Supplemental materials

Table 1. Univariate and Multivariate analyses of event-free survival and overall survival according to clinical and laboratory features in the 384 ALL patients with *TCF3-PBX1*

	Event-free survival				**Overall survival**			
	Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
Variable	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**
Sex		**0.035**		**0.031**		**0.012**		**0.004**
Female	1		1		1		1	
Male	1.8 (1.0-3.2)		2.0 (1.1-3.6)		2.5 (1.2-5.2)		3.4 (1.5-7.9)	
Age		0.160				0.258		
1-10 years	1				1			
< 1y or > 10y	1.5 (0.9-2.7)				1.5 (0.7-2.9)			
Leukocyte count		0.367				0.653		
$< 50 \times 10^9$/L	1				1			
$\geq 50 \times 10^9$/L	0.7 (0.4-1.4)				0.8 (0.4-1.8)			
Hemoglobin level		0.763				0.810		
< 10g/dl	1				1			
≥ 10g/dl	0.9 (0.5-1.7)				1.1 (0.5-2.2)			
Platelet count		0.770				0.255		
$<100 \times 10^9$/L	1				1			
$\geq 100 \times 10^9$/L	1.1 (0.6-2.0)				1.5 (0.8-2.9)			
karyotype								
Normal	1				1			
t(1;19)(q23;p13)	0.8 (0.4-1.8)	0.584			1.0 (0.4-2.6)	0.988		
der t(1;19)(q23;p13)	1.1 (0.6-2.1)	0.737			1.3 (0.6-2.8)	0.524		
Other	1.2 (0.3-4.9)	0.836			2.0 (0.5-8.6)	0.367		
Day19 MRD, %*		**0.005**		**0.021**		0.212		
< 0.01	1		1		1			
≥ 0.01	2.2 (1.3-3.8)		2.0 (1.1-3.6)		1.5 (0.8-3.1)			
Day46 MRD, %*		**<0.001**		**0.009**		**0.019**		**0.012**
< 0.01	1		1		1		1	
≥ 0.01	3.8 (1.8-8.2)		2.9 (1.3-6.4)		3.1 (1.2-8.1)		3.4 (1.3-8.9)	

Abbreviations: CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease.

*Missing data are due to either patients' leukemia cells not having suitable markers for the MRD test or because data were not submitted to the statistics center.

Table 2. Comparison of clinical and biological characteristics between male and female patients

	Male (%)	Female (%)	*P* value
Total	206 (53.6%)	178 (46.4%)	—
Median age in years (range)	5.6 (0.8-16.8)	5.7 (0.7-14.1)	0.465
Median presenting WBC×10^9/L (range)	19.6 (1.4-322.3)	26.4 (1.7-267.6)	**0.003**
Median presenting hemoglobin g/L (range)	86 (37-147)	86 (33-171)	0.526
Median presenting platelet ×10^9/L (range)	54.5 (7-731)	46.5 (2-627)	0.318
Median PB Blasts (%)	47 (0-99)	54 (0-97)	0.088
CNS status			0.303
CNS1	194 (94.1%)	166 (93.3%)	
CNS2	3 (1.5%)	2 (1.1%)	
CNS3	2 (1.0%)	0	
Traumatic	7 (3.4%)	10 (5.6%)	
Testicular leukemia*			-
Yes	10 (5.0%)	-	
No	192 (95.0%)	-	
karyotype			0.082
Normal	85 (46.7%)	84 (53.8%)	
t (1;19) (q23; p13)	30 (16.5%)	34 (21.8%)	
der t (1;19) (q23; p13)	59 (32.4%)	35 (22.4%)	
Other	8 (4.4%)	3 (1.9%)	
Immunophenotype			0.342
Pro-B	4 (2.5%)	1 (0.7%)	
Common-B	92 (57.5%)	89 (62.7%)	
Pre-B	64 (40.0%)	52 (36.6%)	
Day19 MRD, % **			0.706
< 0.01	136 (68.0%)	118 (69.8%)	
≥ 0.01	64 (32.0%)	51 (30.2%)	
Day46 MRD, % **			0.534
< 0.01	188 (94.5%)	157 (92.9%)	
≥ 0.01	11 (5.5%)	12 (7.1%)	
Final risk group			0.214
Intermediate	206 (100%)	176 (98.9%)	
High	0 (0%)	2 (1.1%)	
Relapse			0.235
Yes	25 (12.1%)	15 (8.4%)	
No	181 (87.9%)	163 (91.6%)	
Relapse time			0.386
Very early (<18 months)	16 (64.0%)	12 (80.0%)	
Early (18-36 months)	8 (32.0%)	2 (13.3%)	
Late (>36 months)	1 (4.0%)	1 (6.7%)	

5-year Cumulative risk, % (95%CI)			
Any relapse	13.2 (8.2-18.2)	8.8 (4.5-13.1)	0.245
Isolated BM relapse	8.5 (4.4-12.6)	6.8 (3.1-10.5)	0.699
Any BM relapses	11.4 (6.7-16.1)	6.8 (3.1-10.5)	0.237
Isolated CNS relapse	2.0 (0-4.0)	2.2 (0-4.7)	0.832
Any CNS relapses	3.1 (0.6-5.6)	2.2 (0-4.7)	0.419
Testicular relapse	6.2 (2.4-10.0)	-	-
Death during remission	4.9 (1.9-7.9)	1.8 (0-3.8)	0.085

Abbreviations: BM, bone marrow; CNS, central nervous system; MRD, minimal residual disease; PB, peripheral blood; WBC, white blood cell.

* Testicular leukemia information is missing in 4 boys.

**Missing data are due to either patients' leukemia cells not having suitable markers for the MRD test or because data were not submitted to the statistics center.

Table 3. Univariate analysis of event-free survival and overall survival according to clinical and laboratory features in the male patients with *TCF3-PBX1* ALL

		Event-free survival		**Overall survival**	
Variable	**No.**	**HR (95%CI)**	***P* value**	**HR (95%CI)**	***P* value**
Age at diagnosis			0.178		**0.06**
1-10 years	156	1		1	
< 1y or >10y	50	1.6 (0.8-3.2)		2.1 (0.9-4.4)	
leukocyte count			0.16		0.283
$< 50 \times 10^9$/L	160	1		1	
$\geq 50 \times 10^9$/L	46	0.5 (0.2-1.3)		0.6 (0.2-1.6)	
Hemoglobin level			0.392		0.273
< 10g/dl	150	1		1	
≥ 10g/dl	56	1.4 (0.7-2.7)		1.5 (0.7-3.3)	
Platelet count			0.554		0.227
$< 100 \times 10^9$/L	152	1		1	
$\geq 100 \times 10^9$/L	54	1.2 (0.6-2.5)		1.6 (0.7-3.5)	
Testicular leukemia*			**<0.001**		**<0.001**
No	192	1		1	
Yes	10	5.2 (2.0-13.5)		10.2 (4.2-24.5)	
karyotype					
Normal	85	1		1	
t(1;19) (q23;p13)	30	1.1 (0.4-2.9)	0.817	1.4 (0.5-4.1)	0.356
der t(1;19) (q23;p13)	59	1.2 (0.6-2.6)	0.571	1.5 (0.6-3.6)	0.988
Other	8	0.6 (0.1-4.8)	0.659	1.0 (0.1-7.7)	0.608
Day19 MRD, % **			0.085		0.334
< 0.01	136	1		1	
≥ 0.01	64	1.8 (0.9-3.5)		1.5 (0.7-3.1)	
Day46 MRD, % **			0.069		0.097
< 0.01	188	1		1	
≥ 0.01	11	2.6 (0.9-7.5)		2.8 (0.8-9.3)	

Abbreviations: CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease.

* Testicular leukemia information is missing in 4 boys.

**Missing data are due to either patients' leukemia cells not having suitable markers for the MRD test or because data were not submitted to the statistics center.

Table 4. Related studies on treatment outcome of children with *TCF3-PBX1* ALL

	Frequency (%)	Average age (years)	Male /Female	5-EFS (%)	5-OS (%)	Relapse site	Ethnicity	Treatment period	Treatment Protocol	Rf
Baruchel et al (2005)	110 (ND)	6.9 (3.5-12)	50/60	ND	ND	17 relapse- 13BM, 4CNS	ND		FRALLE83/ 87–89/92/93/ 2000	1
Kager et al (2007)	31/ND (3.6%)	6.9 (1.2-17)	17/14	90 ± 5	ND	3 relapse- 2BM, 1BM + CNS	white	1986–2003	BFM-86/90/95/2000	2
Jeha et al (2009)	41/735 (5.6%)	ND	18/23	84.2 ± 7.1	96.4 ± 3.7	4 relapse- 3 CNS relapse 1CNS and ocular	77% White, 15% Black, 8% others	1991–2008	SJCRH-13/14/15	3
Salzer et al (2010)	259/5356 (4.8%)	ND	ND	74.5 ± 2.8	83.3 ± 2.4	ND	—	1984-2001	POG: 1984-2001	4
Stark et al (2010)	11/337 (3.3%)	ND	ND	81.8 ± 11.6	90.9 ± 8.7	ND	Jew	1984-2003	INS-89	5
Gaynon et al (2010)	67/5121 (1.3%)	ND	ND	68.6 ± 5.8	77.6 ± 5.2	ND	White Black Hispanic	1989-1995	CCG-1800 series:1989-1995	6
Gaynon et al (2010)	67/4464 (1.5%)	ND	ND	77.6 ± 5.5	85.0 ± 4.8	ND	White Black Hispanic	1996-2002	CCG-1900 series:1996-2002	6
Tsuchida et al (2010)	26/597 (4.4%)	ND	ND	70.2 ± 9.5	73.0 ± 8.7	ND	Asian	1995-1999	TCCSGL95-14: 1995-1999	7
Moorman et al (2010)	50/1725 (2.9%)	ND	ND	80.0 ± 5.9	84 ± 5.4	6 relapse- 3BM, 3CNS	White	1997-2002	UKALL97/99	8
Felice et al (2011)	48/1368 (3.5%)	6 (0.8-16)	22/26	85 ± 6	ND	6 relapse- 6 BM	ND	1990-2010	BFM-90/96 12-ALLIC 02	9

Andersen et al (2011)	47/2640 (1.8%)	7 (1-18)	21/26	79.0 ± 6.0	85.0 ± 6.0	9 relapse- 9 BM	White	1992-2007	NOPHO-ALL1992/2000	10
Gao et al (2012)	65/905 (7.2%)	ND	37/28	85.8 ± 4.7	ND	6 relapse- 5 BM, 1Isolated extramedullary	Asian	2003-2010	BCH-2003 CCLG-ALL2008	11
Asai et al (2014)	82/1138 (7.2%)	6 (1-15)	38/44	85.4 ± 3.9 (3y)	89.0 ± 3.5 (3y)	9 relapse- 8 BM, 1CNS	Asian	2002-2008	JACLS-ALL02	12
Asai et al (2014)	30/264 (11.4%)	7 (1-14)	12/18	82.8 ± 7.0	86.3 ± 6.4	5relapse- 4 BM, 1BM + CNS	Asian	2004-2009	CCLSG-ALL2004	12
Li et al (2015)	20/450 (4.4%)	4.5 (1.4-12.8)	10/10	84.4 ± 15.6	86.0 ± 17.6	2 relapse- 2 BM	Asian	2008-2012	CCLG-ALL2008	13
Hu et al (2016)	20/ 349 (5.7%)	3.8 (1.8-7.4)	11/9	95 ± 4.9	95 ± 4.9	ND	Asian	2008-2013	CCLG-ALL2008	14
Yen et al (2017)	64/1129 (5.7%)	6.9 (1.0-16.4)	33/31	85.4 ± 5.1	89.7 ± 4.4	7 relapse- 3 BM, 3 CNS, 1 Testis	Asian	2002-2012	TPOG-ALL-2002	15
Lin et al (2018)	30/624 (4.8%)	4.8 (1.3-14.8)	16/14	100	100	ND	Asian	1997-2016	HKALL 97, IC-BFM 2002, CCLG2008	16
Wang et al (2020)	64/1051 (6.1%)	8 (ND)	37/27	85.2 ± 4.6	76.8 ± 5.5	7 BM relapse	Asian	2004-2017	Modified BFM	17
Zhou et al (2021)	81/1526 (5.6%)	ND	ND	ND	86.9	10 Relapse	Asian	2009-2019	CCLG-ALL2008	18
Ming et al (2021)	48/837 (5.7%)	5 (0.8-12)	26/22	86.2 ± 5.3	90.4 ± 4.6	5 Relapse- 5 BM relapse	Asian	2010-2017	(NPCLC)-ALL-2008	19
Jeha et al (2021)	17/598 (2.8%)	6.2 (1.8-15.0)	12/5	88.2 (71.7–100)	88.2 (71.7–100)	1Relapse- 1 BM relapse	Black 5 White 10 Other 2	2007-2017	St. Jude Total Therapy Study 16	20

Our research	384/ 7677 (5.0%)	5.6 (0.7-16.8)	206/178	84.4 (80.6-88.3)	88.9 (85.5-92.4)	40 Relapse- 28 BM relapse, 7CNS relapse, 2 BM + CNS, 3BM + testicular	Asian	2015-2019	CCCG-ALL-2015	

Abbreviations: BM, bone marrow; CNS, central nervous system; EFS, event-free survival; OS, overall survival; Rf, reference.

Reference

1. Baruchel A, Chevret S, Auvrignon A, Ballerini P, Leverger G. A Plateau after 30 Months of Follow-Up in B -Lineage Childhood Acute Lymphoblastic Leukemia (ALL) with t(1;19) (q23;p13)/E2A-PBX1. *Blood*. 2005; 106:1441-1441.

2. Kager L, Lion T, Attarbaschi A, Koenig M, Strehl S, Haas OA, et al. Incidence and outcome of TCF3-PBX1-positive acute lymphoblastic leukemia in Austrian children. *Haematologica*. 2007; 92: 1561-1564.

3. Jeha S, Pei D, Raimondi SC, Onciu M, Campana D, Cheng C, et al. Increased Risk for CNS Relapse in Pre-B Cell Leukemia with the t(1;19)/TCF3-PBX1. *leukemia*. 2009; 23: 1406-1409.

4. Salzer WL, Devidas M, Carroll WL, Winick N, Pullen J, Hunger SP, et al. Long-term results of the Pediatric Oncology Group Studies for childhood acute lymphoblastic leukemia 1984-2001: A report from the Children's Oncology Group. *Leukemia*. 2010; 24: 355-370.

5. Stark B, Nirel R, Avrahami G, Abramov A, Attias D, Ballin A, et al. Long-term results of the Israeli National Studies in childhood acute lymphoblastic leukemia: INS 84, 89 and 98. *Leukemia*. 2010; 24: 419-424.

6. Gaynon PS, Angiolillo AL, Carroll WL, Nachman JB, Trigg ME, Sather HN, et al. Long term results of the Children's Cancer Group Studies for childhood acute lymphoblastic leukemia 1983–2002: A Children's Oncology Group report. *Leukemia*. 2010; 24: 285-297.

7. Tsuchida M, Ohara A, Manabe A, Kumagai M, Shimada H, Kikuchi A, et al. Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984–1999. *Leukemia*. 2010; 24: 383-396.

8. Moorman AV, Ensor HM, Richards SM, Chilton L, Schwab C, Kinsey SE, et al. Prognostic eff ect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial. *Lancet Oncol*. 2010; 11: 429-438.

9. Felice MS, Gallego MS, Alonso CN, Alfaro EM, Guitter MR, Bernasconi AR, et al. Prognostic impact of t(1;19)/TCF3-PBX1 in childhood acute lymphoblastic leukemia in the context of Berlin-Frankfurt-Munster-based protocols. *Leuk Lymphoma*. 2011; 52: 1215-1221.

10. Andersen MK, Autio K, Barbany G, Borgström G, Cavelier L, Golovleva I, et al. Paediatric B-cell precursor acute lymphoblastic leukaemia with t(1;19) (q23;p13): clinical and cytogenetic characteristics of 47 cases from the Nordic countries treated according to NOPHO protocols. *Br J Haematol*. 2011;155: 235-243.

11. Gao C, Zhao XX, Li WJ, Cui L, Zhao W, Liu SG, et al. Clinical features, early treatment responses, and outcomes of pediatric acute lymphoblastic leukemia in China with or without specific fusion transcripts: A single institutional study of 1,004 patients. *Am J Hematol*. 2012; 87: 1022-1027.

12. Asai D, Imamura T, Yamashita Y, Suenobu S, Moriya-Saito A, Hasegawa D, et al. Outcome of TCF3-PBX1 positive pediatric acute lymphoblastic leukemia patients in Japan: a collaborative study of Japan Association of Childhood Leukemia Study (JACLS) and Children's Cancer and Leukemia Study Group (CCLSG). *Cancer Med*. 2014; 3: 623-631.
13. Pang L, Liang Y, Pan J, Wang JR, Chai YH, Zhao WL. Clinical Features and Prognostic Significance of TCF3-PBX1 Fusion Gene in Chinese Children with Acute Lymphoblastic Leukemia by Using a Modified ALL-BFM-95 Protocol. *Pediatr Hematol Oncol.* 2015; 32: 173-181.
14. Hu Y, He H, Lu J, Wang Y, Xiao P, Li J, et al. E2A-PBX1 exhibited a promising prognosis in pediatric acute lymphoblastic leukemia treated with the CCLG-ALL2008 protocol. *Onco Targets and Ther*. 2016; 9: 7219-7225.
15. Yen HJ, Chen SH, Chang TY, Yang CP, Lin DT, Hung IJ, et al. Pediatric acute lymphoblastic leukemia with t(1;19)/TCF3-PBX1 in Taiwan. *Pediatr Blood Cancer*. 2017; 64-e26557.
16. Lin A, Cheng FWT, Chiang AKS, Luk CW, Li RCH, Ling ASC, et al. Excellent outcome of acute lymphoblastic leukaemia with TCF3-PBX1 rearrangement in Hong Kong. *Pediatr Blood Cancer*. 2018; 65: e27346.
17. Wang Y, Xue YJ, Lu AD, Jia YP, Zuo YX, Zhang LP. Long-Term Results of the Risk-Stratified Treatment of TCF3-PBX1-Positive Pediatric Acute Lymphoblastic Leukemia in China. *Clin Lymphoma Myeloma Leuk*. 2021; 21: e137-e144.
18. Zhou B, Chu X, Tian H, Liu T, Liu H, Gao W, et al. The clinical outcomes and genomic landscapes of acute lymphoblastic leukemia patients with E2A-PBX1: A 10-year retrospective study. *Am J Hematol*. 2021; 96: 1461-1471.
19. Jia M, Hu BF, Xu XJ, Zhang JY, Li SS, Tang YM. Clinical features and prognostic impact of TCF3-PBX1 in childhood acute lymphoblastic leukemia: A single-center retrospective study of 837 patients from China. *Curr Probl Cancer*. 2021; 45: 100758.
20. Jeha S, Choi J, Roberts KG, Pei D, Coustan-Smith E, Inaba H, et al. Clinical significance of novel subtypes of acute lymphoblastic leukemia in the context of minimal residual disease-directed therapy. *Blood Cancer Discov*. 2021; 2: 326-337.