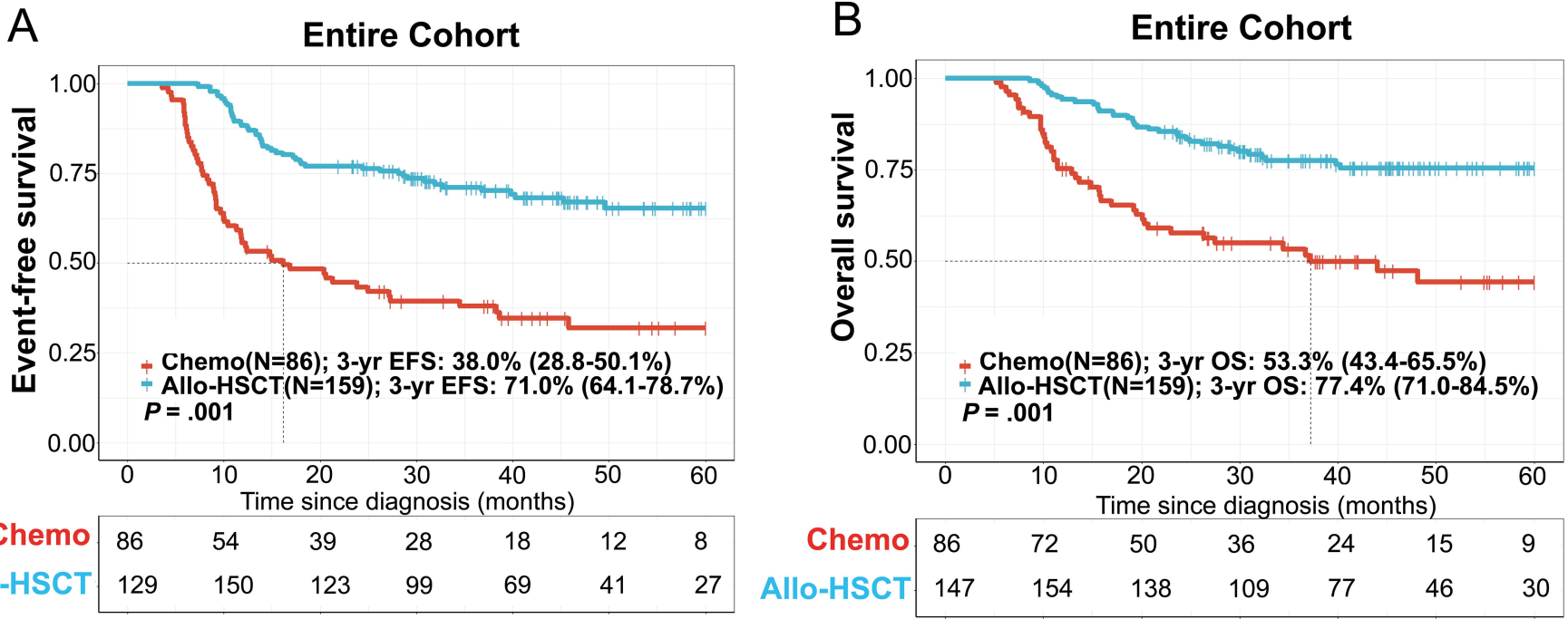
A
Entire Cohort
Event-free survival
1.00
0.75
0.50
0.25
0.00
Chemo(N=86); 3-yr EFS: 38.0% (28.8-50.1%)
Allo-HSCT(N=159); 3-yr EFS: 71.0% (64.1-78.7%)
P = .001
0
10
20
30
40
50
60
Time since diagnosis (months)
Chemo 86 54 39 28 18 12 8
Allo-HSCT 129 150 123 99 69 41 27
B
Entire Cohort
Overall survival
1.00
0.75
0.50
0.25
0.00
Chemo(N=86); 3-yr OS: 53.3% (43.4-65.5%)
Allo-HSCT(N=159); 3-yr OS: 77.4% (71.0-84.5%)
P = .001
0
10
20
30
40
50
60
Time since diagnosis (months)
Chemo 86 72 50 36 24 15 9
Allo-HSCT 147 154 138 109 77 46 30

Figure 2

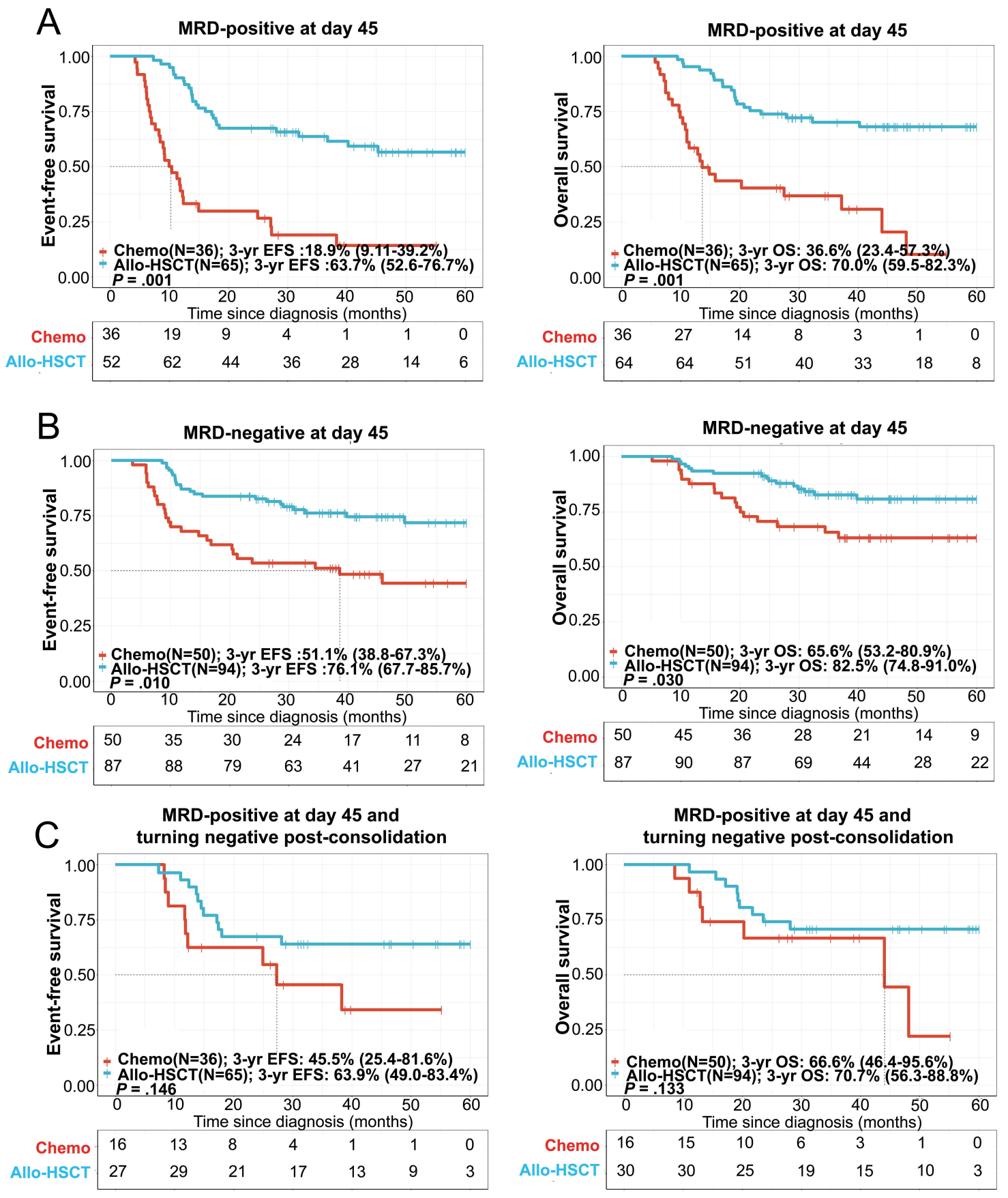
A
MRD-positive at day 45
Event-free survival
Chemo(N=36); 3-yr EFS :18.9% (9.11-39.2%)
Allo-HSCT(N=65); 3-yr EFS :63.7% (52.6-76.7%)
P = .001
Time since diagnosis (months)
Chemo 36 19 9 4 1 1 0
Allo-HSCT 52 62 44 36 28 14 6
MRD-positive at day 45
Overall survival
Chemo(N=36); 3-yr OS: 36.6% (23.4-57.3%)
Allo-HSCT(N=65); 3-yr OS: 70.0% (59.5-82.3%)
P = .001
Time since diagnosis (months)
Chemo 36 27 14 8 3 1 0
Allo-HSCT 64 64 51 40 33 18 8
B
MRD-negative at day 45
Event-free survival
Chemo(N=50); 3-yr EFS :51.1% (38.8-67.3%)
Allo-HSCT(N=94); 3-yr EFS :76.1% (67.7-85.7%)
P = .010
Time since diagnosis (months)
Chemo 50 35 30 24 17 11 8
Allo-HSCT 87 88 79 63 41 27 21
MRD-negative at day 45
Overall survival
Chemo(N=50); 3-yr OS: 65.6% (53.2-80.9%)
Allo-HSCT(N=94); 3-yr OS: 82.5% (74.8-91.0%)
P = .030
Time since diagnosis (months)
Chemo 50 45 36 28 21 14 9
Allo-HSCT 87 90 87 69 44 28 22
C
MRD-positive at day 45 and turning negative post-consolidation
Event-free survival
Chemo(N=36); 3-yr EFS: 45.5% (25.4-81.6%)
Allo-HSCT(N=65); 3-yr EFS: 63.9% (49.0-83.4%)
P = .146
Time since diagnosis (months)
Chemo 16 13 8 4 1 1 0
Allo-HSCT 27 29 21 17 13 9 3
MRD-positive at day 45 and turning negative post-consolidation
Overall survival
Chemo(N=50); 3-yr OS: 66.6% (46.4-95.6%)
Allo-HSCT(N=94); 3-yr OS: 70.7% (56.3-88.8%)
P = .133
Time since diagnosis (months)
Chemo 16 15 10 6 3 1 0
Allo-HSCT 30 30 25 19 15 10 3

Figure S1. Subgroup analysis for Ph-negative HR-ALL

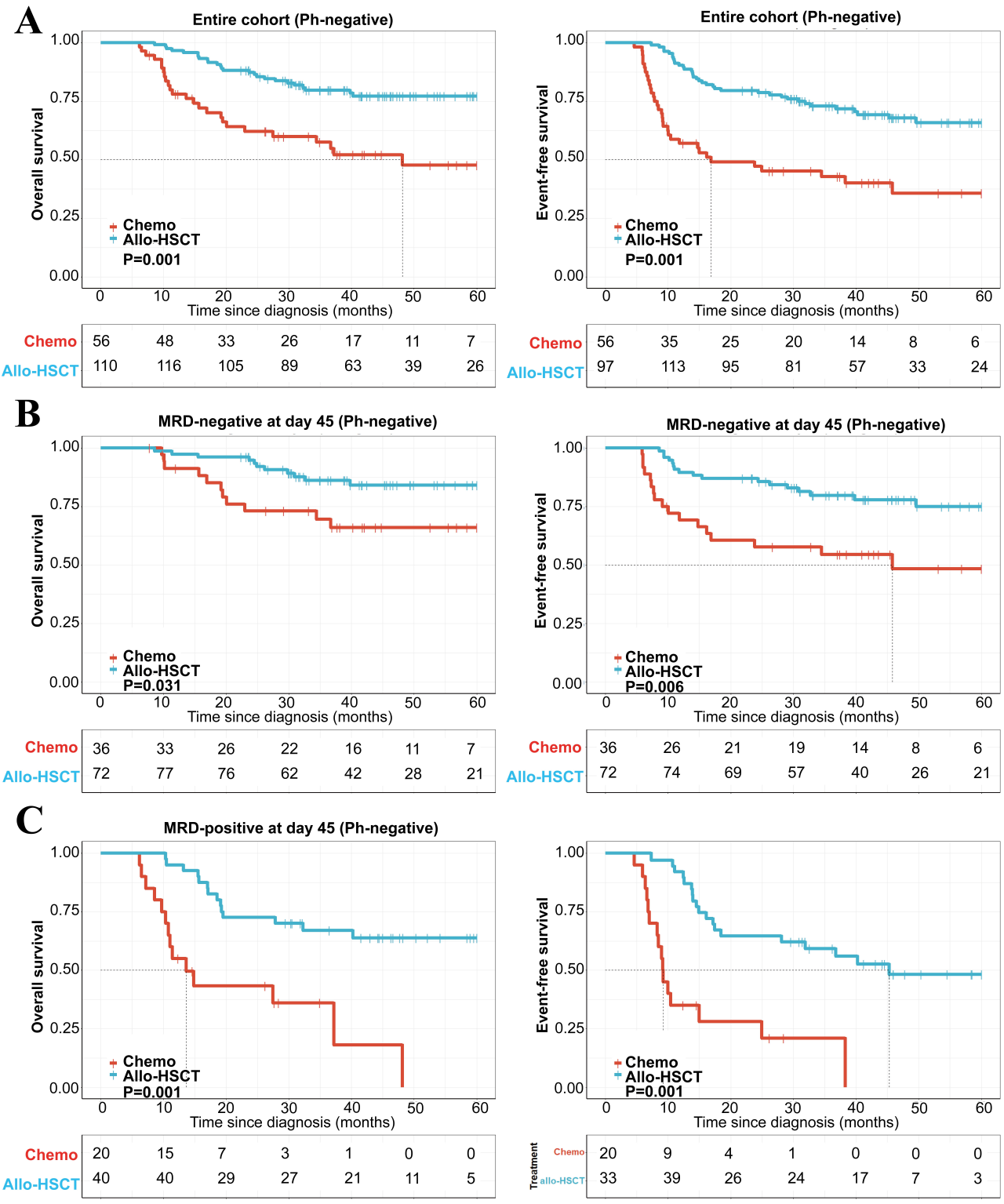

Figure S1: Survival outcomes. (A) Overall survival (OS) and Event-free survival (EFS) for entire cohort (Ph-negative) according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method. (B) OS and EFS for Ph-negative patients who had negative minimal residual disease (MRD) at day 45 (post-induction) according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method. (C) OS and EFS for Ph-negative patients who had positive MRD at day 45 according to allo-HSCT versus chemotherapy by left-truncated Kaplan-Meier method.

Supplemental Tables

Table S1. Multivariate analysis.

	Number	EFS	OS	CIR	NRM
Age					
≥35	72 (31.4%)			Ref	
＜35	157 (68.6%)	0.89 (0.57-1.38, p=.596)	0.64 (0.39-1.05, p=.079)	1.17 (0.66-2.08, p=.591)	0.44(0.17-1.15, p=.101)
Immuno-type					
B-ALL	176 (76.9%)			Ref	
T-ALL	53 (23.1%)	0.64 (0.33-1.25, p=.189)	0.77 (0.35-1.69, p=.511)	0.55 (0.24-1.28, p=.170)	1.40 (0.41-4.82, p=.601)
CNSL at presentation					
No	215 (93.9%)			Ref	
Yes	14 (6.1%)	1.25 (0.49-3.18, p=.636)	1.09 (0.38-3.13, p=.870)	2.28 (0.71-7.30, p=.172)	NA
High WBC [a]					
No	132 (57.6%)			Ref	
Yes	97 (42.4%)	1.66 (1.10-2.53, p=.017)	1.49 (0.93-2.38, p=.097)	1.99 (1.13-3.50, p=.017)	0.99 (0.38-2.55, p=.982)
Cytogenetic features					
Non / other	128 (55.9%)			Ref	
Ph	70 (30.6%)	1.10 (0.65-1.87, p=.715)	1.32 (0.71-2.44, p=.380)	1.32 (0.69-2.50, p=.401)	1.72 (0.52-5.63, p=.371)
MLL	10 (4.4%)	2.08 (0.82-5.23, p=.122)	3.67 (1.39-9.67, p=.009)	2.92 (0.98-8.68, p=.053)	NA

Table S1. Multivariate analysis.

	Number	EFS	OS	CIR	NRM
E2A	7 (3.1%)	2.02 (0.73-5.57, p=.175)	1.70 (0.49-5.92, p=.408)	1.29 (0.22-7.78, p=.785)	2.09(0.15-30.0, p=.594)
IGHdel	14 (6.1%)	1.18 (0.51-2.71, p=.703)	1.48 (0.62-3.54, p=.378)	1.43 (0.52-3.90, p=.490)	1.52 (0.33-7.05, p=.597)
CK					
No	205 (89.5%)			Ref	
Yes	24 (10.5%)	1.18 (0.57-2.46, p=.651)	1.35 (0.61-2.98, p=.462)	2.21 (0.96-5.11, p=.062)	0.34 (0.04-2.71, p=.311)
Allo-HSCT					
No	83 (36.2%)			Ref	
Yes	146 (63.8%)	0.32 (0.20-0.50, p<.001)	0.31 (0.19-0.51, p<.001)	0.12 (0.07-0.22, p<.001)	4.04 (1.23-13.3, p=.022)
Ph-like					
No	199 (86.9%)			Ref	
Yes	30 (13.1%)	2.19 (1.18-4.04, p=.012)	2.21 (1.08-4.52, p=.030)	2.62 (1.19-5.79, p=.017)	2.03 (0.57-7.21, p=.281)
IKZF1mut/del					
No	191 (83.4%)			Ref	
Yes	38 (16.6%)	1.16 (0.68-2.00, p=.586)	1.40 (0.77-2.56, p=.275)	1.18 (0.62-2.26, p=.612)	1.30 (0.43-3.87, p=.642)
MRD					
Negative	137 (59.8%)			Ref	
Positive	92 (40.2%)	2.16 (1.42-3.27, p<.001)	2.68 (1.66-4.33, p<.001)	1.95 (1.14-3.34, p=.015)	1.43(0.56-3.65, p=.462)

Abbreviations: CNSL, central nervous system leukemia; WBC, white blood cell; Ph+, Philadelphia chromosome positive; MLLr, MLL rearrangement; E2Ar, E2A rearrangement; CK, complex karyotype; OS, Overall survival; EFS, Event-free survival; CIR, Cumulative incidence of relapse; NRM, Non-relapse mortality a, For B-ALL, WBC＞30×10^9/L; for T-ALL, WBC＞ 100×10^9/L.

Table S2. Multivariate analysis for MRD subgroup.

	MRD-negative subset			MRD-positive subset		
	Number	**EFS**	**OS**	**Number**	**EFS**	**OS**
Age						
≥35	39 (28.5%)			33 (35.9%)		
＜35	98 (71.5%)	0.63 (0.32-1.23, p=.175)	0.29 (0.13-0.69, p=.005)	59 (64.1%)	1.29 (0.66-2.53, p=.460)	1.07 (0.53-2.16, p=.844)
Immuno-type						
T-ALL	105 (76.6%)			71 (77.2%)		
B-ALL	32 (23.4%)	0.40 (0.14-1.19, p=.099)	0.65 (0.18-2.38, p=.513)	21 (22.8%)	0.63 (0.24-1.67, p=.354)	0.67 (0.24-1.87, p=.444)
CNSL at presentation						
No	129 (94.2%)			86 (93.5%)		
Yes	8 (5.8%)	2.09 (0.61-7.14, p=.241)	2.40 (0.53-10.78, p=.254)	6 (6.5%)	0.68 (0.16-2.99, p=.614)	0.86 (0.19-3.87, p=.846)
High WBC [a]						
No	80 (58.4%)			52 (56.5%)		
Yes	57 (41.6%)	0.91 (0.47-1.77, p=.780)	0.66 (0.30-1.46, p=.303)	40 (43.5%)	2.31 (1.29-4.13, p=.005)	2.00 (1.05-3.79, p=.034)
Cytogenetic features						
Normal	83 (60.6%)			45 (48.9%)		
Ph	37 (27.0%)	1.18 (0.54-2.58, p=.671)	1.55 (0.57-4.18, p=.388)	33 (35.9%)	0.91 (0.39-2.13, p=.831)	1.03 (0.43-2.44, p=.952)
MLL	7 (5.1%)	1.82 (0.48-6.87, p=.379)	3.12 (0.73-13.42, p=.126)	3 (3.3%)	1.77 (0.44-7.19, p=.422)	3.41 (0.85-13.75, p=.085)
E2A	3 (2.2%)	2.46 (0.55-10.93, p=.238)	1.56 (0.19-12.70, p=.678)	4 (4.3%)	1.11 (0.26-4.65, p=.887)	1.05 (0.20-5.39, p=.954)

Table S2. Multivariate analysis for MRD subgroup.

	MRD-negative subset			MRD-positive subset		
	Number	**EFS**	**OS**	**Number**	**EFS**	**OS**
IGHdel	7 (5.1%)	1.87 (0.54-6.55, p=.326)	4.33 (1.13-16.58, p=.032)	7 (7.6%)	0.87 (0.26-2.95, p=.825)	0.74 (0.22-2.55, p=.637)
CK						
No	124 (90.5%)			81 (88.0%)		
Yes	13 (9.5%)	0.22 (0.03-1.65, p=.139)	0.38 (0.05-3.05, p=.363)	11 (12.0%)	2.46 (1.01-6.00, p=.048)	2.08 (0.79-5.45, p=.137)
Allo-HSCT						
No	49 (35.8%)			34 (37.0%)		
Yes	88 (64.2%)	0.45 (0.24-0.83, p=.011)	0.44 (0.21-0.92, p=.030)	58 (63.0%)	0.24 (0.11-0.50, p<.001)	0.20 (0.09-0.43, p<.001)
Ph-like						
No	120 (87.6%)			79 (85.9%)		
Yes	17 (12.4%)	2.06 (0.84-5.02, p=.113)	1.69 (0.52-5.53, p=.383)	13 (14.1%)	2.01 (0.82-4.94, p=.130)	2.75 (1.04-7.26, p=.041)
IKZF1mut/del						
No	116 (84.7%)			75 (81.5%)		
Yes	21 (15.3%)	1.19 (0.54-2.62, p=.673)	1.43 (0.56-3.69, p=.458)	17 (18.5%)	0.99 (0.44-2.27, p=.989)	1.19 (0.50-2.79, p=.697)

Abbreviations: CNSL, central nervous system leukemia; WBC, white blood cell; Ph+, Philadelphia chromosome positive; MLLr, MLL rearrangement; E2Ar, E2A rearrangement; CK, complex karyotype; OS, Overall survival; EFS, Event-free survival; CIR, Cumulative incidence of relapse; NRM, Non-relapse mortality a, For B-ALL, WBC＞30×10^9/L; for T-ALL, WBC＞ 100×10^9/L.