

Outcomes of Children With *BCR-ABL1*-Like Acute Lymphoblastic Leukemia Treated With Risk-Directed Therapy Based on the Levels of Minimal Residual Disease

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose

BCR-ABL1-like acute lymphoblastic leukemia (ALL) is a recently identified B-cell ALL (B-ALL) subtype with poor outcome that exhibits a gene expression profile similar to *BCR-ABL1*-positive ALL but lacks the *BCR-ABL1* fusion protein. We examined the outcome of children with *BCR-ABL1*-like ALL treated with risk-directed therapy based on minimal residual disease (MRD) levels during remission induction.

Patients and Methods

Among 422 patients with B-ALL enrolled onto the Total Therapy XV study between 2000 and 2007, 344 had adequate samples for gene expression profiling. Next-generation sequencing and/or analysis of genes known to be altered in B-ALL were performed in patients with *BCR-ABL1*-like ALL who had available material. Outcome was compared between patients with and those without *BCR-ABL1*-like ALL.

Results

Forty (11.6%) of the 344 patients had *BCR-ABL1*-like ALL. They were significantly more likely to be male, have Down syndrome, and have higher MRD levels on day 19 and at the end of induction than did other patients with B-ALL. Among 25 patients comprehensively studied for genetic abnormalities, 11 harbored a genomic rearrangement of *CRLF2*, six had fusion transcripts responsive to ABL tyrosine kinase inhibitors or JAK inhibitors, and seven had mutations involving the Ras signaling pathway. There were no significant differences in event-free survival ($90.0\% \pm 4.7\%$ [SE] v $88.4\% \pm 1.9\%$ at 5 years; $P = .41$) or in overall survival ($92.5\% \pm 4.2\%$ v $95.1\% \pm 1.3\%$ at 5 years; $P = .41$) between patients with and without *BCR-ABL1*-like ALL.

Conclusion

Patients who have *BCR-ABL1*-like ALL with poor initial treatment response can be salvaged with MRD-based risk-directed therapy and may benefit from identification of kinase-activating lesions for targeted therapies.

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INTRODUCTION

By using genome-wide analysis, two groups of investigators identified a subtype of B-cell acute lymphoblastic leukemia (B-ALL) termed "*BCR-ABL1*-like" or "Ph-like" ALL, which has a gene expression profile similar to that of Philadelphia chromosome (Ph)-positive ALL but lacks *BCR-ABL1* fusion protein expressed from t(9;22)(q34.1;q11.2) and accounts for 10% to 15% of childhood B-progenitor ALL.^{1,2} Similar to Ph-positive ALL, *BCR-ABL1*-like ALL is character-

ized by a high frequency of alterations of the *IKZF1* gene, which encodes the early lymphoid transcription factor IKAROS, and a high risk of relapse when treated with conventional chemotherapy.^{1,2}

Although Ph-positive ALL is a single genetic entity defined by the presence of the Ph chromosome and the *BCR-ABL1* gene fusion, *BCR-ABL1*-like ALL is a genetically heterogeneous disease. Approximately half the patients with *BCR-ABL1*-like ALL harbor abnormalities of the cytokine receptor gene *CRLF2*,³ either as a translocation to the immunoglobulin heavy chain enhancer region

(*IGH-CRLF2*) or as a focal deletion resulting in the expression of a *P2RY8-CRLF2* fusion transcript.^{4,5} Among patients with *CRLF2* rearrangement, approximately half have concomitant activating mutations of the Janus kinase genes, *JAK1* or *JAK2*, resulting in activation of *JAK-STAT* signaling.⁴⁻⁶ Recent transcriptome and whole-genome sequencing genomics of *BCR-ABL1*-like patients without *CRLF2* rearrangements identified a diverse array of genetic alterations that activate cytokine receptor and tyrosine signaling.^{3,7} Because of the lack of uniform definition and different gene expression classifiers used by various groups of investigators, each study of *BCR-ABL1*-like ALL comprised a different, albeit overlapping, cohort of patients.

Although the prognostic impact of high *CRLF2* expression varied according to the study cohort,^{8,9} *BCR-ABL1*-like ALL has been consistently associated with poor treatment outcome in all studies reported to date.^{1,2,9-13} In this study, we examine the clinical heterogeneity and prognostic impact of *BCR-ABL1*-like ALL treated in the context of an effective risk-directed protocol based on minimal residual disease (MRD) levels measured during remission induction therapy.¹⁴

PATIENTS AND METHODS

Patients

From June 2000 to October 2007, 498 evaluable patients (1 to 18 years of age) with newly diagnosed ALL were consecutively enrolled onto the Total Therapy XV study at St. Jude Children's Research Hospital or at Cook Children's Medical Center.¹⁴ This study was limited to patients with B-ALL because all *BCR-ABL1*-like patients have B-lineage immunophenotype. Of the 422 patients enrolled onto the Total Therapy XV study with B-ALL, 344 (81.5%) had adequate samples to screen for the expression profile of *BCR-ABL1*-like ALL (Fig 1). The protocol was approved by the institutional review boards. Signed informed consent was obtained from the patients who were 18 years old or from the parents or guardians of younger patients, with assent from the patients, as appropriate.

Diagnosis and Risk Classification

The diagnosis of ALL was based on morphologic, immunophenotypic, and genetic features of leukemic blast cells, as described previously.¹⁵ MRD

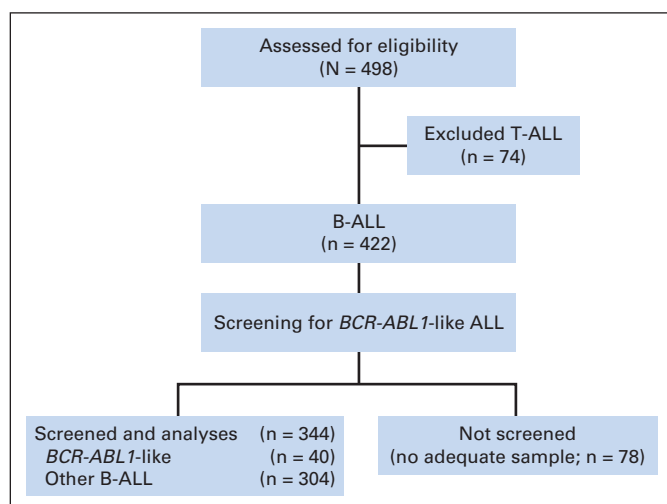


Fig 1. CONSORT diagram. Among the 498 patients enrolled onto the Total Therapy XV trial, 422 had B-cell acute lymphoblastic leukemia (B-ALL), of whom 344 had adequate samples to screen for the expression profile of *BCR-ABL1*-like ALL. T-ALL, T-cell ALL.

was determined by flow cytometry, polymerase chain reaction analysis, or both.^{16,17} Risk classification was based on presenting age and leukocyte count (National Cancer Institute [NCI] risk group), leukemic cell genotype, and response to remission induction treatment. Patients with B-ALL who were between 1 and 10 years old, had a leukocyte count less than $50 \times 10^9/L$ (NCI standard risk), and had a leukemic cell DNA index ≥ 1.16 or $t(12;21)[ETV6-RUNX1]$ were provisionally classified as low-risk ALL. Patients with $t(9;22)[BCR-ABL1]$ were considered to have high-risk ALL, and the remaining patients, including those with T-cell ALL and B-ALL with $t(1;19)[TCF3-PBX1]$ were provisionally classified as standard- (intermediate-) risk ALL. The final risk status was determined by the level of MRD during and after remission induction therapy. Any patient with $\geq 1\%$ leukemic cells in the bone marrow on day 19 of remission induction or 0.01% to 0.99% residual leukemia after completion of 6-week induction therapy was considered to have standard-risk ALL. Patients with $\geq 1\%$ residual disease after completion of induction therapy were assigned to the high-risk group.

Treatment

Details of the treatment regimen have been described previously.¹⁴ In brief, patients with $\geq 1\%$ residual leukemia in the bone marrow on day 19 of remission induction were given three additional doses of asparaginase. At the end of induction (between days 43 and 46), bone marrow aspiration was performed to assess MRD level, and consolidation therapy with high-dose methotrexate and daily mercaptopurine was given for four courses. Low-risk and standard-risk patients then received risk-directed continuation therapy, and high-risk patients were offered the option of allogeneic hematopoietic stem-cell transplantation. All patients received early triple intrathecal therapy, and none received prophylactic cranial irradiation.

Identification and Genomic Characterization of *BCR-ABL1*-Like ALL

Single nucleotide polymorphism 500K or single nucleotide polymorphism 6.0 microarrays and U133A gene expression profiling (Affymetrix) were performed in all patients with suitable genomic material available to identify copy number alterations and distinct genetic subgroups by using reference normalization¹⁸ and circular binary segmentation,¹⁹ as previously described.^{1,20} Prediction analysis for microarrays was used to identify patients with *BCR-ABL1*-like ALL with a gene expression profile similar to that of *BCR-ABL1* ALL.^{3,21} Sequence mutation analysis for genes known to be mutated in B-ALL (including *IKZF1*, *PAX5*, and *JAK2*) was performed for all patients with available material, including 16 patients with *BCR-ABL1*-like ALL, 12 of whom were also studied with next-generation sequencing. Genomic polymerase chain reaction (PCR), Sanger sequencing, and mutation detection were performed as previously described.^{6,20,22} *CRLF2* rearrangements were identified by genomic PCR, real-time PCR, and fluorescent in situ hybridization, as previously described.⁵ Next-generation sequencing was performed by the St. Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project, as previously described,²³⁻²⁵ with messenger RNA (mRNA) sequencing in seven patients, whole-genome sequencing in five patients, and both mRNA sequencing and whole-genome sequencing in nine patients (Appendix Table A1, online only). Fusion transcripts were identified from mRNA sequencing data by using CICERO, a novel analysis algorithm (Li et al, manuscript in preparation). Putative fusions were confirmed by real-time PCR and bidirectional Sanger sequencing. Sequence data are deposited at the European Genome Phenome archive, accession EGAS00001000654.

Statistical Analysis

Event-free survival and survival from diagnosis were estimated by the method of Kaplan-Meier, with associated SEs calculated by the method of Peto and Pike. The cumulative incidence functions of relapse were estimated by the method of Kalbfleisch and Prentice,²⁶ and the functions were compared by using Gray's test. Deaths in remission were considered competing events in the estimation of cumulative incidence of relapse. Outcome data updated on August 23, 2013, were used for this analysis. The median follow-up time for patients remaining in continuous remission was 8.2 years (range, 1.3 to 12.9 years). At the time of analysis, 95% of the survivors had had a follow-up visit within 2 years; only 2.0% of the patients lacked a documented contact within the previous 5 years.

RESULTS

Presenting features and treatment outcome of the 344 patients who were evaluated for the gene expression profile of *BCR-ABL1*-like ALL were not significantly different from those of the 78 patients who were not (data not shown). Of the 344 patients with B-ALL who were evaluated, 40 (11.6%) had *BCR-ABL1*-like ALL. Table 1 summarizes the clinical and biologic features as well as treatment and outcome of these 40 patients (27 males and 13 females). Their median age was 5.3 years (range, 1.3 to 18.6 years), and median presenting leukocyte count was $7.1 \times 10^9/L$ (range, 1.7 to $258.3 \times 10^9/L$). Compared with other patients with B-ALL, those with *BCR-ABL1*-like ALL were more likely to be male ($P = .04$), have Down syndrome ($P = .003$), and have higher MRD on day 19 ($P = .009$) and at the end of induction ($P = .001$; Table 2). There was no significant difference in the distribution of the risk groups between patients with *BCR-ABL1*-like ALL and those with other B-ALL on the basis of initial risk classification of the protocol ($P = .41$) or NCI risk classification ($P = .61$). However, after including response to remission induction based on MRD levels in the risk-classification algorithm, patients with *BCR-ABL1*-like ALL were more likely to be classified as having standard- or high-risk ALL ($P = .02$; Table 2).

All six patients with high-risk *BCR-ABL1*-like ALL received hematopoietic stem-cell transplantation. The proportion of patients with *BCR-ABL1*-like ALL who received a transplantation (15%) was significantly higher than 4.3% for the other patients with B-ALL treated in the same protocol ($P = .015$). Adverse events among patients with *BCR-ABL1*-like ALL included hematologic with or without CNS relapse in four patients (No. 4, 5, 23, and 27), two deaths in remission (No. 34 and 36), and one induction failure (No. 39).

None of the 40 patients had $t(1;19)(TCF3-PBX1)$, $t(4;11)(MLL-AFF1)$, or $t(12;21)(ETV6-RUNX1)$; 11 had hyperdiploidy with gain of at least five chromosomes. Of the 40 patients with *BCR-ABL1*-like ALL identified by gene expression profiling, 11 (27.5%) harbored a genomic rearrangement of *CRLF2*, including nine patients with *P2RY8-CRLF2* and one with *IGH-CRLF2*. An additional patient had marked *CRLF2* overexpression suggestive of rearrangement but was negative for these alterations. Six of these patients with deregulated *CRLF2* had concomitant JAK mutations, including JAK2 p.Arg683Gly (four patients), 683Ser (one patient), and JAK1 p.Val658Phe (one patient).

Twenty-five patients with *BCR-ABL1*-like ALL had suitable material for detailed genomic interrogation and sequencing, including 14 patients who lacked *CRLF2* rearrangement. Four patients had fusion transcripts responsive to ABL tyrosine kinase inhibitors, including *SSBP2-PDGFRB* (patient 12), *SSBP2-CSF1R* (patient 33), *EBF1-PDGFRB* (patient 38), and *NUP214-ABL1* (patient 40). Two patients had genetic lesions predicted to be responsive to JAK inhibition: IL7R p.Val253Gly and JAK1 p.Ala428Pro (patient 7) and IL7R p.Ile241_Ile245delinsCysLeuCys (patient 25). Seven patients harbored mutations activating Ras signaling (patients 6, 11, 13, 18, 23, 28, and 30). Three patients lacked a kinase activating lesion on mRNA sequencing or whole-genome sequencing (patients 16, 29, and 39). Of the four patients with *BCR-ABL1*-like ALL with high hyperdiploidy, two had alterations in the Ras pathway with a complex *FLT3* mutation (patient 6) and *NRAS* p.Gln61Lys substitution (patient 11). Collectively, of the 25 patients subjected to

detailed genomic profiling and sequencing, 22 (88%) had cytokine receptor, kinase, or Ras alterations.

Seven (27%) of 26 patients with *BCR-ABL1*-like ALL studied had deletion of *IKZF1*, a frequency markedly lower than that of patients with *BCR-ABL1*-like ALL in previous pediatric cohorts.^{1,7} Seven patients had other lesions involving the B-lineage transcription factor genes *PAX5* and *EBF1* and, collectively, 11 (42%) had one or more lesions in this pathway.

Despite inferior response to remission induction therapy as shown by overall higher levels of MRD (Table 2), patients with *BCR-ABL1*-like ALL did not have a significantly inferior event-free survival or overall survival compared with patients with other B-ALL subtypes (Figs 2A and 2B). Even when treatment outcome was analyzed separately within the three risk groups, no significant differences in event-free survival or overall survival between the two groups were noted (Table 3).

Consistent with the above results, the cumulative risk of isolated hematologic relapse or any relapse did not differ significantly between patients with *BCR-ABL1*-like ALL and those with other B-ALL subtypes, regardless of whether these parameters were analyzed including all patients (Figs 3A and 3B) or separately within the three risk groups (Table 4). Similar results for the comparison of event-free survival, overall survival, and cumulative risk of relapse were obtained after exclusion of the 10 patients with Down syndrome or those with specific translocations including $t(1;19)(TCF3-PBX1)$, $t(4;11)(MLL-AFF1)$, $t(12;21)(ETV6-RUNX1)$, and $t(9;22)(BCR-ABL1)$ (data not shown).

In multivariable analyses, including known prognostic factors in the Total Therapy XV study (the presence of *BCR-ABL1*, MRD > 5% on day 19 of induction, MRD > 0.01% on day 46 of induction, *IKZF1* alteration, and *BCR-ABL1*-like ALL), only MRD more than 0.01% on day 46 of induction was independently associated with poor survival (hazard ratio, 5.18; 95% CI, 1.59 to 16.9; $P = .006$; Appendix Table A2, online only).

Among patients with *BCR-ABL1*-like ALL, the only prognostic factor is the presence of MRD more than 5% on day 19 of remission induction. The nine patients with MRD more than 5% on day 19 of induction had inferior event-free survival ($66.7\% \pm 14.5\% v 96.7\% \pm 3.3\%$ at 5 years; $P = .006$) and inferior overall survival ($77.8\% \pm 13.0\% v 96.7\% \pm 3.3\%$; $P = .008$) compared with the other 30 patients with lower MRD levels. Event-free survival was not significantly different between the 11 patients with and the 29 patients without rearrangement of *CRLF2* ($90.9\% \pm 8.3\% v 89.7\% \pm 5.9\%$ at 5 years and $90.0\% \pm 15.8\% v 76.8\% \pm 14.0\%$ at 10 years; $P = .40$). The seven patients with *IKZF1* alterations tended to have a poorer event-free survival than the 19 patients without *IKZF1* alterations ($71.4\% \pm 15.6\% v 100\% \pm 0.0\%$ at 5 years and $71.4\% \pm 27.0\% v 94.7\% \pm 8.9\%$ at 10 years; $P = .08$).

DISCUSSION

This study demonstrates that the adverse prognosis of pediatric *BCR-ABL1*-like ALL can be improved by effective risk-directed therapy based primarily on MRD levels during and at the end of remission induction therapy. It should be noted that our patient population and their risk assignment may be different from those of previously reported studies. In contrast to prior studies that selectively examined

Table 1. Clinical and Laboratory Characteristics of the 40 Patients With *BCR-ABL1*-Like ALL

Patient	Risk Group	% MRD		Genomic Lesion	DNA Index ≥ 1.16	Age at Diagnosis (years)	Sex	Race/Ethnicity†	WBC $\times 10^9/L$	Current Status
		Day 19	Day 46							
1	Low	< 0.01	< 0.01	Not tested	Yes	6.7	M	White	1.7	First remission for 8.3+ years
2	Low	< 0.01	< 0.01	Not tested	No	1.29	F	White	4.5	First remission for 10.1+ years
3	Low	< 0.01	< 0.01	Not tested	Yes	1.8	M	Other	4	First remission for 3.9+ years
4	Low	< 0.01	< 0.01	Not tested	Yes	2.66	M	White	5.3	Second remission for 5.5+ years after hematologic relapse
5	Low	< 0.01	< 0.01	Not tested	Yes	3.18	F	White	15.5	Second remission for 6.4+ years after combined hematologic and CNS relapse
6	Low	< 0.01	< 0.01	FLT3 p.Tyr597insGly and Ala680Val	Yes	4.08	M	White	16.8	First remission for 6.2+ years
7	Low	< 0.01	< 0.01	IL7R p.Val253Gly and JAK1 p.Ala428Pro	No	2.11	M	White	45.1	First remission for 11.2+ years
8	Low	< 0.01	< 0.01	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Ser	No	3.99	M	White	23.3	First remission for 12.6+ years
9	Low	0.01	< 0.01	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly	No	5.26	M	White	4.4	First remission for 10.0+ years
10	Low	0.024	< 0.01	<i>P2RY8-CRLF2</i>	No	3.94	M	White	5	First remission for 8.4+ years
11	Low	0.031	< 0.01	NRAS p.Gln61Lys	Yes	3.26	F	Hispanic	7.5	First remission for 7.6+ years
12	Low	0.032	< 0.01	<i>SSBP2-PDGFRB</i>	No	1.9	F	Black	33	First remission for 10.5+ years
13	Low	0.042	< 0.01	FLT3 p.Ile836del	No	3.47	M	White	10.3	First remission for 6.1+ years
14	Low	0.047	< 0.01	<i>P2RY8-CRLF2</i>	No	2.88	F	White	5.2	First remission for 8.7+ years
15	Low	0.63	< 0.01	Not tested	No	8.11	F	White	1.8	First remission for 7.8+ years
16	Low	< 0.01	< 0.01	No lesion by mRNA sequencing or WGS	Yes	18.45	M	White	5.4	First remission for 8.6+ years
17	Standard	< 0.01	< 0.01	Not tested	No	5.95	F	Black	4.8	First remission for 7.8+ years
18	Standard	0.034	< 0.01	<i>NF1</i> deletion	No	3.35	M	White	5.9	First remission for 8.1+ years
19	Standard	0.7	0.429	Not tested	Yes	6.19	M	White	4.3	First remission for 9.1+ years
20	Standard	3.01	0.1	Not tested	No	3.73	M	White	2.9	First remission for 11.2+ years
21	Standard	3.8	< 0.01	Not tested	Yes	1.98	M	Hispanic	8.3	First remission for 8.3+ years
22	Standard	10	0.081	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly	No	3.04	M	White	33.6	First remission for 9.3+ years
23	Standard	37.5	0.096	<i>NF1</i> deletion	No	5.43	M	White	4.1	Died of hematologic relapse 6.0 years after first remission
24	Standard	< 0.01	< 0.01	Not tested	No	11.86	M	White	2.2	First remission for 9.9+ years
25	Standard	< 0.01	< 0.01	IL7R p.Ile241_Ile245delinsCysLeuCys	No	15.76	F	White	2.3	First remission for 11.1+ years
26	Standard	0.015	< 0.01	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly	No	5.35	M	White	245.4	First remission for 7.3+ years
27	Standard	0.024	< 0.01	Not tested	No	14.19	M	Black	10.4	Died of combined hematologic and CNS relapse 1.8 years after first remission
28	Standard	0.057	0.01	<i>P2RY8-CRLF2</i> and NRAS p.Gln61Lys	No	1.87	F	White	258.3	First remission for 9.7+ years
29	Standard	0.218	0.044	No lesion by RNA sequencing or WGS	Yes	16.4	F	Hispanic	6	First remission for 11.4+ years
30	Standard	0.927	< 0.01	<i>P2RY8-CRLF2</i> , IL7R p.Ser185Cys, <i>NF1</i> p.Arg1241* and deletion	No	13.74	F	White	2.7	First remission for 5.8+ years
31	Standard	1.83	0.01	Unknown <i>CRLF2</i> rearrangement	No	18.55	M	White	1.7	First remission for 6.4+ years
32	Standard	2.78	0.059	<i>IGH-CRLF2</i> and JAK2 p.Arg683Gly	No	7.66	M	White	78.1	First remission for 12.1+ years
33	Standard	8.68	0.07	<i>SSBP2-CSF1R</i>	No	12.94	M	White	103.2	First remission for 8.5+ years
34	Standard	10.5	0.133	Not tested	No	16.23	M	Hispanic	9.8	Died as a result of an accident 3.1 years after first remission
35	High	4.8	0.039	Not tested	No	1.7	F	White	8.1	First remission for 6.1+ years
36	High	16.9	3.06	<i>P2RY8-CRLF2</i> and JAK1 p.Val658Phe	No	7.03	F	Hispanic	23.5	Died of respiratory failure after transplantation in first remission for 0.7 years
37	High	18.4	0.82	Not tested	No	7.16	M	Other	11.7	First remission for 5.0+ years
38	High	61	8.69	<i>EBF1-PDGFRB</i>	No	3.97	M	White	41.8	First remission for 9.7+ years
39	High	72.1	36	No lesion by mRNA sequencing or WGS	No	18	M	White	6.6	First remission for 9.5+ years after initial induction failure
40	High	73.1	6.74	<i>NUP214-ABL1</i>	No	16.32	M	White	135.6	First remission for 7.7+ years

NOTE. Patients 17, 18, and 21 were classified as having standard-risk leukemia because of CNS3 status, near-haploidy, and high level of minimal residual disease (MRD) at day 19 of remission induction, respectively. DNA index of > 1.16 indicates cases with high hyperdiploidy.

Abbreviations: ALL, acute lymphoblastic leukemia; WGS, whole-genome sequencing.

†Genetically determined race/ethnicity using the single nucleotide polymorphism–based ancestry information.

Table 2. Comparison of Clinical and Biologic Variables Between Patients With and Without *BCR-ABL1*-Like ALL

Variable	<i>BCR-ABL1</i> -Like ALL				P
	Yes		No		
	No.	%	No.	%	
Age at diagnosis, years					
1-10	29	10.51	247	89.49	.21
> 10	11	16.18	57	83.82	
Leukocyte count × 10 ⁹ /L					
< 50	35	12.92	236	87.08	.22
≥ 50	5	6.85	68	93.15	
DNA index					
≥ 1.16	10	11.49	77	88.51	1.00
< 1.16	30	11.67	227	88.33	
Sex					
Male	27	15.08	152	84.92	.04
Female	13	7.88	152	92.12	
Down syndrome					
No	35	10.48	299	89.52	.003
Yes	5	50.00	5	50.00	
Race/ethnicity*					
White	30	13.64	190	86.36	.557
Black	3	5.66	50	94.34	
Asian	0	0.00	4	100.00	
Hispanic	5	10.00	45	90.00	
Other	2	11.76	15	88.24	
CNS status					
CNS1 combined with traumatic tap without blasts	26	10.36	225	89.64	.24
CNS3 ≥ 5 WBC/μL with blasts	2	28.57	5	71.43	
CNS2 < 5 WBC/μL with blasts	9	13.04	60	86.96	
Traumatic tap with blasts	3	17.65	14	82.35	
NCI risk group					
Standard	26	12.50	182	87.50	.61
High	14	10.29	122	89.71	
t(9;22)(<i>BCR-ABL1</i>)					
Absent	40	11.90	296	88.10	.60
Present	0	0.00	8	100.00	
t(1;19)(<i>TCF3-PBX1</i>)					
Absent	40	12.54	279	87.46	.10
Present	0	0.00	25	100.00	
t(4;11)(<i>MLL-AFF1</i>)					
Absent	40	11.73	301	88.27	1.00
Present	0	0.00	3	100.00	
t(12;21)(<i>ETV6-RUNX1</i>)					
Absent	40	15.38	220	84.62	< .001
Present	0	0.00	84	100.00	
Ploidy					
Hyperdiploidy > 50	11	10.78	91	89.22	.72
Others	29	12.78	198	87.22	
Initial risk classification					
Low	24	10.48	205	89.52	.41
Standard	16	14.81	92	85.19	
High	0	0.00	7	100.00	
Final risk classification†					
Low	16	8.21	179	91.79	.02
Standard	18	14.17	109	85.83	
High	6	27.27	16	72.73	

(continued in next column)

Table 2. Comparison of Clinical and Biologic Variables Between Patients With and Without *BCR-ABL1*-Like ALL (continued)

Variable	<i>BCR-ABL1</i> -Like ALL				P
	Yes		No		
	No.	%	No.	%	
MRD on day 19					
< 5%	30	9.84	275	90.16	.009
≥ 5%	9	26.47	25	73.53	
MRD at the end of induction					
< 0.01%	24	8.60	255	91.40	.001
≥ 0.01%	16	25.81	46	74.19	

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; NCI, National Cancer Institute.

*Genetically determined race/ethnicity using the single nucleotide polymorphism-based ancestry information.

†Based on MRD levels measured on days 19 and 46 of remission induction.

high-risk B-ALL and did not apply MRD measurement for risk-directed therapy,^{1,2,10,27} this study included all patients with newly diagnosed ALL and used MRD level to direct intensity of therapy. In this regard, patients with *BCR-ABL1*-like ALL in this study do not have a significantly higher frequency of NCI high-risk ALL at diagnosis compared with patients with other B-ALL subtypes. However, a high proportion of patients with *BCR-ABL1*-like ALL in this study were subsequently classified as having higher-risk leukemia (standard or high risk according to Total Therapy XV criteria) based on MRD levels during and after completion of remission induction therapy.

Patients with *BCR-ABL1*-like ALL in Total Therapy XV had the same proportion of high hyperdiploidy as did other patients with B-ALL but lacked other genetic abnormalities with prognostic or therapeutic implications such as t(1;19)(*TCF3-PBX1*), t(4;11)(*MLL-AFF1*), and t(12;21)(*ETV6-RUNX1*). A notable finding was a lower frequency of *CRLF2* (27.5%) and *IKZF1* (27%) alterations in *BCR-ABL1*-like ALL than in prior studies (approximately 50% and 70%, respectively). This may, in part, reflect differences in study cohorts, because prior studies selectively examined high-risk ALL, included patients older than 18 years, and were enriched for patients of Hispanic ethnicity (22% to 29%) treated in clinical trials by the Children's Oncology Group.^{1,3,10} In this regard, in the Children's Oncology Group studies, Hispanic patients with high Native American genetic ancestry have a high frequency of rearrangements of *CRLF2*²⁸ and inherited *GATA3* rs3824662 risk allele,²⁹ which were associated with *BCR-ABL1*-like ALL and inferior treatment outcome. In contrast, the Total Therapy XV study enrolled consecutive patients 1 to 18 years old from all risk groups and had a relatively low frequency (14.5%) of patients with Hispanic ethnicity.

In a risk classification schema based solely on the presenting age, initial leukocyte count, and conventional cytogenetic and molecular genetic features, approximately 60% of our patients would have been treated as having low-risk ALL. Thus, many of the patients with *BCR-ABL1*-like ALL in the other series with resistant leukemia might not have received intensive treatment because they were not recognized as a result of a lack of response evaluation. By contrast, the Total Therapy XV study used MRD measurements for risk-directed treatment. With this additional information, only 40% of the patients received treatment for low-risk ALL, and the remaining patients were treated with

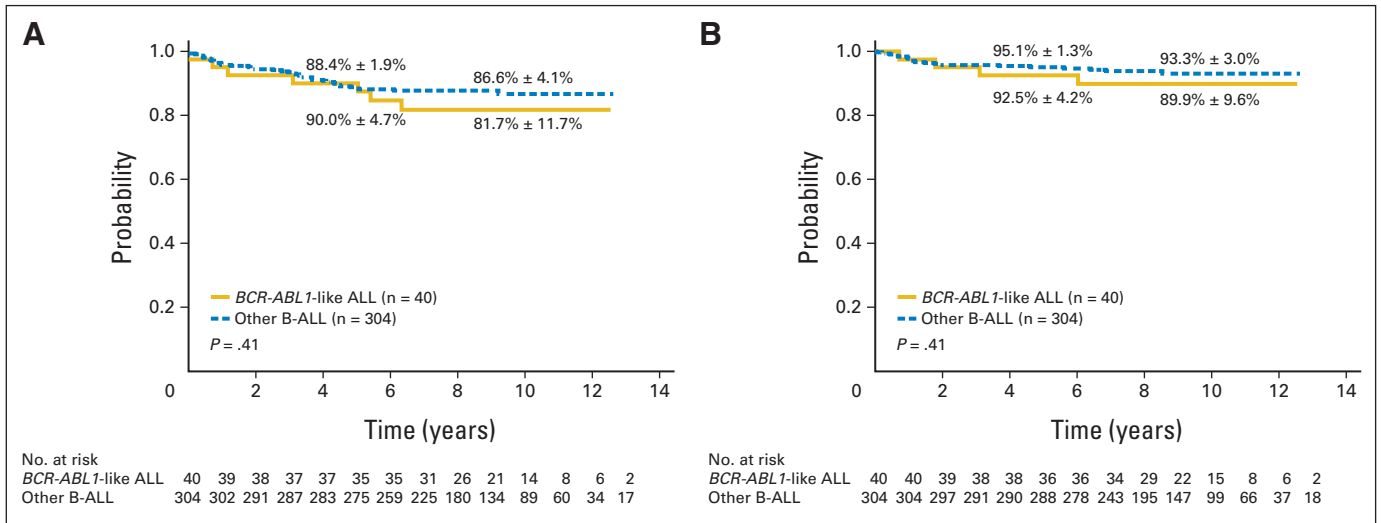


Fig 2. Kaplan-Meier estimates of (A) event-free survival and (B) overall survival for patients with *BCR-ABL1*-like acute lymphoblastic leukemia (ALL) and other B-cell ALL (B-ALL) subtypes. Five- and 10-year rates are reported as means ± SE.

more intensive therapy for standard-risk (45%) or high-risk (15%) ALL.

With improved risk assessment based on MRD measurements, comparable results between *BCR-ABL1*-like ALL and other B-ALL subtypes were achieved in the Total Therapy XV study; these results extended to all three risk groups (Tables 3 and 4). Therefore, for centers that lack the capability to identify *BCR-ABL1*-like ALL, excellent overall treatment results can still be achieved, provided that reliable methods for monitoring MRD are available. However, we argue that it is still clinically important to identify *BCR-ABL1*-like ALL because many of these patients harbor genetic lesions that are sensitive to tyrosine kinase inhibitors (eg, *ABL1* and *PDGFRB* rearrangements) or JAK inhibitors (eg, *EPOR*, *IL7R*, *JAK2*, and *SH2B3* that activate JAK-STAT signaling) in preclinical models using cell lines and human leukemic cells.^{3,7,30,31} The incorporation of these agents in the treatment of patients with targetable lesions could potentially help reduce the intensity of chemotherapy. Although our series had only a limited number of refractory or relapsed patients and was not large enough to capture the full spectrum of targetable lesions, anecdotal reports of refractory *BCR-ABL1*-like ALL that responded well to tyrosine kinase

inhibitors are already emerging.³²⁻³⁴ Because of their high level of MRD at the end of remission induction, six (15%) of the 40 patients with *BCR-ABL1*-like ALL in this series received hematopoietic stem-cell transplantation, a proportion much higher than 4.3% for the other patients with B-ALL treated in the same protocol.¹⁴ Conceivably, identification of patients with *BCR-ABL1*-like ALL with targetable genetic lesions followed by treatment with tyrosine kinase inhibitors or JAK inhibitors might avoid transplantation in some of these patients, similar to the use of tyrosine kinase inhibitors in *BCR-ABL1*-positive childhood ALL, which have improved outcome and reduced the number of patients requiring transplantation.^{35,36} Of note, among four of the six patients with *BCR-ABL1*-like ALL who received transplantations and were retrospectively tested for genomic lesions in this series, two had fusion transcripts that would respond to ABL tyrosine kinase inhibitors.

Only two of 16 low-risk patients with *BCR-ABL1*-like ALL treated with an antimetabolite-based regimen in this series (and one of six females 1 to 3 years old with the *ZMIZ1-ABL1* fusion treated with conventional therapy in another report)³⁷ had a late relapse after completion of therapy. Both relapsed patients who were initially

Table 3. Comparison of EFS and OS Between Patients With *BCR-ABL1*-Like ALL and Other Patients With B-ALL, According to Final Risk Group

Risk Group*	No. of Patients	% EFS (± SE)			% OS (± SE)		
		Year 5	Year 10	P	Year 5	Year 10	P
Low							
<i>BCR-ABL1</i> -like	16	100 ± 0.0	85.6 ± 14.5	.36	100 ± 0.0	100 ± 0.0	.49
Other B-ALL	179	95.0 ± 1.6	92.5 ± 4.2		98.3 ± 1.0	96.2 ± 3.0	
Standard							
<i>BCR-ABL1</i> -like	18	88.9 ± 7.2	83.3 ± 15.2	.97	88.9 ± 7.2	83.0 ± 15.3	.32
Other B-ALL	109	84.3 ± 3.6	83.3 ± 6.9		92.7 ± 2.6	91.6 ± 5.0	
High							
<i>BCR-ABL1</i> -like	6	66.7 ± 17.2	66.7 ± 38.5	.49	83.3 ± 13.9	83.3 ± 34.0	.58
Other B-ALL	16	41.3 ± 12.0	41.3 ± 22.4		74.0 ± 10.9	64.8 ± 22.2	

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL; EFS, event-free survival; OS, overall survival.
 *Based on minimal residual disease levels measured on days 19 and 46 of remission induction.

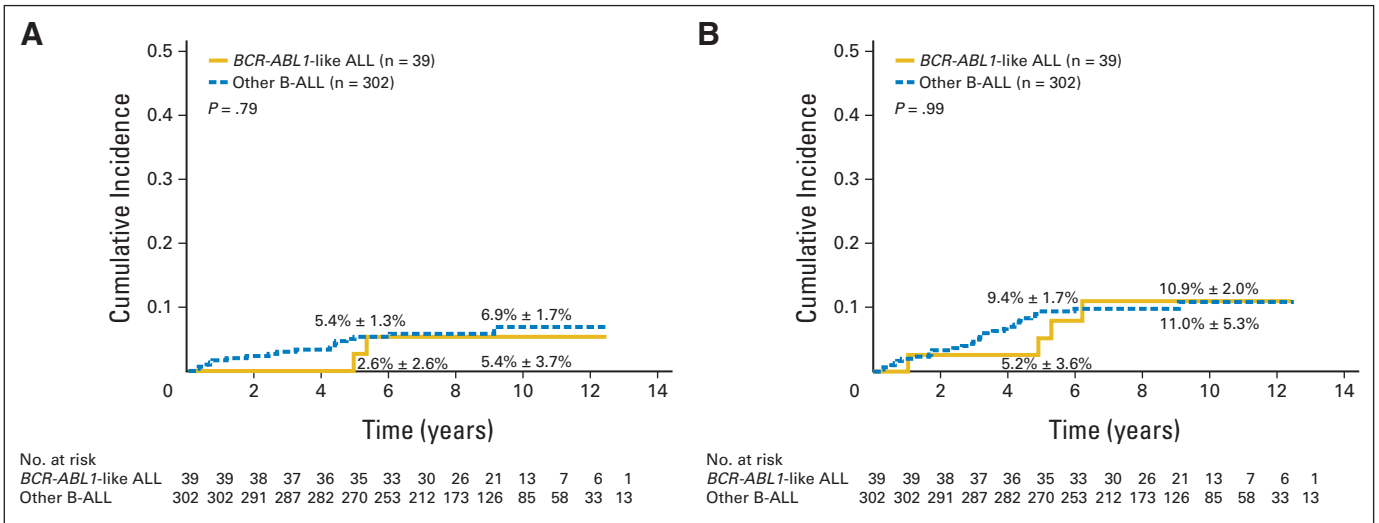


Fig 3. Cumulative risk of (A) isolated hematologic relapse or (B) any relapse for patients with *BCR-ABL1*-like acute lymphoblastic leukemia (ALL) and other B-cell ALL (B-ALL) subtypes. Five- and 10-year rates are reported as means ± SE.

treated with low-risk therapy in this study are long-term survivors after retrieval chemotherapy. Thus, in the setting of limited resources, screening for *BCR-ABL1*-like ALL may not be necessary for low-risk patients with negative MRD after remission induction and may be reserved for those with refractory or high-risk ALL, especially patients with high levels of MRD, and for patients with relapsed B-ALL. If our finding of the lack of *t(1;19)(TCF3-PBX1)*, *t(4;11)(MLL-AFF1)*, or *t(12;21)(ETV6-RUNX1)* in *BCR-ABL1*-like ALL is confirmed by additional studies, patients with these genetic abnormalities could also be excluded from screening. However, detailed genomic studies were not performed in both relapsed patients with *BCR-ABL1*-like ALL in the low-risk group in this study. Conceivably, they had genetic lesions responsive to tyrosine kinase inhibitors. Thus, additional studies are still needed to characterize the low-risk patients.

In summary, the advances in cure rates brought about by contemporary MRD-based treatment of childhood ALL have extended to patients with *BCR-ABL1*-like ALL despite their initial inferior response to treatment. Identification of this ALL subtype and administration of targeted therapy may further improve overall cure rates

beyond 90% achieved in some of the contemporary clinical trials³⁸ and improve their quality of life.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Table 4. Comparison of Cumulative Risk of Isolated Hematologic Relapse or Any Relapse Between Patients With *BCR-ABL1*-Like ALL or Other B-ALL, According to Final Risk Group

Risk Group*	No. of Patients	% Cumulative Risk of Isolated Hematologic Relapse (± SE)			% Cumulative Risk of Any Relapse (± SE)		
		Year 5	Year 10	P	Year 5	Year 10	P
Low							
<i>BCR-ABL1</i> -like	16	0	6.7 ± 6.7	.46	0	14.4 ± 9.9	.23
Other B-ALL	178	1.7 ± 1.0	4.2 ± 2.2		4.0 ± 1.5	6.4 ± 2.4	
Standard							
<i>BCR-ABL1</i> -like	18	5.6 ± 5.6	5.6 ± 5.6	.58	11.1 ± 7.6	11.1 ± 7.6	.74
Other B-ALL	109	9.3 ± 2.8	9.3 ± 2.8		13.9 ± 3.4	13.9 ± 3.4	
High							
<i>BCR-ABL1</i> -like	5	0	0	.28	0	0	.11
Other B-ALL	15	21.3 ± 11.6	21.3 ± 11.6		42.0 ± 13.9	42.0 ± 13.9	

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL.

*Based on minimal residual disease levels measured on days 19 and 46 of remission induction.

Identification of two novel mutant alleles of human TPMT, and diagnostic uses thereof **Other Remuneration:** None

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GLOSSARY TERMS

cumulative incidence of relapse: the use of competing risk analyses indicated in the presence of competing events (such as death and relapse); the Gray's test is a recommended method to estimate cumulative incidence of relapse.

genomics: the scientific discipline in which multiple genes, gene products, or regions of the genome are analyzed via large-scale, high-throughput molecular approaches directed to DNA and RNA. This definition is a deviation from that of the original term, which meant an analysis of the whole genome.

JAK/STAT pathway: the pathway usually (not always) activated by cytokine receptors, where binding of a ligand to the cytokine receptor leads to recruitment and subsequent autophosphorylation of JAK proteins (activated state) at the cellular membrane level. Activated JAKs phosphorylate the receptor, creating docking sites for specific signaling proteins, including STAT proteins. When coupled to the activated receptor, STAT proteins are phosphorylated (activated) by JAK proteins. In contrast to cytokine receptor signaling, receptors with intrinsic tyrosine kinase activity (eg, epidermal growth factor receptor, platelet-derived growth factor) may bypass JAK activation and directly phosphorylate STAT proteins. See JAK (Janus kinase) and STAT.

Appendix

Table A1. Genomic Analysis of *BCR-ABL1*-Like ALL

Sample No.	Sample ID	Group	Analysis Type						Genomic Lesion
			Genomic	Sanger	RT-PCR	NGS	RNA Sequencing	WGS	
1	SJHYPER089	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
2	SJBALL070	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
3	SJHYPER088	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
4	SJHYPER201	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
5	SJBALL159	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
6	SJHYPER150	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	No	Yes	No	Yes	FLT3 p.Tyr597insGly and Ala680Val
7	SJHYPO109	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	Yes	Yes	IL7R p.Val253Gly and JAK1 p.Ala428Pro
8	SJBALL191	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	Yes	Yes	No	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Ser
9	SJHYPER013	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	Yes	Yes	Yes	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly
10	SJBALL206	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	No	No	No	<i>P2RY8-CRLF2</i>
11	SJHYPER146	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	No	Yes	Yes	Yes	NRAS p.Gln61Lys
12	SJBALL153	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	Yes	Yes	No	Yes	<i>SSBP2-PDGFRB</i>
13	SJHYPER120	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	No	Yes	Yes	Yes	FLT3 p.Ile836del
14	SJBALL208	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	No	No	No	<i>P2RY8-CRLF2</i>
15	SJBALL084	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
16	SJHYPER021	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	Yes	Yes	No lesion by RNA sequencing or WGS
17	SJDOWN009	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
18	SJHYPO123	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	Yes	Yes	<i>NF1</i> deletion
19	SJHYPER015	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
20	SJHYPER053	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
21	SJHYPER135	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
22	SJBALL203	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	No	No	No	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly
23	SJHYPO146	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	No	Yes	<i>NF1</i> deletion
24	SJHYPO137	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
25	SJBALL063	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	No	Yes	No	Yes	IL7R p.Ile241_Ile245delinsCysLeuCys
26	SJBALL083	<i>BCR-ABL1</i> -like_CRLF2	Yes	No	Yes	Yes	Yes	No	<i>P2RY8-CRLF2</i> and JAK2 p.Arg683Gly
27	SJHYPO140	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
28	SJHYPO110	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	Yes	Yes	Yes	<i>P2RY8-CRLF2</i> and NRAS p.Gln61Lys
29	SJHYPER003	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	Yes	Yes	No lesion by RNA sequencing or WGS
30	SJBALL101	<i>BCR-ABL1</i> -like_CRLF2	Yes	No	Yes	Yes	Yes	No	<i>P2RY8-CRLF2</i> , IL7R p.Ser185Cys, NF1 p.Arg1241* and deletion
31	SJBALL096	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	No	No	No	No	Unknown CRLF2 rearrangement
32	SJBALL195	<i>BCR-ABL1</i> -like_CRLF2	Yes	Yes	Yes	Yes	Yes	No	<i>IGH-CRLF2</i> and JAK2 p.Arg683Gly
33	SJBALL204	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	Yes	Yes	Yes	No	<i>SSBP2-CSF1R</i>
34	SJBALL105	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
35	SJBALL100	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
36	SJDOWN013	<i>BCR-ABL1</i> -like_CRLF2	Yes	No	Yes	Yes	Yes	No	<i>P2RY8-CRLF2</i> and JAK1 p.Val658Phe
37	SJBALL071	<i>BCR-ABL1</i> -like_non-CRLF2	No	No	No	No	No	No	Not tested
38	SJBALL012	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	Yes	Yes	No	Yes	<i>EBF1-PDGFRB</i>
39	SJBALL011	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	Yes	No	Yes	Yes	Yes	No lesion by RNA sequencing or WGS
40	SJBALL085	<i>BCR-ABL1</i> -like_non-CRLF2	Yes	No	Yes	Yes	Yes	No	<i>NUP214-ABL1</i>

Abbreviations: ALL, acute lymphoblastic leukemia; ID, identification; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction; WGS, whole-genome sequencing.

BCR-ABL1-Like Acute Lymphoblastic Leukemia

Table A2. Multivariable Analyses of Factors Associated With EFS or OS

Factors	EFS			OS		
	HR	95% CI	P	HR	95% CI	P
Presence of <i>BCR-ABL1</i>	2.28	0.69 to 7.54	.18	3.23	0.59 to 17.8	.18
Presence of <i>IKZF1</i> alteration	2.08	0.81 to 5.29	.13	0.85	0.19 to 3.73	.83
MRD > 5% at day 19 of induction	2.43	0.94 to 6.31	.07	1.31	0.37 to 4.62	.67
MRD > 0.01% at day 46 of induction	1.93	0.79 to 4.70	.15	5.18	1.59 to 16.9	.006
Presence of <i>BCR-ABL1</i> -like subtype	1.89	0.53 to 6.77	.33	1.36	0.28 to 6.65	.70

Abbreviations: EFS, event-free survival; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival.