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Pediatric-inspired therapy and blinatumomab consolidation improve outcomes in young adults with Philadelphia-like acute lymphoblastic leukemia

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Short Title: Treatment strategies in adults with Ph-like ALL

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ABSTRACT

Philadelphia (Ph)-like acute lymphoblastic leukemia (ALL) is a high-risk subtype of B-cell ALL associated with poor response to induction chemotherapy, suboptimal measurable residual disease (MRD) clearance, and inferior survival outcomes compared to non-Ph-like subtypes. We retrospectively analyzed 140 consecutive adult patients with Ph-like ALL treated at our institution. The median age was 33.5 years, and the majority harbored *CRLF2* rearrangements (85%). *IKZF1plus* deletion and *JAK* mutations were identified in 26% and 37% of patients, respectively. The majority (75%) received pediatric-inspired regimens (PIR), which were associated with higher complete remission (CR) rates ($p=0.034$), reduced risk of relapse ($p<0.001$), and improved overall survival ($p=0.008$), but did not significantly improve MRD negativity ($p=0.6$) compared to non-PIR approaches. Notably, non-*CRLF2*–rearranged cases demonstrated lower CR rates ($p=0.022$). The presence of *IKZF1plus* predicted inferior relapse-free survival (RFS; $p=0.032$). Among patients who achieved MRD negativity following induction ± consolidation, blinatumomab consolidation was associated with lower risk of relapse ($p=0.043$) and showed a trend toward improved RFS ($p=0.055$). In a landmark analysis of young adult patients (<55 years) in MRD-negative first CR (CR1), allogeneic hematopoietic cell transplantation did not confer benefit in RFS ($p=0.24$) or relapse ($p=0.124$). Notably, young adult patients treated with PIR who achieved MRD-negative CR by clonoSEQ and subsequently received blinatumomab consolidation demonstrated excellent early outcomes despite low transplant rate. In conclusion, contemporary treatment strategies for Ph-like ALL in adults, including the use of PIR in younger adults, incorporation of blinatumomab in MRD-negative CR1, and risk-adapted transplant decisions, are associated with improved clinical outcomes.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous malignancy driven by diverse genetic alterations, which significantly influence treatment selection, therapeutic response, and overall prognosis. Among the high-risk subtypes of B-cell ALL, Philadelphia–like (Ph-like), also known as *BCR::ABL1*-like ALL has emerged as a distinct and prevalent entity, accounting for approximately 20–30% of newly diagnosed adult cases of B-ALL.(1-5) The incidence of Ph-like ALL varies considerably across geographic regions and ethnic groups, with a notably higher frequency observed among Hispanic populations in the United States.(2, 6)

At the molecular level, Ph-like ALL is highly heterogeneous and comprises a variety of genetic drivers and subtypes.(1, 7) The most common alterations involve *CRLF2* (Cytokine Receptor-Like Factor 2), frequently occurring with concomitant *JAK2* mutations.(1, 2, 6) Clinically, Ph-like ALL is associated with inferior outcomes compared with other ALL subtypes, characterized by higher rates of induction failure and persistent measurable residual disease (MRD) following both induction and consolidation therapy.(2, 4, 5, 8) In adult patients treated with chemotherapy in the GIMEMA LAL1913 study, those with Ph-like ALL exhibited significantly higher rates of persistent MRD than patients with non–Ph-like ALL, with MRD positivity observed in 78% versus 41%, 53% versus 20%, and 42% versus 14% of patients at weeks 4, 10, and 16 following treatment initiation, respectively. These findings further support the association between Ph-like ALL and relative resistance to conventional chemotherapy(4). Long-term survival in adults with Ph-like ALL is poor with conventional chemotherapy, generally around 20%,(1, 2, 8) underscoring the aggressive nature of this subtype and highlighting the urgent need for improved risk-adapted and targeted therapeutic strategies.

However, the optimal frontline therapy for adults with Ph-like ALL remains undefined, and outcomes have been suboptimal with both pediatric-inspired and conventional adult treatment regimens.(2, 4, 8) While blinatumomab consolidation following achievement of chemotherapy-induced MRD negativity has improved outcomes in adults with B-ALL overall, including patients with Ph-like disease,(9) in patients with Ph-like ALL with persistent MRD post chemotherapy, blinatumomab has demonstrated limited efficacy in improving long-term survival despite high rate of MRD clearance.(5) This highlights the need for more effective targeted approaches in the frontline setting. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is frequently utilized in adults with Ph-like ALL in first complete remission (CR1) and has been associated with encouraging outcomes.(6, 10) Nonetheless, it remains unclear whether alloHSCT should be routinely recommended for all patients with Ph-like ALL in CR1 irrespective of MRD status, particularly in the era of MRD-directed therapy and incorporation of blinatumomab. This

ongoing uncertainty underscores a critical need to better define risk-adapted treatment strategies and optimize therapeutic sequencing for this high-risk population.

Here, we sought to further understand the impact of modern frontline therapy, blinatumomab, consolidation with allogeneic HSCT and the role of ultrasensitive MRD assessment on the prognostic outcomes of adults with newly diagnosed Ph-like ALL.

METHODS

Study Population: We retrospectively reviewed the medical records of 140 adult patients with newly diagnosed B-cell ALL with diagnostic Ph-like fusions who were treated at City of Hope (COH) between January 2014 and February 2026. The focus of this analysis was patients who received frontline therapy at COH before relapse. The study was reviewed and approved by the COH Institutional Review Board.

Frontline treatment strategies, including the use of blinatumomab and allogeneic HCT in CR1, evolved over the study period and were guided by physician discretion. Following the ECOG-ACRIN E1910 results, blinatumomab was increasingly incorporated into consolidation for patients achieving MRD-negative CR1. However, it remained the standard approach for patients with persistent MRD after chemotherapy. The decision to proceed with HCT in CR1 was individualized and based on molecular risk, MRD status by flow cytometry and, more recently, clonoSEQ, as well as donor availability and patient-specific psychosocial factors.

Objectives and Endpoints: The primary objective was to characterize outcomes in adults with Ph-like ALL treated with contemporary frontline therapies. We aimed to evaluate how modern treatment strategies—including pediatric-inspired regimens (PIRs), the timing and depth of MRD response, and the incorporation of blinatumomab consolidation as well as alloHSCT in CR1—influence clinical outcomes. PIRs were defined as multiagent chemotherapy protocols adapted from pediatric ALL treatment studies and incorporating adequate asparaginase therapy.

Outcomes assessed included rates of CR/CRi, MRD response measured by multiparameter flow cytometry (MFC) and next-generation sequencing (NGS), cumulative incidence of relapse (CIR), relapse-free survival (RFS), and overall survival (OS).

Subgroup analyses were performed according to Ph-like ALL fusion subtypes, the presence of *IKZF1plus* deletions, and concurrent *JAK1* or *JAK2* mutations.

Ph-like ALL was defined based on the identification of characteristic gene fusions using NGS, fluorescence in situ hybridization (FISH), microarray profiling, and conventional cytogenetics, as previously described.(6, 11) In house comprehensive targeted NGS was

additionally utilized to detect somatic mutations, including alterations in *JAK1* and *JAK2* as well as other mutations.

Outcome Definitions: Response was defined as complete remission (CR) or CR with incomplete count recovery (CRi). CR was defined as <5% lymphoblasts in the bone marrow (BM), and the absence of circulating lymphoblasts or extramedullary disease, and absolute neutrophil count (ANC) >1x10^9/L and platelet count >100x10^9/L. CRi was defined as CR with either platelet count <100x10^9/L or/and ANC <1x10^9/L. MRD was assessed by MFC at a reference laboratory with a sensitivity threshold of 0.01%, and MRD negativity was defined as a level <0.01% of total nucleated cells. Next-generation sequencing (NGS)-based clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA) was performed when possible on BM samples post-induction (after the first treatment cycle) and post-consolidation (after the second treatment cycle). IGH V(D)J NGS MRD results were normalized to residual clonal cells per million nucleated cells and negativity was defined as <0.0001%. *IKZF1plus* deletion status was defined as the presence of an *IKZF1* deletion co-occurring with deletions in *CDKN2A, CDKN2B, PAX5*, or *PAR1* in the absence of *ERG* deletion.(12) RFS was defined as the time from achievement of CR/CRi to relapse or death from any cause, whichever occurred first. OS was defined as the time from diagnosis to death from any cause. CIR was defined as the probability of relapse over time, accounting for death without relapse as a competing event. Relapse was defined as either morphological relapse in the bone marrow or evidence of extramedullary disease recurrence.

Statistical Analysis: Patient and disease characteristics were summarized using medians (first and third quartiles) for continuous variables and frequencies (percentages) for categorical variables. Categorical treatment characteristics and early outcomes were compared across frontline therapy groups using Fisher's exact test. For subgroup comparisons of baseline characteristics, continuous variables were analyzed using the Wilcoxon rank-sum test and categorical variables using Fisher's exact test, given modest subgroup sizes.

Univariable and multivariable logistic regression models were used to identify factors associated with CR/CRi and post-induction MRD negativity. OS and RFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox proportional hazards models were used to evaluate factors associated with survival outcomes. CIR was analyzed using competing risks methodology, with death without relapse treated as a competing event. Group comparisons were performed using Gray's test, and regression analyses were conducted using the Fine–Gray subdistribution hazards model.

Given that transplantation in CR1 is a time-dependent exposure, landmark analyses were performed to mitigate immortal time bias. Outcomes were compared among patients who

remained event-free up to the predefined landmark, according to transplant status at that time point. The landmark was set at180 days from CR.

RESULTS

Patient and Disease Characteristics: A total of 246 adult patients with Ph-like ALL treated at COH during the study period were identified, of whom 106 presented after receiving prior therapy in the relapsed or refractory setting. The distribution of genetic subtypes in the overall cohort is shown in **Figure 1A.** Among these, 140 patients were treated in the frontline setting at COH and constitute the population for the present analysis. The median age at diagnosis was 33.5 years (range: 18-78), with 24 patients (17%) aged ≥55 years. The majority of patients were male (67%) and of Hispanic ethnicity (87%). The median presenting white blood cell (WBC) count was 27.4 × 10^9/L (6.0, 72.2).

CRLF2-rearranged ALL comprised the predominant subtype (n=120; 85%), including 90 patients with *IGH::CRLF2* and 30 with *P2RY8::CRLF2* fusions. Less frequent subtypes included *ABL*-class fusions in 9 patients (7%), *JAK2* fusions in 7 (5%), and *IGH::EPOR* fusions in 3 (2%) **(Figure 1B).** Concurrent *JAK1* or *JAK2* mutations were identified in 46 patients (37%), and *IKZF1plus* deletions were present in 33 (26%).

Induction therapy primarily consisted of pediatric-inspired regimens (PIRs), administered to 105 patients (75%). Seventeen patients (12%) received hyper-CVAD, while 15 patients (11%) were treated with frontline immunotherapy and/or targeted therapy (blinatumomab, inotuzumab, or venetoclax) with or without low-intensity chemotherapy; 2 patients received other regimens, and 1 patient did not receive therapy. Among PIRs, the most used regimen was CALGB 10403 (n=67; 64%), followed by modified BFM (n=19; 18%) and COG-based regimens (n=16; 15%), with 3 patients receiving alternative PIR approaches. Patients treated with PIRs were younger than those receiving hyper-CVAD or frontline immunotherapy ± low-intensity chemotherapy, with median ages of 29, 54, and 68 years, respectively. Baseline patient and disease characteristics are summarized in **Table 1.** No patients in this cohort received frontline ABL- or JAK-targeted tyrosine kinase inhibitors in conjunction with induction therapy.

Response to Initial Therapy: The overall CR/CRi rate following induction was 77%, including 82% with PIRs, 53% with hyper-CVAD, and 73% with frontline immunotherapy ± low-intensity chemotherapy (p=0.063). **Table S1** depicts treatment outcomes by frontline therapy. In univariable analysis, no baseline demographic, clinical, or biologic variables were associated with CR/CRi **(Table S2).** However, hyper-CVAD was associated with lower odds of CR/CRi compared with PIRs (OR: 0.25, 95% CI: 0.09–0.73; p=0.012), as was non-PIR therapy overall (OR: 0.41, 95% CI: 0.17–0.97; p=0.040). In multivariable analysis, non-PIR frontline therapy remained independently associated with lower odds of CR/CRi (adjusted OR: 0.36, 95% CI: 0.14–0.93, p=0.034), and patients with Other Ph-like fusion subtypes had lower odds of CR compared with patients with

CRLF2::IGH fusions (adjusted OR 0.24, 95% CI 0.07–0.82, p=0.022) **(Table 2).** *IKZF1plus* deletions and concurrent *JAK* mutations were not associated with CR/CRi.

Among evaluable responders, MRD negativity after induction was achieved in 40% (43/108) by MFC and 20% (9/46) by clonoSEQ, improving after consolidation to 82% (68/83) and 51% (20/39), respectively. By flow cytometry, MRD-negative CR/CRi rates after induction and consolidation were 44% and 82% with PIRs, and 33% and 83% with hyper-CVAD. No variables were significantly associated with post-induction MRD negativity in univariable analyses **(Table S3).** In multivariable analysis, frontline treatment approach was not associated with MRD negativity by MFC (non-PIR vs PIR: adjusted OR: 0.74, 95% CI: 0.23–2.21; p=0.60).

Among patients with MRD-positive disease by flow cytometry following chemotherapy (n=27), 26 (96%) achieved MRD negativity after blinatumomab treatment, and 21 (78%) subsequently underwent allogeneic transplantation in CR1. Of the six patients who did not proceed to transplant, three experienced relapse.

Survival and Relapse: Unadjusted Kaplan–Meier analysis demonstrated differences in RFS across the frontline treatment groups (log-rank p=0.0352) **(Figure 2A-B).** In multivariable analysis adjusting for selected baseline covariates, treatment with non-PIR frontline therapy was associated with a higher hazard of relapse or death compared with PIR, although this did not reach statistical significance (adjusted HR: 2.57, 95% CI: 0.92–7.22; p=0.073). *IKZF1plus* deletion was independently associated with inferior RFS (adjusted HR: 2.55, 95% CI: 1.08–6.02; p=0.032) **(Table 3).** Age at diagnosis, Ph-like fusion subgroup, and concurrent *JAK* mutation status were not significantly associated with RFS.

Unadjusted Kaplan–Meier analysis demonstrated a significant difference in OS across frontline treatment groups (log-rank p=0.00142), with patients treated with PIR exhibiting the most favorable survival **(Figure 2C-D).** After multivariable adjustment, frontline treatment strategy remained significantly associated with OS. Patients receiving non-PIR frontline therapy had a higher hazard of death compared with those treated with PIR (adjusted HR: 3.75, 95% CI: 1.42–9.89; p=0.008) **(Table 4)**. None of the additional covariates included in the model—age at diagnosis, *IKZF1plus* deletion status, Ph-like fusion subgroup, and concurrent *JAK* mutation—were significantly associated with OS.

Differences in relapse risk across treatment groups were observed in unadjusted analyses (Gray's test p=0.025) **(Figure 2E)**, and patients treated with non-PIR frontline therapy exhibited higher relapse incidence relative to those treated with PIR (Gray's test p=0.005) **(Figure 2F)**. In the adjusted competing risks model, non-PIR frontline therapy remained significantly associated with an increased CIR compared with PIR (adjusted HR: 5.50, 95% CI: 2.03–14.93; p<0.001). Age at diagnosis, *IKZF1plus* status, Ph-like

fusion subgroup, and concurrent *JAK* mutation status were not significantly associated with relapse in the adjusted model.

Blinatumomab Consolidation in MRD- CR1: Blinatumomab was administered in 98 patients (70%) across the following settings: during induction in 7 patients, as consolidation in MRD-negative CR1 in 33 patients, for MRD-positive disease in 27 patients, and in the relapsed/refractory setting in 31 patients. Among 65 young adult patients (<55 years) with Ph-like ALL who achieved MRD-negative CR1 by flow after induction ± consolidation, 30 (46%) received blinatumomab consolidation, with a median number of 2 (range; 1-4) cycles. Baseline characteristics were comparable between the two groups, with no major imbalances **(Table S4).** Blinatumomab consolidation was associated with a trend toward improved RFS (log-rank p = 0.055) and numerically higher OS (p = 0.16), though not statistically significant. Notably, the CIR was significantly lower in the blinatumomab group (Gray's test p = 0.043) **(Figure 3A-C).**

AlloHSCT in MRD- CR1: AlloHSCT was performed in 79 (56%) patients in CR1 and 16 beyond CR1. The rate of alloHSCT in CR1 was 63% with PIRs, 59% with hyper-CVAD, and 27% with immunotherapy ± low-intensity chemotherapy (p=0.01). Among young adults (<55 years; n= 65) who achieved MRD-negative CR1 by MFC following induction ± consolidation, baseline demographic and disease characteristics were generally similar between those who did (n= 33) and those who did not undergo transplant in CR1 (n= 32), with no major imbalances observed **(Table S5).** The median from diagnosis to transplant was 6.8 months (IQR: 5.6-8.9). There was a trend toward improved RFS among those who underwent alloHSCT in CR1, although this did not reach statistical significance (log-rank p=0.085). OS did not differ by transplant status (p=0.98). Competing risks analysis demonstrated a significantly lower CIR among patients undergoing transplant in CR1 (Gray's test p=0.026).

To address potential immortal time bias, a landmark analysis was performed at 180 days from CR1. Of MRD-negative patients, 51 were eligible for inclusion; 8 relapsed before the landmark and 6 had insufficient follow-up. After landmark adjustment, no significant differences were observed between transplant and non-transplant groups in RFS (log-rank p=0.24), OS (log-rank p=0.34), or CIR (Gray's test p=0.124) **(Figure 3D-F).** The attenuation of the transplant effect in the landmark analysis suggests that the apparent benefit observed in unadjusted analyses was likely influenced by immortal time bias.

In addition to the landmark analysis, we also performed a Cox proportional hazards analysis treating transplantation as a time-dependent covariate. The time-dependent Cox model showed no significant association between transplantation and relapse-free survival (HR: 0.92, 95% CI: 0.36–2.37; p=0.862). Consistent with this finding, the corresponding Mantel–Byar test was also not statistically significant (χ^2=0.03, p = 0.862) (**Supplementary Figure 1).**

Outcomes of AYA patients who achieved clonoSEQ- with chemotherapy: There were 17 patients who achieved MRD negativity by clonoSEQ following induction ± consolidation, with a median age of 32 years. All patients had *CRLF2* rearrangements; 8 harbored *JAK2* mutations, and 7 had *IKZF1plus* deletions. All were treated with PIRs, with 7 (41%) achieving clonoSEQ negativity after induction. The majority (n=13; 76%) received blinatumomab consolidation while in clonoSEQ-negative CR1, whereas only 3 patients (17%) proceeded to alloHSCT in CR1 **(Table S6)**.

With a median follow-up of 10.5 months (range, 5.3–28.4), outcomes were favorable, with one patient experienced relapse, and one died in CR due to therapy-related AML. At last follow-up, 88% of patients remained alive and relapse-free.

DISCUSSION

We report outcomes from a relatively large homogenous cohort of newly diagnosed adult patients with Ph-like ALL. Most young adult patients in our cohort were treated with PIRs, which were associated with higher CR rates compared with non-PIRs approaches, and the rate of alloHSCT in CR1 was similar between the two groups. Notably, PIRs were associated with lower relapse and led to improved OS. Despite rates of MRD negativity were comparable between PIR and Hyper-CVAD, this finding should be interpreted cautiously given the smaller proportion of patients in the Hyper-CVAD cohort who underwent MRD assessment, as these patients were largely treated in earlier treatment eras. While major societies such as the American Society of Hematology and the European LeukemiaNet recommend PIRs for fit younger adults with Ph–negative ALL(13, 14), evidence supporting this approach specifically in Ph-like ALL remains limited. To our knowledge, only one prior study has compared PIR with Hyper-CVAD in adults with Ph-like ALL and found similar survival outcomes(2). Our analysis adds to the existing literature by demonstrating that the advantages of PIR extend to young adults with Ph-like ALL, supporting its use in this particularly high-risk subgroup.

The majority (85%) of patients carried *CRLF2*-rearrangements, with *IGH::CRLF2* being the most common, likely reflective of our largely Hispanic population represented in our cohort. Prior studies have demonstrated a higher prevalence of inherited GATA3 risk polymorphisms among individuals of Hispanic ancestry, which has been associated with an increased incidence of CRLF2-rearranged Ph-like ALL(15-17). Patients with non-*CRLF2* rearrangements demonstrated inferior response to frontline therapy, and *IKZF1plus* deletions were independently associated with inferior RFS. In contrast, concurrent *JAK*1/2 mutations were not associated with response or survival outcomes. The inferior outcomes observed in the non-*CRLF2*-rearranged subgroup are likely related to the heterogeneous composition of this cohort, with more than half harboring *JAK2* or *EPOR* fusions, both of which have been associated with adverse outcomes(1, 2). *IKZF1* deletions and *IKZF1plus* alterations occur at a higher frequency in patients with Ph-like

ALL, particularly among cases harboring kinase or cytokine receptor rearrangements(1, 2, 7, 17), and have been associated with poor prognosis(7). This association may be especially relevant in Hispanic populations, in whom *IKZF1* deletions frequently co-occur with *CRLF2* rearrangements(17).

The incorporation of blinatumomab appeared to further reduce relapse risk among young adult patients achieving MRD-negative CR1 with frontline chemotherapy, the majority of whom received frontline PIRs. Blinatumomab use was also associated with a trend toward improved RFS. Nonetheless, considering that Ph-like ALL is a chemotherapy-refractory disease,(4) most remaining patients in this cohort received blinatumomab in the setting of persistent MRD, relapsed/refractory disease, or as part of frontline therapy.

Allogenic HSCT in CR1 is recommended in Ph-like ALL, particularly in the presence of persistent MRD following frontline chemotherapy,(4, 18) however, its role in MRD- CR1 remains uncertain. In our cohort of young adult patients achieving MRD- CR1 by MFC, transplant did not confer a survival benefit after introducing a landmark analysis, suggesting that earlier observed advantages may reflect immortal time bias. However, we acknowledge that the cohort is small and follow up is short, and there may be some variation in recommending transplant based on post chemotherapy persistent MRD by clonoSEQ despite MRD negativity by MFC. Nonetheless, allogeneic transplantation in CR1 remains an important component of therapy for patients with Ph-like ALL who have persistent MRD following chemotherapy, even when MRD is subsequently cleared with immunotherapy. However, the role of transplantation in CR1 remains uncertain for young patients with Ph-like ALL who achieve MRD negativity by flow cytometry but have persistent clonoSEQ positivity after chemotherapy, as well as for older patients who are unable to receive PIRs because of age and achieve MRD-negative remission following frontline immunotherapy. These clinically relevant questions are not addressed by the present study.

Patients who achieved clonoSEQ negativity prior to blinatumomab consolidation experienced excellent outcomes, despite the relatively low use of alloHSCT in this group. These observations are limited by small patient numbers and short follow-up, but they suggest a favorable disease biology. Most of these patients also received blinatumomab consolidation, which may have further contributed to their positive outcomes. Overall, this cohort appears to represent individuals with exceptional chemotherapy sensitivity who are more likely to be cured with non-transplant approaches, particularly when blinatumomab consolidation is incorporated. Longer follow-up is needed to confirm the durability of these responses.

While PIRs appear to improve outcomes of younger patients with Ph-like, their application in older adults with Ph-like is not feasible, and the disease is not uncommon even within this age population. Therefore, novel approaches incorporating novel immunotherapy

have the promise to improve these patients outcomes. Among our older adults with Ph-like treated with frontline blinatumomab, inotuzumab or venetoclax, the MRD- CR rate was high, but the majority relapsed shortly afterward. Therefore, additional novel consolidation approaches are warranted. Recently, there has been increasing interest in substituting allogeneic transplantation with CAR T-cell therapy as consolidation for patients with B-cell ALL, particularly those with high-risk disease who achieve CR1 irrespective of MRD response. This strategy has the potential to reduce treatment-related toxicity while maintaining antileukemic efficacy. Ph-like ALL may be an especially suitable subtype in which to explore this approach, given its relative refractoriness to chemotherapy and its demonstrated susceptibility to immunotherapy.

This study is limited by its retrospective, single-center design and treatment heterogeneity. Furthermore, the majority of patients in our cohort had CRLF2-rearranged Ph-like ALL, which may limit the generalizability of our findings to other molecular subtypes of Ph-like ALL. Nonetheless, it provides important insights into the evolving management of Ph-like ALL, highlighting the contributions of PIR-based therapy, ultrasensitive MRD assessment, blinatumomab consolidation, and selective use of alloHSCT in refining risk stratification and improving outcomes.

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TABLES

Table 1: Baseline Patient Characteristics

Variable	Overall (N=140) [1]
Age at diagnosis, years	33.5 (24.0, 49.5)
Sex	
Female	46 (33%)
Male	94 (67%)
Race/Ethnicity	
Hispanic	122 (87%)
White	10 (7.1%)
Asian	5 (3.6%)
Other	3 (2.1%)
Initial WBC ($\times 10^9$/L)	27.4 (6.0, 72.2)
Unknown	1
Ph-like fusion group	
CRLF2::IGH	90 (64%)
CRLF2::P2RY8	30 (21%)
Other Ph-like	20 (14%)
Concurrent JAK mutation	46 (37%)
Unknown	15
IKZF1plus deletion	
Yes	33 (26%)
Others	94 (74%)
Unknown	13
Initial therapy	
PIR	105 (75%)
Hyper-CVAD	17 (12%)
Immunotherapy ± Low-intensity chemo	15 (11%)
Others	3 (2.1%)

[1] *Median (Q1, Q3); N (%)*

Table 2. Multivariable Analysis for Complete Remission

Predictor	Adjusted OR	95% CI	p-value
Frontline therapy			
PIR	Reference	—	—
Non-PIR	0.36	0.14, 0.93	0.034
***IKZF1plus* deletion**			
No	Reference	—	—
Yes	1.02	0.36, 3.10	>0.9
Ph-like fusion group			
CRLF2::IGH	Reference	—	—
CRLF2::P2RY8	0.71	0.25, 2.15	0.5
Other Ph-like	0.24	0.07, 0.82	0.022
Concurrent JAK mutations			
No	Reference	—	—
Yes	0.81	0.30, 2.23	0.7

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 3. Multivariable Analysis for RFS

Predictor	Adjusted HR	95% CI	p-value
Frontline therapy			
PIR	Reference	—	—
Non-PIR	2.57	0.92, 7.22	0.073
Age at diagnosis, years	1.00	0.97,1.04	0.8
***IKZF1plus* deletion**			
No	Reference	—	—
Yes	2.55	1.08, 6.02	0.032
Ph-like fusion group			
CRLF2::IGH	Reference	—	—
CRLF2::P2RY8	1.23	0.54. 2.80	0.6
Other Ph-like	0.67	0.17, 2.65	0.6
Concurrent JAK mutations			
No	Reference	—	—
Yes	0.92	0.40, 2.13	0.9

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 4. Multivariable Analysis for OS

Predictor	Adjusted HR	95% CI	p-value
Frontline therapy			
PIR	Reference	—	—
Non-PIR	3.75	1.42, 9.89	0.008
Age at diagnosis, years	1.01	0.98, 1.04	0.6
***IKZF1plus* deletion**			
No	Reference	—	—
Yes	1.07	0.43, 2.63	0.9
Ph-like fusion group			
CRLF2::IGH	Reference	—	—
CRLF2::P2RY8	1.05	0.47, 2.36	>0.9
Other Ph-like	0.81	0.22, 2.95	0.7
Concurrent *JAK* mutations			
No	Reference	—	—
Yes	1.51	0.67	0.3

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

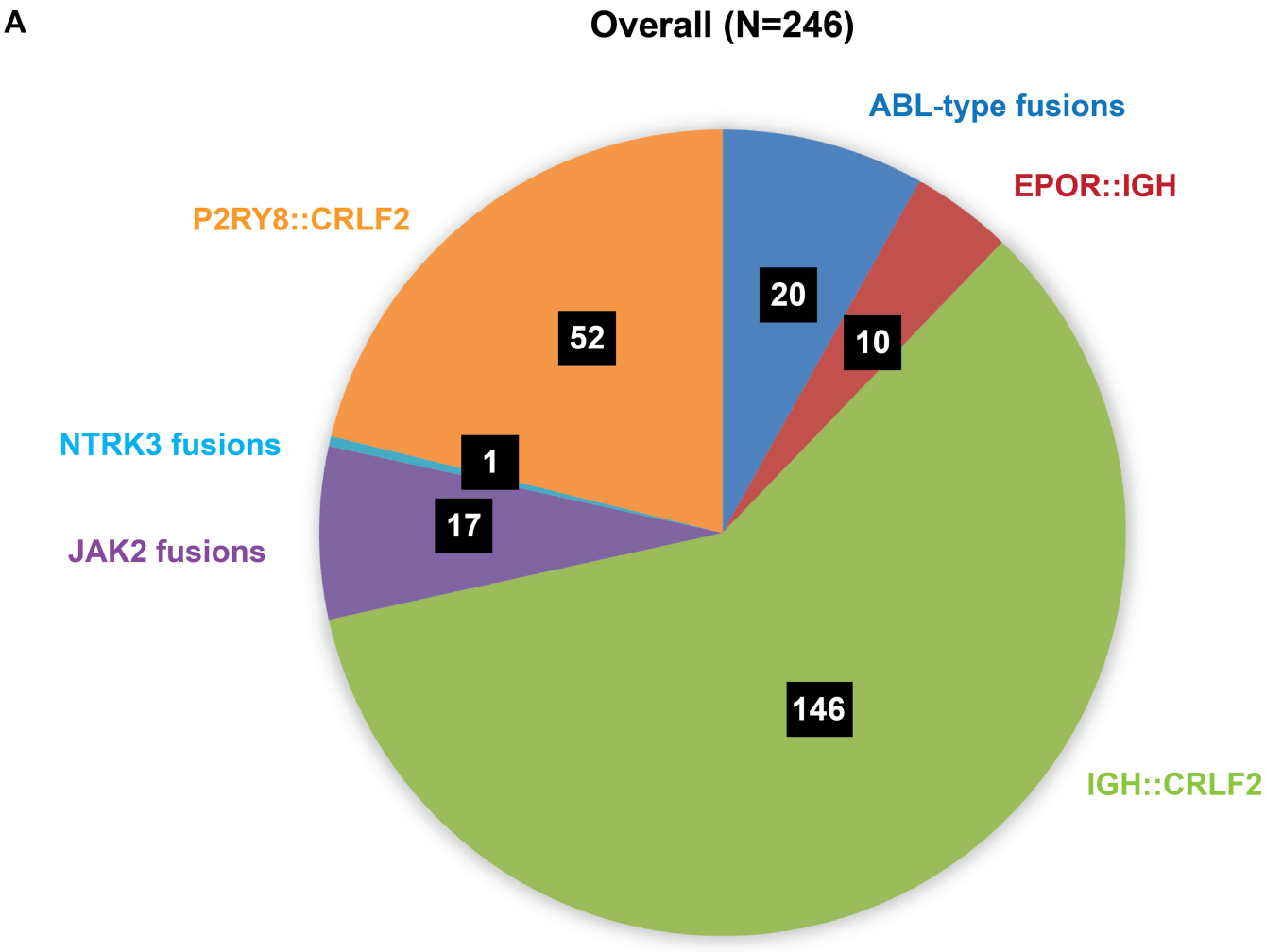
Figure Legend

Figure 1. Distribution of Ph-like genetic subtypes. (A) Distribution among all patients, including those with newly diagnosed and relapsed/refractory disease. (B) Distribution among patients with newly diagnosed disease.

Figure 2. Relapse and survival outcomes among all patients, including those with newly diagnosed and relapsed/refractory disease. (A) Relapse-free survival (RFS) according to frontline therapy (pediatric-inspired regimens [PIR], Hyper-CVAD, immunotherapy, or other therapies). (B) RFS according to frontline therapy (PIR vs. non-PIR). (C) Overall survival (OS) according to frontline therapy (PIR, Hyper-CVAD, immunotherapy, or other therapies). (D) OS according to frontline therapy (PIR vs. non-PIR). (E) Cumulative incidence of relapse (CIR) according to frontline therapy (PIR, Hyper-CVAD, immunotherapy, or other therapies). (F) CIR according to frontline therapy (PIR vs. non-PIR).

Figure 3. Relapse and survival outcomes among young adults (18–54 years) who achieved MRD-negative CR1 after induction and/or consolidation. (A) RFS, according to receipt of blinatumomab consolidation. (B) OS, according to receipt of blinatumomab consolidation. (C) CIR, according to receipt of blinatumomab consolidation. (D) RFS, according to receipt of allogeneic transplantation in CR1. (E) OS, according to receipt of allogeneic transplantation in CR1. (F) CIR, according to receipt of allogeneic transplantation in CR1.

Figure 1


A
Overall (N=246)
ABL-type fusions
EPOR::IGH
P2RY8::CRLF2
NTRK3 fusions
JAK2 fusions
IGH::CRLF2
20
10
52
1
17
146

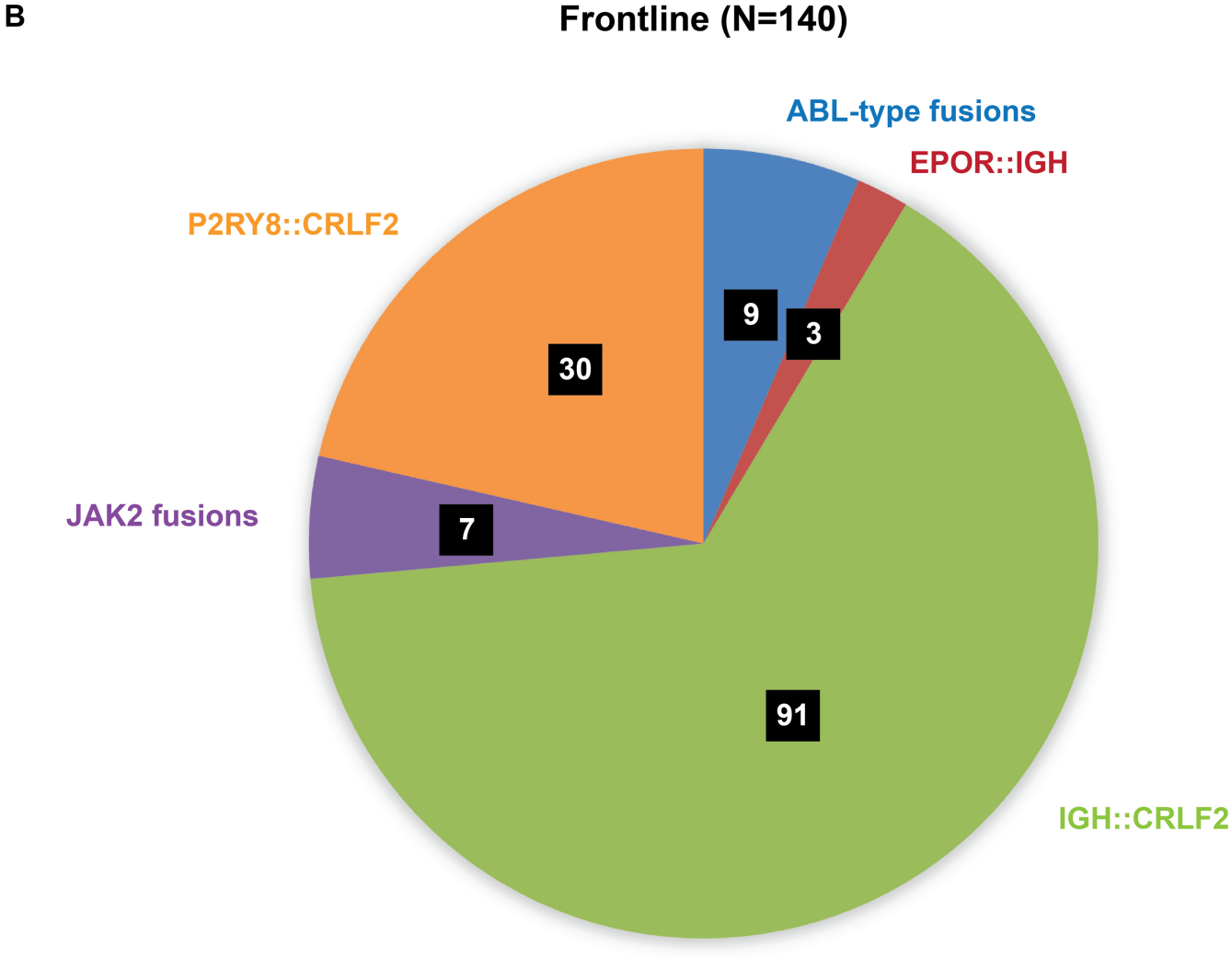

B
Frontline (N=140)
ABL-type fusions
EPOR::IGH
P2RY8::CRLF2
JAK2 fusions
IGH::CRLF2
9
3
30
7
91

Figure 2

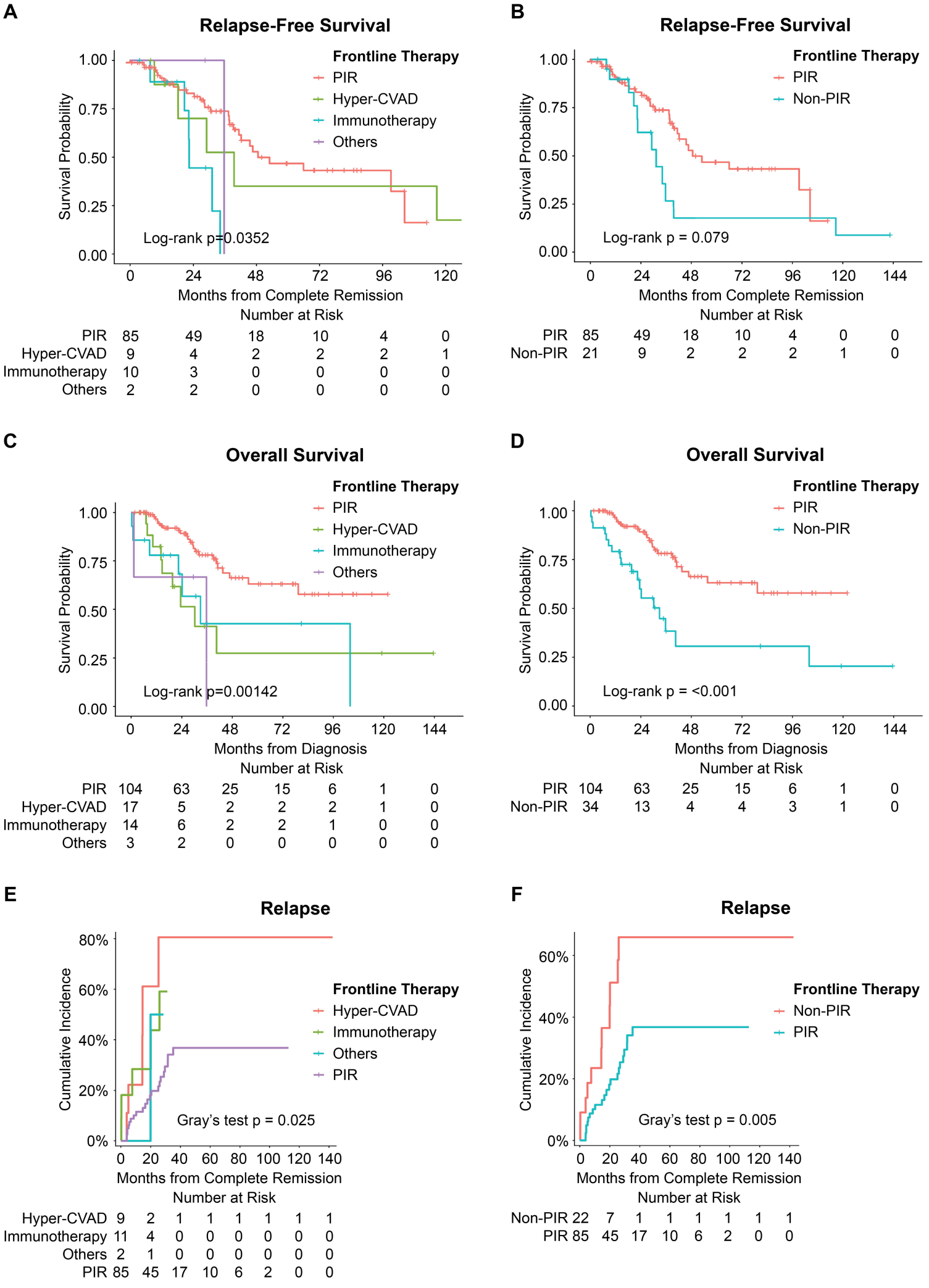

A
Relapse-Free Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Frontline Therapy
PIR
Hyper-CVAD
Immunotherapy
Others
Log-rank p=0.0352
0 24 48 72 96 120
Months from Complete Remission
Number at Risk
PIR 85 49 18 10 4 0
Hyper-CVAD 9 4 2 2 2 1
Immunotherapy 10 3 0 0 0 0
Others 2 2 0 0 0 0
B
Relapse-Free Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Frontline Therapy
PIR
Non-PIR
Log-rank p = 0.079
0 24 48 72 96 120 144
Months from Complete Remission
Number at Risk
PIR 85 49 18 10 4 0 0
Non-PIR 21 9 2 2 2 1 0
C
Overall Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Frontline Therapy
PIR
Hyper-CVAD
Immunotherapy
Others
Log-rank p=0.00142
0 24 48 72 96 120 144
Months from Diagnosis
Number at Risk
PIR 104 63 25 15 6 1 0
Hyper-CVAD 17 5 2 2 2 1 0
Immunotherapy 14 6 2 2 1 0 0
Others 3 2 0 0 0 0 0
D
Overall Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Frontline Therapy
PIR
Non-PIR
Log-rank p = <0.001
0 24 48 72 96 120 144
Months from Diagnosis
Number at Risk
PIR 104 63 25 15 6 1 0
Non-PIR 34 13 4 4 3 1 0
E
Relapse
Cumulative Incidence
80%
60%
40%
20%
0%
Frontline Therapy
Hyper-CVAD
Immunotherapy
Others
PIR
Gray's test p = 0.025
0 20 40 60 80 100 120 140
Months from Complete Remission
Number at Risk
Hyper-CVAD 9 2 1 1 1 1 1 1
Immunotherapy 11 4 0 0 0 0 0 0
Others 2 1 0 0 0 0 0 0
PIR 85 45 17 10 6 2 0 0
F
Relapse
Cumulative Incidence
60%
40%
20%
0%
Frontline Therapy
Non-PIR
PIR
Gray's test p = 0.005
0 20 40 60 80 100 120 140
Months from Complete Remission
Number at Risk
Non-PIR 22 7 1 1 1 1 1 1
PIR 85 45 17 10 6 2 0 0

Figure 3

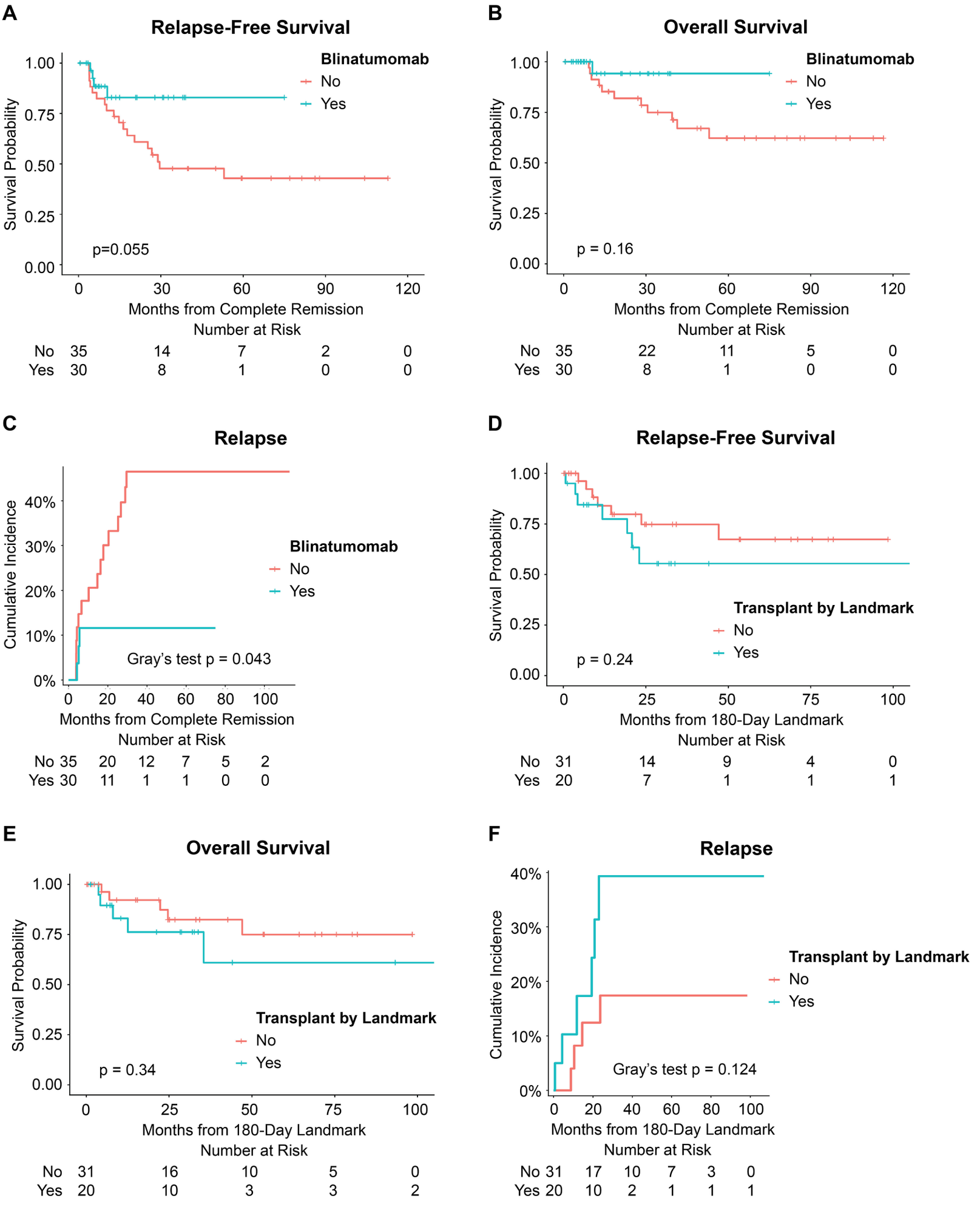

A
Relapse-Free Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Blinatumomab
No
Yes
p=0.055
0
30
60
90
120
Months from Complete Remission
Number at Risk
No 35 14 7 2 0
Yes 30 8 1 0 0
B
Overall Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Blinatumomab
No
Yes
p = 0.16
0
30
60
90
120
Months from Complete Remission
Number at Risk
No 35 22 11 5 0
Yes 30 8 1 0 0
C
Relapse
Cumulative Incidence
40%
30%
20%
10%
0%
Blinatumomab
No
Yes
Gray's test p = 0.043
0
20
40
60
80
100
Months from Complete Remission
Number at Risk
No 35 20 12 7 5 2
Yes 30 11 1 1 0 0
D
Relapse-Free Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Transplant by Landmark
No
Yes
p = 0.24
0
25
50
75
100
Months from 180-Day Landmark
Number at Risk
No 31 14 9 4 0
Yes 20 7 1 1 1
E
Overall Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
Transplant by Landmark
No
Yes
p = 0.34
0
25
50
75
100
Months from 180-Day Landmark
Number at Risk
No 31 16 10 5 0
Yes 20 10 3 3 2
F
Relapse
Cumulative Incidence
40%
30%
20%
10%
0%
Transplant by Landmark
No
Yes
Gray's test p = 0.124
0
20
40
60
80
100
Months from 180-Day Landmark
Number at Risk
No 31 17 10 7 3 0
Yes 20 10 2 1 1 1

Table S1. Treatment Characteristics and Outcomes by Frontline Therapy

Variable	PIR (N=105)[1]	Hyper-CVAD (N=17)[1]	Immunotherapy ± Low-intensity chemo (N=15)[1]	Others (N=3)[1]	p-value[2]
Complete remission					0.063
CR	86 (82%)	9 (53%)	11 (73%)	2 (100%)	
Not CR	19 (18%)	8 (47%)	4 (27%)	0 (0%)	
MRD post induction[3]					>0.9
MRD-negative	36 (44%)	2 (33%)	5 (45%)	0 (0%)	
MRD-positive	46 (56%)	4 (67%)	6 (55%)	1 (100%)	
MRD post consolidation[3]					0.8
MRD-negative	58 (81%)	5 (83%)	5 (100%)	0 (0%)	
MRD-positive	14 (19%)	1 (17%)	0 (0%)	0 (0%)	
Blinatumomab use					0.12
Yes	30 (100%)	1 (50%)	2 (100%)	0 (0%)	
No	0 (0%)	1 (50%)	0 (0%)	0 (0%)	
Transplant in CR1					0.010
Yes	65 (63%)	10 (59%)	4 (27%)	0 (0%)	
No	39 (38%)	7 (41%)	11 (73%)	3 (100%)	

[1]N (%) among non-missing observations for each variable.
[2]P-values from Fisher's exact test.
[3]Percentages are based on the number of patients evaluable for MRD assessment by multiparameter flow cytometry.

Table S2. Univariable Analysis for Complete Remission

Predictor	CR	Not CR	OR	95% CI	p-value
Age at diagnosis, years			0.98	0.96, 1.01	0.2
Sex					
Male	73	21	0.99	0.41, 2.29	>0.9
Female	35	10	—	—	
Initial WBC			1.00	0.99, 1.00	0.6
Ph-like fusion group					
CRLF2::P2RY8	23	7	0.78	0.29, 2.22	0.6
Other Ph-like	13	7	0.44	0.15, 1.32	0.13
CRLF2::IGH	72	17	—	—	
Concurrent JAK mutation					
Yes	36	10	1.08	0.46, 2.67	0.9
No	60	18	—	—	
IKZF1plus deletion					
Yes	26	7	1.15	0.46, 3.19	0.8
Others	71	22	—	—	

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table S3. Univariable Analysis for MRD-Negativity

Predictor	MRD-negative[1]	MRD-positive[1]	OR	95% CI	p-value
Age at diagnosis, years			1.01	0.98, 1.03	0.6
Sex					
Male	27	40	0.72	0.31, 1.67	0.4
Female	16	17	—	—	
Initial WBC			1.00	0.99, 1.00	0.6
Frontline therapy					
Non-PIR	7	11	0.81	0.27, 2.28	0.7
PIR	36	46	—	—	
Ph-like fusion group					
CRLF2::P2RY8	8	13	0.69	0.25, 1.86	0.5
Other Ph-like	3	8	0.42	0.09, 1.60	0.2
CRLF2::IGH	32	36	—	—	
Concurrent JAK mutation					
Yes	13	21	0.66	0.27, 1.57	0.4
No	27	29	—	—	
IKZF1plus deletion					
Yes	11	14	1.07	0.42, 2.70	0.9
Others	28	38	—	—	

[1]*MRD-negativity was determined by multiparameter flow cytometry*

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table S4. Baseline Characteristics by Blinatumomab Use Among AYA Patients in MRD- CR1

Variable	No (N=35)[1]	Yes (N=30)[1]	p-value[2]
Age at diagnosis, years	28.0 (22.0, 35.0)	32.0 (25.0, 43.0)	0.3
Sex			0.8
Female	11 (31%)	8 (27%)	
Male	24 (69%)	22 (73%)	
Race/Ethnicity			0.2
Hispanic	31 (89%)	30 (100%)	
Other	1 (2.9%)	0 (0%)	
White	3 (8.6%)	0 (0%)	
Initial WBC ($\times 10^9$/L)	11.0 (4.1, 74.7)	27.5 (4.6, 65.9)	0.4
Unknown	1	0	
Ph-like fusion group			0.3
CRLF2::IGH	22 (63%)	24 (80%)	
CRLF2::P2RY8	8 (23%)	5 (17%)	
Other Ph-like	5 (14%)	1 (3.3%)	
Concurrent JAK mutation	11 (39%)	11 (37%)	>0.9
Unknown	7	0	
IKZF1plus deletion			0.4
Others	21 (72%)	18 (60%)	
Yes	8 (28%)	12 (40%)	
Unknown	6	0	
Initial therapy			0.6
Hyper-CVAD	3 (8.6%)	1 (3.3%)	
PIR	32 (91%)	29 (97%)	

[1]*Median (Q1, Q3); N (%)*

[2]*Wilcoxon rank sum test; Fisher's exact test*

[3]*MRD-negativity was determined by multiparameter flow cytometry*

Table S5. Baseline Characteristics by Transplant Status Among AYA MRD-Negative Patients

Variable	No (N=32)[1]	Yes (N=33)[1]	p-value[2]
Age at diagnosis, years	30.0 (22.5, 36.0)	30.0 (24.0, 41.0)	0.7
Sex			0.3
Female	7 (22%)	12 (36%)	
Male	25 (78%)	21 (64%)	
Race/Ethnicity			
Hispanic	29 (91%)	32 (97%)	
Other	0 (0%)	1 (3.0%)	
White	3 (9.4%)	0 (0%)	
Initial WBC ($\times 10^9$/L)	11.9 (4.6, 73.2)	26.2 (4.2, 65.9)	>0.9
Unknown	1	0	
Ph-like fusion group			>0,9
CRLF2::IGH	23 (72%)	23 (70%)	
CRLF2::P2RY8	6 (19%)	7 (21%)	
Other Ph-like	3 (9.4%)	3 (9.1%)	
Concurrent JAK mutation	10 (33%)	12 (43%)	0.6
Unknown	2	5	
***IKZF1plus* deletion**			0.8
Others	21 (68%)	18 (64%)	
Yes	10 (32%)	10 (36%)	
Unknown	1	5	
Initial therapy			0.4
Hyper-CVAD	3 (9.4%)	1 (3.0%)	
PIR	29 (91%)	32 (97%)	

[1]*Median (Q1, Q3); N (%)*

[2]*Wilcoxon rank sum test; Fisher's exact test*

Table S6. Descriptive Summary of clonoSEQ MRD-Negative Subgroup

Characteristic	N=17[1]
Age at diagnosis, years	32.0 (24.0, 38.0)
Initial WBC (×10^9/L)	9.1 (4.1, 108.3)
Sex	
Female	5 (29%)
Male	12 (71%)
Race/Ethnicity	
Hispanic	16 (94%)
Other	1 (5.9%)
Frontline therapy	
PIR	17 (100%)
Received blinatumomab	13 (76%)
Underwent HSCT in CR1	3 (18%)
Relapse	1 (5.9%)
Death	1 (5.9%)
Alive and relapse-free at last follow-up	15 (88%)
Follow-up from CR1, months	10.5 (5.3, 28.4)

[1]*Median (Q1, Q3); N (%)*

Supplementary Figure 1