

## High Frequency and Poor Outcome of Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia in Adults

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### A B S T R A C T

#### Purpose

Philadelphia chromosome (Ph) –like acute lymphoblastic leukemia (ALL) is a high-risk subtype of childhood ALL characterized by kinase-activating alterations that are amenable to treatment with tyrosine kinase inhibitors. We sought to define the prevalence and genomic landscape of Ph-like ALL in adults and assess response to conventional chemotherapy.

#### Patients and Methods

The frequency of Ph-like ALL was assessed by gene expression profiling of 798 patients with B-cell ALL age 21 to 86 years. Event-free survival and overall survival were determined for Ph-like ALL versus non-Ph-like ALL patients. Detailed genomic analysis was performed on 180 of 194 patients with Ph-like ALL.

#### Results

Patients with Ph-like ALL accounted for more than 20% of adults with ALL, including 27.9% of young adults (age 21 to 39 years), 20.4% of adults (age 40 to 59 years), and 24.0% of older adults (age 60 to 86 years). Overall, patients with Ph-like ALL had an inferior 5-year event-free survival compared with patients with non-Ph-like ALL (22.5% [95% CI, 14.9% to 29.3%; n = 155] v 49.3% [95% CI, 42.8% to 56.2%; n = 247], respectively;  $P < .001$ ). We identified kinase-activating alterations in 88% of patients with Ph-like ALL, including *CRLF2* rearrangements (51%), ABL class fusions (9.8%), *JAK2* or *EPOR* rearrangements (12.4%), other JAK-STAT sequence mutations (7.2%), other kinase alterations (4.1%), and Ras pathway mutations (3.6%). Eleven new kinase rearrangements were identified, including four involving new kinase or cytokine receptor genes and seven involving new partners for previously identified genes.

#### Conclusion

Ph-like ALL is a highly prevalent subtype of ALL in adults and is associated with poor outcome. The diverse range of kinase-activating alterations in Ph-like ALL has important therapeutic implications. Trials comparing the addition of tyrosine kinase inhibitors to conventional therapy are required to evaluate the clinical utility of these agents in the treatment of Ph-like ALL.

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### INTRODUCTION

Despite remarkable improvements in the treatment outcome for children with acute lymphoblastic leukemia (ALL),<sup>1</sup> the prognosis of adults with ALL is poor, with 5-year survival rates of 40% overall<sup>2</sup> and approximately 7% for patients who experience relapse.<sup>3</sup> Current chemotherapy regimens are limited in adults as a result of toxicity. Compared with children, adult patients

with ALL have an increased frequency of high-risk genetic alterations, such as *BCR-ABL1*, *IGH*, or *MLL* rearrangements, and complex karyotypes.<sup>4,5</sup> However, the genetic basis of adult ALL is incompletely understood.

Philadelphia chromosome (Ph) –like or *BCR-ABL1*–like ALL<sup>6,7</sup> is a high-risk subtype of ALL characterized by rearrangements, sequence mutations, and copy number alterations involving kinase or cytokine receptor genes.<sup>8,9</sup> The prevalence of Ph-like ALL increases from 10% in

#### ASSOCIATED CONTENT

 Appendix  
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 Data Supplement  
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standard-risk childhood ALL to more than 25% in young adults.<sup>8</sup> Preclinical studies and case reports indicate that the addition of tyrosine kinase inhibitors (TKIs) to current chemotherapeutic regimens may improve the poor outcome of patients with Ph-like ALL.<sup>10-13</sup>

The prevalence of Ph-like ALL in adults is unclear. A recent report from the Dutch-Belgium Hemato-Oncology Cooperative Group identified Ph-like ALL in 17% of patients age 16 to 71 years.<sup>14</sup> Another report from the German Multicenter ALL group observed a peak prevalence of Ph-like ALL of approximately 20% in adolescents and young adults, which decreased to less than 10% in adults age 40 to 84 years.<sup>15</sup> Both studies examined small numbers of patients, used different methods for identifying the Ph-like ALL gene signature, and lacked genomic characterization. A comprehensive understanding of the prevalence, outcome, and genetic basis of Ph-like ALL in adults is needed to identify patients who may benefit from TKI therapy and to determine the optimal TKIs to use. Here, we demonstrate that the incidence of Ph-like ALL exceeds 20% in patients age 21 to 86 years at diagnosis, is associated with a poor outcome, and is composed of genetic alterations that activate tyrosine kinase or cytokine receptor signaling. These results suggest that the identification of patients with Ph-like ALL should be incorporated into the design of future clinical trials.

## PATIENTS AND METHODS

### Patients and Treatment

We studied leukemia samples from banked material obtained at diagnosis from 909 patients with precursor B-cell ALL (B-ALL), 798 of whom had suitable material for genomic analysis (Appendix Fig A1, online only). Patients were enrolled onto clinical trial protocols of the following groups or centers: Alliance for Clinical Trials in Oncology Group (Cancer and Leukemia Group B) protocols C19802 (ClinicalTrials.gov identifier: NCT00003700),<sup>16</sup> C10102 (NCT00061945), and C10403 (NCT00558519); the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network protocols E2993<sup>2</sup> (NCT00002514) and E1910 (NCT02003222); The University of Texas MD Anderson Cancer Center (MDACC)<sup>17-20</sup>; Northern Italy Leukemia Group protocols 09-2000<sup>21</sup> and 10/07 (NCT00795756); Princess Margaret Cancer Centre<sup>22</sup>; Southwest Oncology

Group protocols S0333 (NCT00109837) and S9400 (NCT00002665)<sup>23</sup>; and City of Hope. The cohort was divided into the following three age groups: young adults (n = 344; age 21 to 39 years), adults (n = 304; age 40 to 59 years), and older adults (n = 150; age 60 to 86 years; Table 1; Data Supplement). Details for patient samples are provided in the Data Supplement. Patients gave written informed consent for sample collection and research. The study was approved by the St Jude Institutional Review Board.

### Genomic Profiling

Gene expression profiling was performed at the University of New Mexico Cancer Center on 798 RNA samples using either U133 Plus 2.0 microarrays (Affymetrix, Santa Clara, CA)<sup>8</sup> or a 15-gene Taqman (Thermo Fisher, Waltham, MA) quantitative reverse transcriptase polymerase chain reaction (PCR) low-density array (LDA) that identifies the Ph-like ALL gene signature, *P2RY8-CRLF2*, *BCR-ABL1*, *ETV6-ABL1*, *TCF3-PBX1*, and *DUX4/ERG*-deregulated ALL (Data Supplement).<sup>24</sup> Analysis of the 15 genes results in an integrated value between 0 and 1, termed the Ph-like coefficient. Patients with a coefficient of 0.5 to 1 were designated as having Ph-like ALL. All other genomic assays were performed at St Jude Children's Research Hospital (Memphis, TN). High expression of *CRLF2* was determined by the LDA card, and *CRLF2* rearrangements (*IGH-CRLF2* or *P2RY8-CFRL2*) were confirmed using fluorescence in situ hybridization (FISH) as described in the Data Supplement. PCR and Sanger sequencing of tumor cDNA was performed to detect sequence mutations in *JAK1* and *JAK2* (Data Supplement). A flowchart outlining the genomic assays performed is provided in the Data Supplement. Single nucleotide polymorphism (SNP) analysis was performed on 165 of 194 Ph-like samples with available DNA using either SNP 6.0 microarrays (Affymetrix; n = 49) or the Infinium Omni2.5Exome-8 BeadChip Kit (Illumina, San Diego, CA; n = 116). Details for the LDA algorithm and SNP processing are provided in the Data Supplement.

### Transcriptome Sequencing

Transcriptome sequencing (RNA-seq) was performed using the TruSeq library preparation on the Illumina HiSeq 2000 platform. All sequencing was paired end and performed using either total RNA and stranded RNA sequencing (n = 63) or polyadenylated-selected non-stranded sequencing (n = 23).<sup>8</sup> Sequencing metrics and processing details are provided in the Data Supplement. Samples were analyzed by CICERO<sup>8</sup> and FusionCatcher<sup>25</sup> to detect fusions. Sequence mutations were analyzed from RNA-seq according to the Genome Analysis Toolkit pipeline.<sup>26</sup>

**Table 1.** Clinical Characteristics of All Patients

Characteristic	Young Adult Patients (n = 344)	Adult Patients (n = 304)	Older Adult Patients (n = 150)	All Patients (N = 798)
Median age, years (range)	28 (21-39)	48 (40-59)	66 (60-86)	42 (21-86)
Median WBC count, × 10 <sup>9</sup> /L (range)	61.1 (0.4-658)	48.7 (0.2-588)	53.2 (0.7-670)	54.8 (0.2-670)
Sex, No. (%)				
Male	194 (56.4)	135 (44.0)	71 (47.3)	400 (50.1)
Female	148 (43.0)	169 (56.0)	78 (52.0)	395 (49.5)
Unknown	2 (0.6)	0 (0)	1 (0.7)	3 (0.4)
Genomic subtype, No. (%)				
<i>BCR-ABL1</i>	66 (19.2)	73 (24.0)	46 (30.7)	185 (23.2)
Philadelphia chromosome-like	96 (27.9)	62 (20.4)	36 (24.0)	194 (24.3)
<i>MLL</i>	51 (14.8)	52 (17.1)	20 (13.3)	123 (15.4)
<i>ETV6-RUNX1</i>	7 (2.0)	1 (0.3)	0 (0)	8 (1.0)
<i>TCF3-PBX1</i>	10 (2.9)	12 (3.9)	1 (0.7)	23 (2.9)
<i>DUX4/ERG</i>	11 (3.2)	7 (2.3)	0 (0)	18 (2.3)
B-cell other	103 (29.7)	97 (31.9)	47 (31.3)	247 (31.0)

## Statistical Analysis

Associations between categorical values were examined using Fisher's exact test. Event-free survival and overall survival from diagnosis were estimated using the Kaplan-Meier method. All groups were compared using the log-rank test.<sup>27</sup> An event was defined as a failure to achieve remission, a relapse after remission, or the development of a second malignancy. A multivariable analysis of event-free and overall survival was performed using the Cox proportional hazards regression model.<sup>28</sup> Analyses were performed using Prism software version 6.0 (GraphPad Software, La Jolla, CA), R software ([www.r-project.org](http://www.r-project.org)), and SAS software version 9.1.2 (SAS Institute, Cary, NC).

## RESULTS

### Clinical Characteristics

Overall, 194 (24.3%) of 798 patients with B-ALL were classified as having Ph-like ALL. The prevalence of *ETV6-RUNX1*, *TCF3-PBX1*, and *DUX4/ERG* ALL was low (1.0%, 2.9%, and 2.3%, respectively), whereas the prevalence of patients with *BCR-ABL1* and *MLL*-rearranged ALL was 23.2% and 15.4%, respectively. The prevalence of Ph-like ALL exceeded 20% in all age groups (27.9% in young adults, 20.4% in adults, and 24.0% in older adults; [Table 1](#); [Data Supplement](#)). Patients with Ph-like ALL had higher WBC counts at diagnosis compared with patients with non-Ph-like ALL (excluding *BCR-ABL1* and *MLL*), both overall (mean,  $56.6 \nu 26.8 \times 10^9/L$ , respectively;  $P < .001$ ) and in the different age cohorts ([Table 2](#); [Data Supplement](#)). A higher proportion of patients with Ph-like ALL were male compared with patients with non-Ph-like ALL (61.3%  $\nu$  50%, respectively;  $P = .0094$ ; [Table 2](#)).

### Treatment Outcomes

Among all patients, increasing age was associated with inferior outcome. The 5-year event-free survival rates for young adults, adults, and older adults were 40.4% (95% CI, 34.1% to 46.8%), 29.8% (95% CI, 23.3% to 36.0%), and 18.9% (95% CI, 8.9% to 27.1%;  $P < .001$ ), respectively, with 5-year overall survival rates of 45.2% (95% CI, 38.8% to 51.9%), 35.1% (95% CI, 28.4% to 41.8%), and 16.2% (95% CI, 4.7% to 24.8%;  $P < .001$ ; [Fig 1](#)), respectively. Overall, the outcome of patients with Ph-like ALL was inferior compared with the outcome of patients with non-Ph-like

ALL (excluding *BCR-ABL1* and *MLL*), with 5-year event-free survival rates of 22.5% (95% CI, 14.9% to 29.3%) compared with 49.3% (95% CI, 42.8% to 56.2%;  $P < .001$ ) and overall survival rates of 23.8% (95% CI, 16.0% to 32.4%) compared with 52.4% (95% CI, 45.4% to 59.9%;  $P < .001$ ; [Fig 2](#) and [Data Supplement](#)), respectively. In multivariable analyses, age (hazard ratio [HR], 2.55;  $P < .001$ ), sex (HR, 1.97;  $P < .001$ ), and the presence of Ph-like ALL (HR, 1.48;  $P = .014$ ) were independently associated with poor survival ([Data Supplement](#)). Minimal residual disease at the end of induction was assessed by six-color flow cytometry for patients treated on The University of Texas MD Anderson Cancer Center protocols. Of those tested, patients with Ph-like ALL were less likely to achieve minimal residual disease–negative remission ( $< 0.01\%$  minimal residual disease) compared with patients with non-Ph-like ALL (47% [ $n = 19$ ]  $\nu$  94% [ $n = 17$ ], respectively;  $P = .002$ ). Outcome after hematopoietic stem-cell transplantation was available for patients enrolled onto E2993. There was no significant difference in survival between patients who did ( $n = 7$ ) and did not receive transplantation ( $n = 14$ ;  $P = .2$ ; [Data Supplement](#)).

Inferior outcome was observed for patients with Ph-like ALL compared with patients with non-Ph-like ALL among young adults and adults, with 5-year event-free survival rates of 24.1% (95% CI, 12.6% to 34.1%) compared with 60.5% (95% CI, 51.2% to 71.4%;  $P < .001$ ) and 21.4% (95% CI, 7.6% to 32.5%) compared with 38.7% (95% CI, 27.6% to 50.0%;  $P = .0021$ ; [Data Supplement](#)), respectively. The difference in outcomes was not significant for older adults, with 3-year event-free survival rates of 8.0% (95% CI, 0.5% to 21.6%) and 33.3% (95% CI, 15.8% to 52.2%;  $P = .47$ ) for patients with Ph-like ALL and non-Ph-like ALL, respectively. Likewise, the 5-year overall survival rates for patients with Ph-like ALL were inferior to those of patients with non-Ph-like ALL in young adults (25.4% [95% CI, 14.8% to 37.5%]  $\nu$  64.2% [95% CI, 53.1% to 73.3%], respectively;  $P < .001$ ) and adults (27.0% [95% CI, 13.3% to 42.7%]  $\nu$  44.9% [95% CI, 33.5% to 55.7%], respectively;  $P = .023$ ), but the difference in 3-year survival rates in older adults was not significant between the two groups (13.5% [95% CI, 2.3% to 34.3%]  $\nu$  37.9% [95% CI, 19.2% to 56.6%], respectively;  $P = .64$ ; [Data Supplement](#)). The lack of significance in older adults may be a result of the small number of patients available for outcome analysis ( $n = 44$ ); therefore,

**Table 2.** Clinical Characteristics of Patients by Genomic Subtype

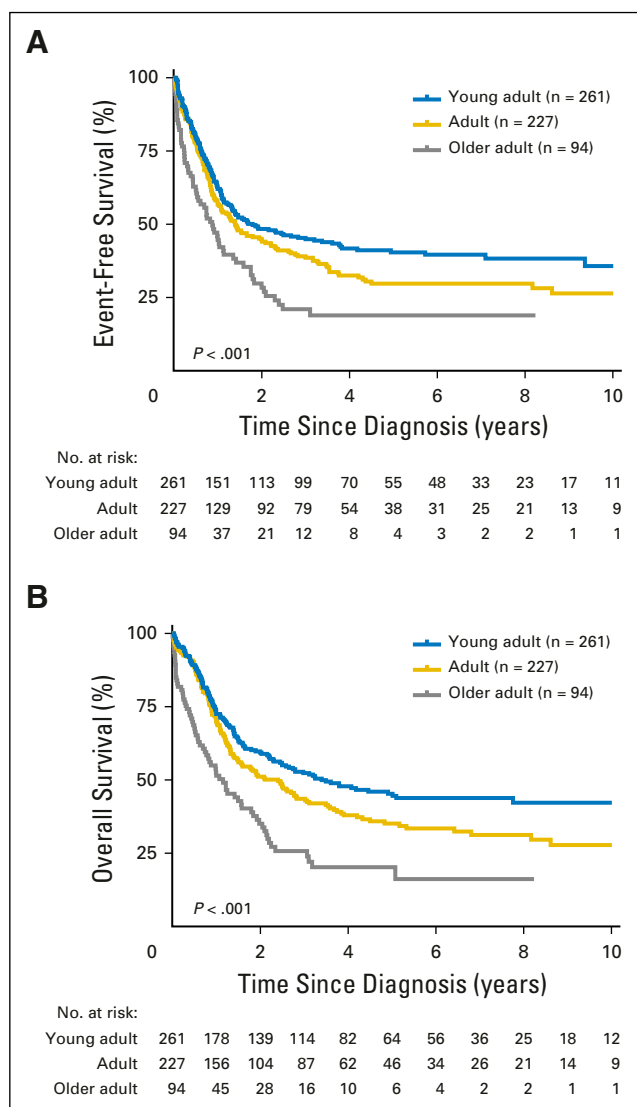
Characteristic	<i>BCR-ABL1</i> (n = 185)	Ph-Like* (n = 194)	<i>MLL</i> † (n = 123)	B-Cell Other (n = 296)	P
Median age, years (range)	47 (21-84)	40 (21-86)	43 (21-86)	41 (21-80)	
Median WBC, $\times 10^9/L$ (range)	58.0 (0.7-658)	56.6 (0.2-434)	119.8 (0.5-670)	26.8 (0.4-600)	$< .001$
WBC, %					$< .001$
< $50 \times 10^9/L$	64.4	66.7	34.6	89.0	
$\geq 50 \times 10^9/L$	35.6	33.3	65.4	11.0	
Sex, No. (%)					.0094
Male	89 (48.1)	119 (61.3)	44 (35.8)	148 (50.0)	
Female	96 (51.9)	73 (37.6)	78 (63.4)	148 (50.0)	

NOTE. B-cell other includes *ETV6-RUNX1*, *TCF3-PBX1*, *DUX4/ERG*, and remaining pre-B ALL. WBC count comparison by Kruskal-Wallis rank sum test. Sex comparison by Fisher's exact test between Ph-like and B-other B-ALL.

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; Ph-like, Philadelphia chromosome-like.

\*Two patients with unknown sex status.

†One patient with unknown sex status.



**Fig 1.** Overall outcome of adult acute lymphoblastic leukemia. Kaplan-Meier estimates of (A) event-free survival and (B) overall survival of young adults, adults, and older adults combined. Outcome data were available for 582 of 798 patients studied.

screening larger cohorts of patients older than age 60 years will be important to assess the outcome of Ph-like ALL in the elderly.

### Genomic Landscape of Ph-Like ALL in Adults

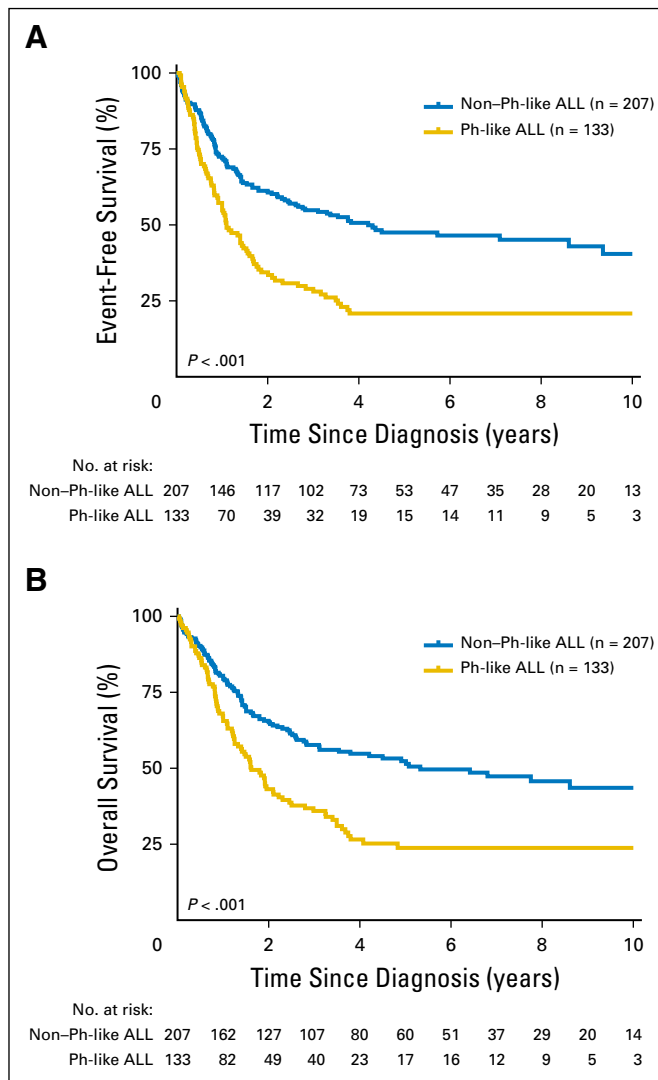
Genomic alterations activating kinase signaling were identified in 171 (88.1%) of 194 patients with Ph-like ALL and 171 (95.0%) of 180 patients with materials enabling genomic analysis. Overall, 99 (51%) of 194 patients with Ph-like ALL had high *CRLF2* expression. The frequency was 51.1% in young adults, 46.8% in adults, and 58.4% in older adults. We identified *IGH-CRLF2* (n = 57; 57.6%) and *P2RY8-CRLF2* (n = 21; 21.2%) rearrangements; for 21 patients, there was insufficient material for analysis. Concomitant Janus kinase (*JAK1/JAK2*) mutations were identified in 25 (25%) of 99 patients with high *CRLF2* expression (Data Supplement).

Transcriptome sequencing was performed in 86 of the remaining 95 patients with Ph-like ALL. Genetic alterations were classified into subgroups of kinase and cytokine receptor signaling pathways (Fig 3). These included rearrangements of *CRLF2* (51% of patients), ABL class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*; 9.8%), *JAK2* (7.2%), or *EPOR* (5.2%); sequence mutations of *IL7R*, *SH2B3*, *JAK1*, or *JAK3* and rearrangement of *TYK2* (termed other JAK-STAT; 7.2%); Ras pathway mutations (*KRAS*, *NF1*, *PTPN11*, and *CBL1*; 3.6%); and uncommon fusions (*FLT3*, *NTRK3*, *BLNK*, and *PTK2B*; 4.1%). A subset of patients did not have a kinase-activating alteration identified by transcriptome analysis (4.6%) or lacked material for genomic analysis (7.2%).

Rearrangements activating kinase signaling were identified in 126 (65%) of 194 patients, including 32 different rearrangements (10 of which were recurrent) in the following 14 kinase or cytokine receptor genes (Table 3; Data Supplement): *JAK2* (eight fusion partners), *ABL1* (n = 5), *ABL2* (n = 3), *EPOR* (n = 3), *CRLF2* (n = 2), *PDGFRB* (n = 2), *TYK2* (n = 2), *BLNK* (n = 1), *CBL* (n = 1), *CSF1R* (n = 1), *FLT3* (n = 1), *NTRK3* (n = 1), *PDGFRA* (n = 1), and *PTK2B* (n = 1). The following 11 rearrangements had not previously been identified in B-ALL: *FIP1L1-PDGFRB*, *SNX29-PDGFRB*, *SMU1-JAK2*, *ZNF340-JAK2*, *THADA-EPOR*, *SMARCA4-TYK2*, *ZNF340-TYK2*, *ZYMM2-FLT3*, *DNTT-BLNK*, *TMEM2-PTK2B*, and *KANK1-CBL1*. All kinase fusions retained an intact tyrosine kinase domain (Data Supplement) and showed increased expression of the kinase gene downstream of the exon breakpoint (Data Supplement). With the exception of *EPOR* rearrangements, we did not observe significant differences in the frequency of kinase subtypes across the age groups (Data Supplement).

Sequence mutations in genes activating JAK-STAT signaling were identified in 14 patients with low *CRLF2* expression, including *IL7R* (seven patients), *JAK1* (two patients), *JAK3* (one patient), and *SH2B3* (two patients) and two patients with rearrangements involving *TYK2*. Seven patients harbored alterations within the Ras pathway only, including sequence mutations in *KRAS* (five patients) and *PTPN11* (one patient) and one patient with a novel rearrangement involving *CBL*. In addition, two patients with *KRAS* mutations also harbored sequence mutations within *NF1* (Data Supplement).

Patients with Ph-like ALL were classified on the basis of an LDA coefficient between 0.5 and 1.<sup>24</sup> Within this classification, we observed differences between the distribution of kinase groups on the basis of the coefficient. For patients with Ph-like ALL with a rearrangement involving ABL class genes, *CRLF2*, or *JAK2/EPOR*, we observed 90%, 68%, and 79% of patients, respectively, with a coefficient between 0.9 and 1. In contrast, 41% of patients with other kinase or JAK-STAT alterations exhibited a coefficient between 0.9 and 1. Patients harboring Ras pathway alterations had a weaker coefficient, with 86% of patients classified in the 0.5 to 0.74 category (Data Supplement). Altogether, patients harboring a kinase rearrangement were more likely to have a coefficient greater than 0.9 than patients with a sequence mutation (73% v 31%, respectively;  $P < .001$ ). Patients harboring rearrangements of *CRLF2* or *JAK2/EPOR* had a trend toward inferior 5-year event-free and overall survival compared with patients harboring ABL class or other JAK-STAT alterations ( $P = .057$  and  $P = .072$ , respectively; Data Supplement).



**Fig 2.** Outcome of adults with Philadelphia chromosome (Ph)-like acute lymphoblastic leukemia (ALL). Kaplan-Meier estimates of (A) event-free survival and (B) overall survival of all patients with Ph-like ALL compared with patients with non-Ph-like ALL (including *ETV6-RUNX1*, *TCF3-PBX1*, *DUX4/ERG*, and all other ALLs). Outcome data were available for 340 of 490 patients with Ph-like and non-Ph-like ALL.

Analysis of DNA copy number alterations confirmed a high frequency of *IKZF1* alterations (deletion and mutation) in patients with Ph-like ALL (120 of 165 patients; 73%). *IKZF1* alterations were also more common in patients with a kinase or cytokine receptor rearrangement (109 of 137 patients; 80%) than a sequence mutation (eight of 17 patients; 47%;  $P < .001$ ). Other common targets of genetic alteration included *CDKN2A/B* (51%), *PAX5* (38%), *BTG1* (33%), and *EBF1* (22%; Data Supplement). We also observed enrichment of copy number alterations of *IKZF1*, *PAX5*, *EBF1*, and *CDKN2A/B* in patients harboring a Ph-like coefficient greater than 0.9 (Data Supplement). A summary of all copy number alterations identified in Ph-like ALL is provided in the Data Supplement. Overall, 142 (86%) of 165 patients with Ph-like ALL assessed by SNP profiling harbored alterations affecting lymphoid development (*IKZF1*, *PAX5*, *EBF1*, *ETV6*, and *RUNX1*),

and 89 (54%) of 165 patients had alterations of the cell cycle (*CDKN2A/B*, *TP53*, and *RB1*).

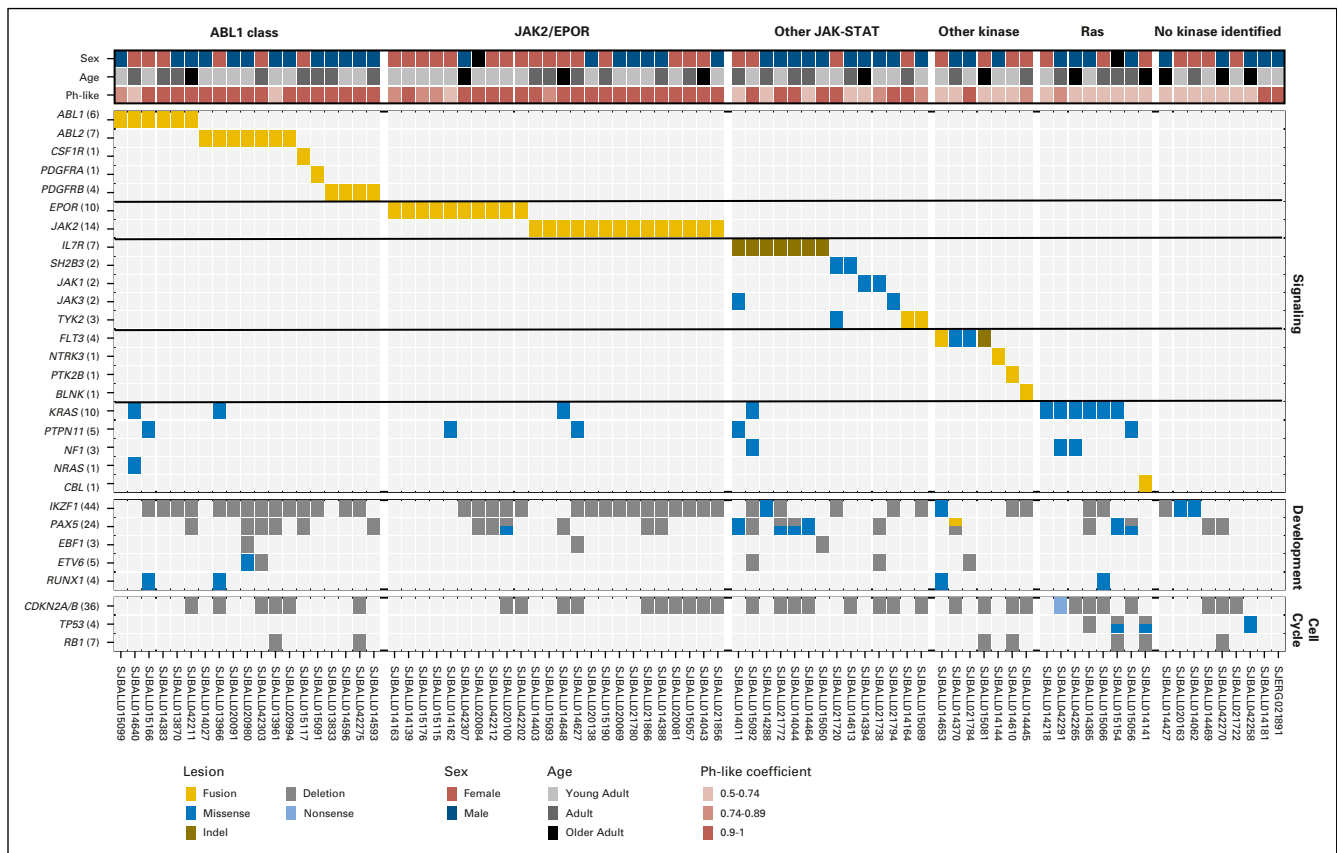
## DISCUSSION

In this comprehensive retrospective study of 798 patients with B-ALL age 21 to 86 years, we have demonstrated that the frequency of Ph-like ALL exceeds 20% across the adult age spectrum. With the combined analysis of patients treated on different protocols, Ph-like ALL is independently associated with a poor prognosis. We show that Ph-like ALL in adults is characterized by a variety of genetic alterations that activate kinase or cytokine receptor signaling and that the majority of lesions are targetable with US Food and Drug Administration–approved TKIs.

A similar spectrum of kinase-activating alterations was identified in adults with Ph-like ALL as that found in children. The overall frequency of *CRLF2* rearrangement (51%) is similar to that identified in previous reports, with older adults showing the highest frequency at 58%. However, we observed a 25% frequency of *JAK* mutations in *CRLF2*-rearranged adult patients, which is lower than the frequency reported for childhood ALL (50%).<sup>8</sup> Additional targets of mutation in *CRLF2*-rearranged patients include *IL7R*, *FLT3*, and *SH2B3*.<sup>8</sup> Identification of the other co-operating lesions in adult patients will provide important insights into the mechanisms of oncogenic signaling by *CRLF2* in ALL.

We also show a high frequency of *JAK2* and *EPOR* rearrangements in the adult ALL population. Overall, approximately 70% of adult patients with Ph-like ALL harbor genetic alterations that may be targetable with *JAK* inhibitors, such as ruxolitinib. These include *CRLF2* rearrangements with or without *JAK1/JAK2* mutation, rearrangements involving *JAK2* and *EPOR*, and sequence mutations of *JAK1*, *JAK3*, *IL7R*, and *SH2B3*. The only exception is *TYK2*, which is not sensitive to ruxolitinib and will require development of selective *TYK2* inhibitors.<sup>32</sup> Multiple studies have demonstrated potent activity of ruxolitinib in pre-clinical models of Ph-like ALL or early T-cell precursor ALL. Although variations in response were observed in *CRLF2*-rearranged cells, this was independent of *JAK* mutation<sup>12,33</sup> and is likely a result of the presence of other genetic alterations activating *JAK-STAT* signaling (eg, *IL7R* mutations).<sup>8</sup> These preclinical studies have shown that the efficacy of ruxolitinib is determined by the degree of *JAK-STAT* activation rather than *JAK* mutational status. To determine the efficacy of *JAK* inhibition in patients harboring lesions activating the *JAK-STAT* pathway, ruxolitinib in combination with conventional chemotherapy will be assessed in trials from the Children's Oncology Group and The University of Texas MD Anderson Cancer Center.

Another major Ph-like ALL genetic subgroup involves kinases that are targeted by *ABL* inhibitors (imatinib and dasatinib), including *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDFGRB*. Rearrangements resulting in *FIP1L1-PDGFR*A have been identified in eosinophilic leukemia and are responsive to *ABL* inhibitors.<sup>31</sup> We report this fusion for the first time, to our knowledge, in Ph-like ALL. An additional new target of rearrangement is B-cell linker (*BLNK*), an adaptor protein that transduces signals from the B-cell receptor and activates the Ras pathway via ERK.<sup>34</sup> Another putative mechanism of Ras activation was identified through the



**Fig 3.** Kinase alterations identified in patients with Philadelphia chromosome (Ph)-like acute lymphoblastic leukemia (ALL). Data are shown for 86 patients with Ph-like ALL who underwent transcriptome sequencing. The cohort is divided into patients with ABL class fusions (*ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, and *PDGFRB*); *EPOR* or *JAK2* rearrangements; other JAK-STAT sequence mutations (*IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *TYK2*); other kinase alterations (*FLT3*, *NTRK3*, *PTK2B*, and *BLNK*); RAS pathway alterations (*KRAS*, *PTPN11*, *NF1*, *NRAS*, and *CBL*); or no kinase identified. The Ph-like coefficient was obtained from the low-density array card using an algorithm including 15 genes highly expressed in patients with Ph-like ALL.

*KANK1-CBL* fusion. *CBL* is a negative regulator of signal transduction pathways, including Ras. Fusion with *KANK1* likely inactivates *CBL* by disrupting the open reading frame, leading to hyperactivation of Ras signaling. Overall, we identified 11 new rearrangements that had not previously been identified in Ph-like ALL. These data further highlight the genetic heterogeneity of Ph-

like ALL and the importance of incorporating comprehensive sequencing to identify all genetic alterations.

To enable prompt delivery of TKIs, accurate and fast diagnosis of patients with Ph-like ALL is a critical factor when designing clinical trials for TKI therapy. In the research setting, we identified patients with the Ph-like ALL signature using a TaqMan LDA card,

**Table 3.** Kinase Fusions Identified in Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia

Kinase	Tyrosine Kinase Inhibitor	No. of Partners	No. of Patients	5' Genes
<i>ABL1</i>	Dasatinib	5	6	<i>ETV6</i> , <sup>8</sup> <i>NUP214</i> , <sup>8</sup> <i>RCS1</i> , <sup>8</sup> <i>SNX2</i> , <sup>8</sup> <i>SFPQ</i> <sup>29</sup>
<i>ABL2</i>	Dasatinib	3	7	<i>PAG1</i> , <sup>8</sup> <i>RCS1</i> , <sup>8</sup> <i>ZC3HAV1</i> <sup>8</sup>
<i>CSF1R</i>	Dasatinib	1	1	<i>MEF2D</i> <sup>30</sup>
<i>PDGFRA</i>	Dasatinib	1	1	<i>FIP1L1</i> <sup>31</sup>
<i>PDGFRB</i>	Dasatinib	2	4	<i>EBF1</i> , <sup>8</sup> <i>SNX29</i>
<i>CRLF2</i>	JAK2 inhibitor	2	99	<i>IGH</i> , <sup>8</sup> <i>P2RY8</i> <sup>8</sup>
<i>JAK2</i>	JAK2 inhibitor	8	14	<i>ATF7IP</i> , <sup>8</sup> <i>BCR</i> , <sup>8</sup> <i>ETV6</i> , <sup>8</sup> <i>PAX5</i> , <sup>8</sup> <i>PPFIBP1</i> , <sup>8</sup> <i>SMU1</i> , <i>SSBP2</i> , <sup>8</sup> <i>ZNF340</i>
<i>EPOR</i>	JAK2 inhibitor	3	10	<i>IGH</i> , <sup>8</sup> <i>IGK</i> , <sup>8</sup> <i>THADA</i>
<i>TYK2</i>	TYK2 inhibitor	2	2	<i>SMARCA4</i> , <i>ZNF340</i>
<i>FLT3</i>	FLT3 inhibitor	1	1	<i>ZMYM2</i>
<i>NTRK3</i>	NTRK inhibitor	1	1	<i>ETV6</i> <sup>8</sup>
<i>PTK2B</i>	FAK inhibitor	1	1	<i>TMEM2</i>
<i>BLNK</i>		1	1	<i>DNTT</i>
<i>CBL</i>		1	1	<i>KANK1</i>

which is rapidly performed in a Clinical Laboratory Improvement Amendments–compliant laboratory. This is only a screening tool, and additional approaches are required for the identification of specific kinase alterations. FISH was performed on patients with high *CRLF2* expression to identify *CRLF2* rearrangements, and RNA-seq was performed on the remainder of patients to identify additional kinase alterations. Although effective for research studies, this tiered approach may delay identification of the kinase-activating lesions in the diagnostic setting. A number of approaches are being evaluated for the clinical identification of Ph-like ALL and underlying kinase-activating alterations. As a result of the genetic complexity of Ph-like ALL, assays to identify rearrangements that are agnostic of the 5' fusion partner are ideal. A simple and cost-effective approach is to perform FISH for break apart of the kinase gene, which will identify most fusions involving key kinase genes.<sup>9</sup> Reverse transcriptase PCR may be used as a screening or confirmatory approach but will only confirm known fusions. Another option is the digital molecular barcoding platform NanoString (NanoString, Seattle, WA), which can multiplex more than 200 different genetic alterations. This assay is simple and requires little material but also only identifies known fusions. Capture-based RNA sequencing (eg, Archer Fusion-Plex Oncology Research Kit, Archer DX, Boulder, CO; Foundation One Heme, Foundation Medicine, Cambridge, MA<sup>35</sup>) effectively identifies kinase fusions and is agnostic of the 5' fusion partner but requires Clinical Laboratory Improvement Amendments–approved sequencing capability. Thus, although FISH or targeted approaches are satisfactory for a subset of alterations, it is likely that next-generation sequencing technologies in diagnostic laboratories are required for the comprehensive and timely identification of patients with Ph-like ALL. Although these assays may not be feasible for all clinical laboratories at present, they will be increasingly available in the future.

In summary, Ph-like ALL is common across the age spectrum of adult ALL, including more than 20% of patients age 21 to 86 years, with a notably high prevalence of JAK-STAT activating alterations. These findings warrant the development of clinical trials in adults that assess the efficacy of TKIs, similar to those that are being established for pediatric ALL.

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Disclosures provided by the authors are available with this article at [ascopubs.org/journal/jco](http://ascopubs.org/journal/jco).

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

## High Frequency and Poor Outcome of Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia in Adults

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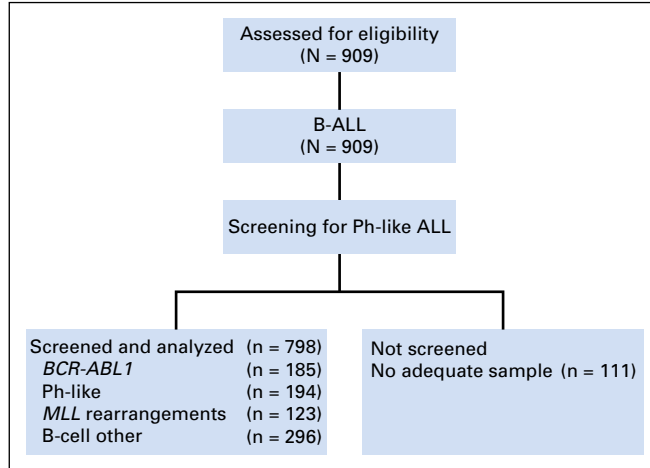
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**Appendix**



**Fig A1.** CONSORT diagram. Among the 909 eligible patients with B-cell acute lymphoblastic leukemia (B-ALL), 798 had adequate samples to screen for the Philadelphia chromosome (Ph)-like ALL signature.