# Frontline ponatinib plus hyper-CVAD over imatinib in adults with Ph-positive acute lymphoblastic leukemia: real-world efficacy and risks of early ponatinib dose reduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) remains a challenging subtype of adult ALL due to its high relapse rates and adverse genetic features, particularly in patients with *IKZF1*-plus deletions. While ponatinib has demonstrated superior molecular responses compared to imatinib in clinical trials,[1-4] real-world data remain limited, especially in settings without post-transplant maintenance therapy. In this retrospective study, we found that ponatinib significantly improved measurable residual disease (MRD) progression-free survival (70.1% *vs.* 33.1%) and showed a trend toward better overall survival (OS). Notably, early reduction of ponatinib to 15 mg/day was associated with a significantly increased relapse risk, even among patients who achieved early complete molecular response (CMR). These findings were more significantly observed in patients with high-risk genetic profiles such as triple deletions of *IKZF1*, *CDKN2A/B*, and *PAX5*. This study was approved by the data review board and the institutional review board of the Catholic University of Korea (approval number KC25RISI0371). The requirement for written informed consent was waived due to the retrospective nature of the study involving only de-identified data and procedures were conducted in accordance with the Declaration of Helsinki.

We retrospectively analyzed 39 adult patients with newly diagnosed Ph-positive ALL treated with frontline ponatinib plus hyper-CVAD at our institution between October 2023 and July 2025, compared to 158 historical patients who received imatinib-based induction between April 2018 and September 2023. In both groups, we excluded cases of early death during induction therapy (2 [5.1%] in ponatinib and 10 [6.3%] in imatinib) and then we finally focused on 37 in the ponatinib group and 148 in the imatinib group. All of them had MRD results at both time point 1 (TP1), after completion of hyper-CVAD cycle 1A (post-induction) and TP2, after completion of cycle 1B (first consolidation). TP3 was defined as the last MRD assessment performed either before allogeneic hematopoietic cell transplantation (allo-HCT) or, in non-transplanted patients, after completion of hyper-CVAD cycle 2A. MRD monitoring for *BCR*::*ABL1* transcripts was centrally evaluated by real-time quantitative PCR (RT-qPCR) with 5.0-log sensitivity, with relapses defined by a significant MRD increase by at least 1-log. Poor molecular response (PMR) was defined by ratio of *BCR*::*ABL1* to ABL1 ≥0.1%, while CMR was defined as absence of detectable *BCR*::*ABL1* transcripts. Major molecular response (MMR) was defined as a detectable *BCR*::*ABL1* transcript level with a BCR::ABL1/ABL1 ratio <0.1%. In cases of CMR discordance, we followed next-generation sequencing results (NGS) or multiparameter flow cytometry (MFC) results indicating higher MRD levels.[5] For genetic analysis, we have conducted multiplex ligation probe amplification (MLPA) assay to detect common gene deletion and/or amplification targeting *IKZF1, CDKN2A, CDKN2B, PAX5, BTG1, EBF1, ETV6, JAK2, RB1*, and *PAR1* region using the SALSA MLPA Probemix Kit (P335 ALL-IKZF1; MRC Holland, Amsterdam, the Netherlands), as well as NGS to identify mutations of 73 genes. Ponatinib was administered at 45 mg/day for 14 days at the first cycle of hyper-CVAD, and then maintained 30 mg/day, followed by dose reduction to 15 mg/day upon achieving CMR. Imatinib was administered at 600 mg/day, but the dose was reduced to 400 mg for many intolerant patients, and dasatinib and ponatinb were sequentially applied in cases of resistance. Excluding some unfit patients, we mostly conducted allo-HCT for post-remission therapy. No post-HCT prophylactic therapy was administered, as such use has not been approved by the Korean national regulatory authority. To date, only preemptive imatinib is officially recognized and permitted in Korea.

Complete remission (CR) was observed in 96.6% in imatinib and 100% in ponatinib group ($P$=0.585), and 27 of them in the imatinib group relapsed before transplantation, while no one relapsed in the ponatinib group ($P$=0.004). Median time from induction to allo-HCT was not significantly different between patients with early ponatinib dose reduction (< 3 months of 30 mg/day) and those maintaining 30 mg/day (median 5.4 *vs*. 5.6 months; $P$=0.506). Between imatinib and ponatinib, median interval from induction start to allo-HCT was 5.9 and 5.5 months ($P$=0.101). To evaluate the dynamics of molecular response, we analyzed MRD status across three defined time points (TP1, TP2, TP3) in both imatinib and ponatinib frontline treatment cohorts (Table 1). Both subgroups exhibited progressive shifts from PMR to MMR and eventually CMR over time. At TP1, a considerable proportion of patients in both groups remained in the PMR category (43.2% in imatinib *vs*. 29.7% in ponatinib), with relatively low CMR rates (27.7% in imatinib *vs*. 24.3% in ponatinib) showing no different statistical values. However, by TP2, ponatinib demonstrated a notably reduced proportion of PMR (5.4% *vs*. 25.7%; $P$=0.011) compared to imatinib, followed by a significantly higher rate of CMR (73.5% *vs*. 54.0%; $P$=0.003) and a lower PMR rate

at pre-transplant TP3 (2.9% *vs*. 21.4%; *P*<0.001), indicating a statistically significant improvement over time (*Online Supplementary Figure S1*).

At a median follow-up of 20.1 months (range, 11.8-25.4) for ponatinib and 52.4 months (range, 23.8-88.5) for imatinib, the ponatinib group exhibited better 2-year OS (91.8% *vs*. 77.7%; *P*=0.053) and significantly superior progression-free survival (PFS) involving disease-free survival (DFS) and MRD relapse or increment (70.1% *vs*. 33.1%; *P*<0.001) (Figure 1). Cumulative incidence of relapse (CIR) of the ponatinib group was 12.9%, which was lower than 31.8% of the imatinib (*P*=0.057), and relapse including MRD progression was significantly lower in ponatinib group (24.4% *vs*. 56.8%; *P*<0.001). All five hematological relapses were observed in early dose-reduction group, especially with high-risk molecular cytogenetics. The patterns of relapse included BM relapse alone in one patient, isolated EMR in one, and concomitant BMR and EMR in three patients (including one central nervous system relapse). Thus, analysis of the ponatinib dose reduction strategy revealed

**Table 1.** Baseline characteristics between imatinib and ponatinib frontline therapy subgroups.

| Characteristics | Imatinib N=148 | Ponatinib N=37 | *P* |
|---|---|---|---|
| Age, years | | | |
| Median (range) | 44 (19-71) | 42 (20-72) | 0.857 |
| > 40, N (%) | 83 (56.1) | 21 (56.8) | 1.000 |
| Sex: male, N (%) | 59 (39.95) | 18 (48.6) | 0.433 |
| Leucocyte count ×10$^9$/L, N (%) | | | |
| >30.0 | 68 (45.9) | 22 (59.5) | 0.198 |
| *BCR*::*ABL*1 transcript, N (%) | | | |
| Minor | 120 (81.1) | 31 (83.8) | - |
| Major | 28 (18.9) | 6 (16.2) | - |
| Gene deletions, available, N (%) | 143 (100) | 33 (89.2) | |
| *IKZF1* | 119 (80.4) | 26 (78.8) | 1.000 |
| *CDKN2* | 58 (39.2) | 16 (48.5) | 0.432 |
| *PAX5* | 56 (37.8) | 14 (42.4) | 0.771 |
| Triple deletions | 37 (25.0) | 11 (33.3) | 0.445 |
| MRD, qPCR, N (%) | | | |
| TP1 | | | |
| CMR, not detected | 41 (27.7) | 9 (24.3) | 0.626 |
| MMR, any to <0.1% | 43 (29.1) | 17 (45.9) | 0.019 |
| PMR ≥0.1% | 64 (43.2) | 11 (29.7) | 0.056 |
| TP2 | | | |
| CMR, not detected | 69 (46.6) | 21 (56.8) | 0.150 |
| MR4 | 82 (55.4) | 28 (75.7) | 0.025 |
| MMR, any to < 0.1% | 41 (27.7) | 14 (37.8) | 0.130 |
| PMR ≥0.1% | 38 (25.7) | 2 (5.4) | <0.001 |
| TP3 (pre-HCT) | | | |
| CMR, not detected | 68 (54.0) | 25 (73.5) | 0.003 |
| MR4 | 80 (63.5) | 31 (91.2) | 0.002 |
| MMR, any to <0.1% | 31 (24.6) | 8 (23.5) | 1.000 |
| PMR ≥0.1% | 27 (21.4) | 1 (2.9) | <0.001 |
| Median time to transplantation, months (range) | 5.9 (4.1-16.7) | 5.5 (5.0-7.1) | 0.101 |
| Allo-HCT, N (%) | 126 (85.1) | 34 (91.9) | 0.420 |
| Donor | | | |
| Matched sibling donor | 33 (26.2) | 8 (23.5) | 0.003 |
| Unrelated donor | 49 (38.9) | 16 (47.1) | |
| Haploidentical donor | 15 (11.9) | 10 (29.4) | |
| Cord blood units | 29 (23.0) | 0 (0.0) | |
| Intensity | | | |
| Myeloablative | 62 (49.2) | 2 (5.9) | < 0.001 |
| Reduced toxicity | 64 (50.8) | 32 (94.1) | |
| Allo-HCT in CR1, N (%) | 107 (72.3) | 34 (91.9) | 0.034 |

MRD: measurable residual disease; qPCR: quantitative polymerase chain reaction; TP: MRD time point; CMR: complete molecular response; MMR: major molecular response; PMR: poor molecular response; allo-HCT: allogeneic hematopoietic cell transplantation; CR: complete remission.

that patients who were rapidly dose-reduced to 15 mg/day upon achieving CMR showed a significantly higher relapse incidence (23.0% *vs*. 0.0%; *P*=0.038) compared to those who maintained 30 mg/day of ponatinib due to insufficient MRD response (Figure 2). After excluding MRD as a treatment-dependent variable, baseline clinical and molecular characteristics were comparable between the two subgroups (*Online Supplementary Table S1*). There were no significantly different treatment outcomes in terms of OS, PFS, CIR, and non-relapse mortality according to the donor, graft source, preconditioning regimen intensity, and garft-*versus*-host disease (GVHD) prophylaxis although those parameters were imbalanced between the two Tyrosine kinase inhibitor (TKI) cohorts. The adverse outcome was not overcome by allo-HCT consequently.

The prognostic impact of *IKZF1, CDKN2A/B*, and *PAX5* gene deletions (del) were evaluated in terms of survival and relapse incidence. As single-gene deletions, *IKZF1*del was observed in 78.3% of patients, while *CDKN2*del and *PAX5*del were identified in 40.0% and 38.4%, respectively. As PAR1 region alteration or *ERG*del were not detected in our study cohort, we operationally classified *IKZF1*-plus based on the presence of double-gene deletions (*IKZF1*del plus either *CDKN2*del or *PAX5*del, N=32) or triple-gene deletions (concurrent deletions in all 3 genes, N=48). Patients harboring triple-gene deletions exhibited significantly inferior survival outcomes, with a DFS rate of 41.6%, compared with 65.5% in the single-gene deletion group and 62.1% in the double-gene deletion group. Subgroup analysis according to TKI type further confirmed the adverse prognostic impact of triple-gene deletions. In the imatinib-treated group, patients with triple-gene deletions had a DFS of 37.8%, compared to 61.3% in those without (*P*=0.004). Similarly, in the ponatinib-treated group, DFS was 52.6% in the triple-deletion cohort *versus* 90.7% in others (*P*=0.017). Notably, among patients receiving ponatinib, the relapse incidence was also significantly higher in the triple-gene deletion group (38.6% *vs*. 5.0%; *P*=0.029), as shown in *Online Supplementary Figure S2*.

Most significant adverse events were observed during administration of the initial 45 mg dose of ponatinib, while no serious adverse events were observed when we used 30 mg or a lower dose. Clinically significant vascular events were infrequent across both ponatinib dose groups: stroke (N=1), pulmonary embolism (N=1), and coronary disease (N=1). No excess incidence was noted among patients who continued 30 mg/day for >3 months compared with those with early reduction (*Online Supplementary Table S2*).

Our data highlights several key messages. First, ponatinib-based frontline therapy shows clear real-world advantages over imatinib in MRD response and survival after allo-HCT. In the PhALLCON trial, the primary endpoint - MR4-negative CR at 3 months - was higher with ponatinib (43.0% *vs*. 22.1%).[3] Similarly, in our study, MR4-negative CR was significantly higher with ponatinib (75.7% *vs*. 55.4%) than with historical imatinib data. Although follow-up was short, both PhALLCON and our study demonstrated superior PFS with ponatinib. However, while the trial showed no OS difference, our data suggested a trend toward better OS in the ponatinib group (91.8% *vs*. 77.7% at 20 months; *P*=0.053). Second, timing and patient selection for ponatinib dose reduction require caution. Early reduction to 15 mg/day - resulting in <3 months of 30 mg exposure - was linked to higher relapse rates post-HCT. Notably, all early-reduction patients had achieved early CMR, underscoring that tapering should not rely solely on

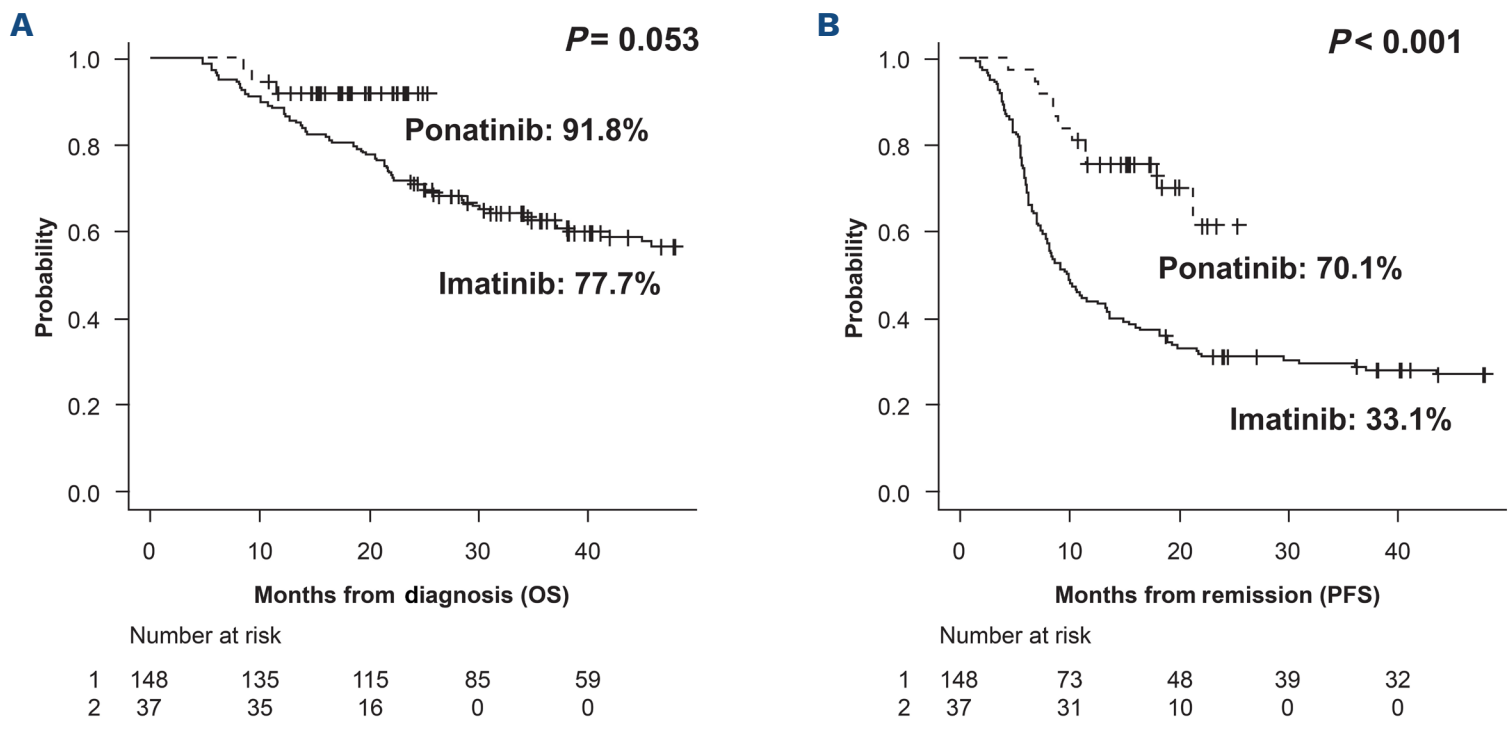


**Figure 1. Comparison of overall survival and progression-free survival between imatinib and ponatinib groups.** (A) The 2-year overall survival (OS) was 77.7% (95% confidence interval [CI]: 70.1-83.6%) in the imatinib group and 91.8% (95% CI: 76.7-97.3%) in the ponatinib group. (B) The 2-year progression-free survival (PFS) was significantly superior in the ponatinib group (70.1%; 95% CI: 50.3-83.2%) compared to the imatinib group (33.1%; 95% CI: 25.6-40.7%).

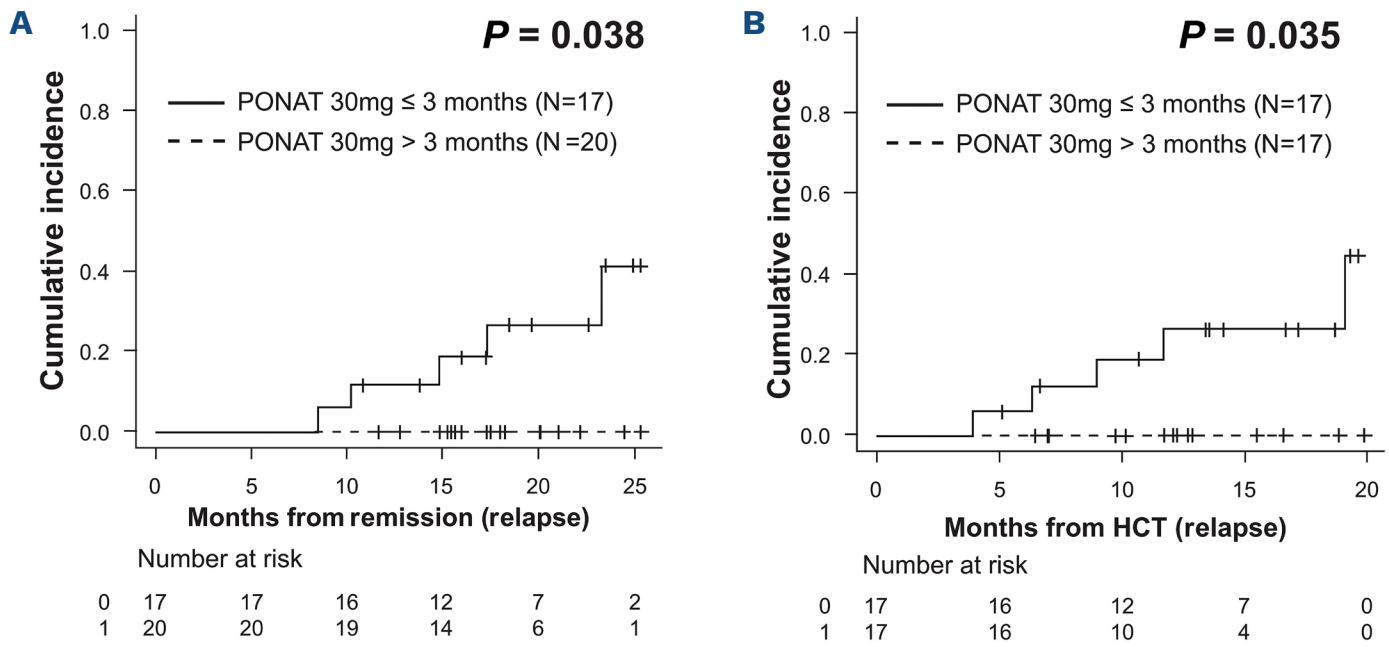


**Figure 2. Cumulative incidence of relapse stratified by ponatinib dose reduction strategy.** (A) Patients who were rapidly dose-reduced to 15 mg/day showed a significantly higher relapse incidence of 23.0% (95% confidence interval [CI]: 6.4-45.6%) compared to 0% (95% CI: 0.0-0.0%) in those who maintained 30 mg/day of ponatinib (PONAT). (B) Post-allogeneic hematopoietic cell transplantation (HCT) relapse was also higher (26.3%; 95% CI: 7.5-50.2%) in patients who were rapidly dose-reduced to 15 mg/day, while no relapse was observed in those who maintained 30 mg/day of ponatinib.

early response. Thus, optimizing both timing and intensity of ponatinib exposure appears essential to sustain remission and prevent relapse. Third, unlike the PhALL-CON trial population, many in our cohort did not receive post-HCT ponatinib maintenance, underscoring an unmet need for standardized post-transplant strategies. This is particularly critical for high-risk patients where relapse prevention remains a challenge.[6]

Based on previous genetic analyses focusing on specific gene deletions in Ph-positive ALL during the era of frontline imatinib treatment,[7,8] we sought to explore whether similar genetic alterations would yield different clinical implications in the current era of ponatinib-based frontline therapy. This transition in treatment landscape raises important and timely questions, but our data still showed very poor survival outcome of patients with triple-gene deletions (*IKZF1*del, *CDKN2*del, and *PAX5*del) even after ponatinib-based frontline therapy followed by allo-HCT. Finally, the poor prognosis associated with triple-gene deletions was consistently observed across both imatinib and ponatinib cohorts, highlighting that this genetic signature retains its predictive value of intrinsically high-risk disease regardless of TKI potency. On the other hand, these findings may also reflect the limitations of our transplantation-focused strategy in the absence of post-HCT maintenance therapy, suggesting that such an approach may have been insufficient to prevent relapse in patients with high-risk genetic features. Therefore, these findings underscore the need for enhanced therapeutic strategies or post-transplant interventions in high-risk patients. We may suggest intensive MRD surveillance, maintaining an optimal dose of ponatinib prior to transplantation, and incorporation of post-transplant maintenance therapy, particularly using potent TKI like ponatinib, in future protocols for patients harboring triple-gene deletions or other adverse-risk profiles. Moreover, integrating broad genomic profiling and evaluating TKI-based combinations with immunotherapeutic or epigenetic agents will be key for patients with poor response or early relapse.[9,10]

Several limitations apply. First, this was a retrospective, single-center small cohort, limiting generalizability. Multivariable analyses were not performed due to the limited number of relapse events in the ponatinib cohort to avoid model overfitting. Second, while we focused on three key deletions, other components of the *IKZF1*-plus definition, such as PAR1 region and *ERG*del, were not assessed, possibly underestimating risk. Third, the comparison with historical imatinib data has inherent limitations, although treatment practices aside from TKI were largely similar. Finally, nearly all patients in this study proceeded to allo-HCT and no standardized post-transplant ponatinib maintenance was implemented, our findings should be interpreted within this transplantation-oriented context. They may not directly extend to non-transplant protocols where ponatinib is continued with chemotherapy or blinatumomab for prolonged periods.[9] Nevertheless, because no patients in our cohort proceeded to allo-HCT within the first 3 months (median time to transplant 5.5 months), the shorter exposure to 30 mg/day ponatinib in the early-reduction group cannot be attributed to early transplantation. Thus, the observed inferior outcomes are more likely associated with intentional dose reduction after CMR rather than confounding by early HCT timing.

In conclusion, our findings highlight the unmet need for optimized ponatinib exposure and post-transplant strategies, particularly for patients with triple-gene deletions who remain at high risk of relapse despite potent TKI-based induction.

## Authors

Jae-Ho Yoon,[1] Kyoung Il Min,[1] Daehun Kwag,[1] Gi-June Min,[1] Sung-Soo Park,[1] Silvia Park,[1] Sung-Eun Lee,[1] Byung-Sik Cho,[1] Ki-Seong Eom,[1] Yoo-Jin Kim,[1] Hee-Je Kim,[1] Chang-Ki Min,[1] Seok-Goo Cho[1] and Seok Lee[2]

[1]Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea and [2]Hematology, Department of Internal Medicine, Mokdong Hospital, College of Medicine, Ewha Womans University, Seoul, Korea

Correspondence:
J-H. YOON - royoon@catholic.ac.kr

https://doi.org/10.3324/haematol.2025.300099

Received: October 24, 2025.
Accepted: January 21, 2026.
Early view: January 29, 2026.



**Disclosures**

No conflicts of interest to disclose.

**Contributions**

JHY and KIM designed the analysis. DK, GJM, SSP, SP, SEL, BSC, KSE, YJK, HJK, CKM, and SGC acquired data. SL analyzed data. JHY and SL contributed to the writing and editing of the manuscript.

**Acknowledgments**

The authors express their gratitude to the clinical staff of the Catholic Hematology Hospital for their assistance in data collection and to the patients whose records contributed to this research. The authors would also like to thank the institutional review board for their oversight and guidance.

**Funding**

The author(s) received financial support from Pfizer for the research and publication of this article.

**Data-sharing statement**

The data supporting the findings of this study are not publicly available due to participant privacy concerns but upon reasonable request and with approval from the institutional review board of the Catholic University of Korea are available from the corresponding author.

## References

1. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. Cancer. 2016;122(23):3650-3656.
2. Kantarjian H, Short NJ, Jain N, et al. Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. Am J Hematol. 2023;98(3):493-501.
3. Jabbour E, Kantarjian HM, Aldoss I, et al. Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. JAMA. 2024;331(21):1814-1823.
4. Jabbour E, Short NJ, Jain N, et al. The evolution of acute lymphoblastic leukemia research and therapy at MD Anderson over four decades. J Hematol Oncol. 2023;16(1):22.
5. Jung J, Yoon J-H, Lee S, et al. Measurable residual disease in adult b lymphoblastic leukemia: a study of concordance between multiparametric flow cytometry, next-generation sequencing of immunoglobulin gene rearrangements, and quantitative PCR. Blood. 2024;144(Suppl 1):1468.
6. Candoni A, Chiusolo P, Lazzarotto D, et al. Ponatinib as a prophylactic or pre-emptive strategy to prevent cytological relapse after allogeneic stem cell transplantation in patients with philadelphia chromosome-positive acute lymphoblastic leukemia transplanted in complete cytological remission. Cancers (Basel). 2024;16(11):2108.
7. Park SY, Kwag D, Jung J, et al. Poor prognostic implication of CDKN2 deletion in adult patients with Philadelphia chromosome-positive ALL. Blood Cancer J. 2025;15(1):102.
8. Kim M, Park J, Kim DW, et al. Impact of IKZF1 deletions on long-term outcomes of allo-SCT following imatinib-based chemotherapy in adult Philadelphia chromosome-positive ALL. Bone Marrow Transplant. 2015;50(3):354-362.
9. Jabbour E, Short NJ, Jain N, et al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. Lancet Haematol. 2023;10(1):e24-e34.
10. Liu L, Li M, Cui Q, et al. Chemotherapy-free treatment with venetoclax, azacitidine and flumatinib induces an early and deep molecular response in patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia: what Is the underlying mechanism? Blood. 2024;144(Suppl 1):5915.