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Front-line Treatment of B-cell Acute Lymphoblastic Leukemia in Canada: Current Strategies and Evolving Paradigms

Curtis Marcoux, MD

Introduction

The treatment landscape for adults with B-cell acute lymphoblastic leukemia (B-ALL) has evolved considerably, with pediatric-inspired regimens, targeted therapies, and measurable residual disease (MRD)-guided approaches improving outcomes. However, treatment strategies in the clinic remain highly variable due to heterogeneity in prospective trials, a lack of randomized comparative data, and the continued evolution of therapies—particularly with the increasing use of targeted agents and immunotherapies in the front-line setting. The absence of national standardization further contributes to variability in clinical practice.

This review provides an overview of current front-line treatment strategies for B-ALL in Canada, highlighting key therapeutic approaches and recent advancements in optimizing care.

Front-line Treatment of *BCR::ABL1*-negative B-ALL

Multiple cooperative groups have developed front-line protocols for *BCR::ABL1*-negative B-ALL based on age, fitness, and prognostic factors.[1] However, the lack of randomized comparisons and significant heterogeneity among protocols have led to global variability, including differences among Canadian centres, without a standardized approach.

Early retrospective analyses showed superior outcomes in adolescents and young adults (AYA) treated with pediatric versus adult regimens,[2,3] prompting prospective trials to evaluate the feasibility of pediatric regimens in adults.[4-10] Although no cooperative group trials have directly randomized patients to pediatric or adult regimens, data favour pediatric-based approaches,[11,12] which are now preferred for AYA patients at experienced centres. However, age cut-offs for 'young adults' vary widely across trials and clinical practice.

Despite becoming standard at many centres in Canada and globally, pediatric regimens present unique challenges.

Pediatric regimens are complex, incorporating multiple phases and, in some cases, risk-adapted therapy. Beyond induction, regimens are designed for outpatient administration, requiring robust clinic and day hospital infrastructure for frequent patient visits. Unlike conventional adult regimens (e.g., hyperCVAD; hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), pediatric approaches emphasize non-myelosuppressive agents such as asparaginase, glucocorticoids, and vincristine, alongside intensive early central nervous system (CNS) prophylaxis.[4,5,9] Derived from Berlin-Frankfurt-Münster (BFM) protocols, these regimens include extended induction, consolidation, delayed intensification, and prolonged maintenance. In contrast, adult-based protocols rely more on myelosuppressive agents like cyclophosphamide, cytarabine, and anthracyclines, with later and less frequent CNS prophylaxis.[13] Historically, adult regimens have also incorporated allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first remission (CR1) as an intensification strategy in those at high risk of relapse. While pediatric-inspired regimens improve outcomes in AYA patients, they increase risks such as hepatotoxicity, pancreatitis, and avascular necrosis, primarily linked to asparaginase.[12] Nevertheless, the benefit-to-toxicity ratio remains favourable. CNS-directed therapy remains essential in all ALL treatment regimens.

In Canada, modified versions of the Dana-Farber Cancer Institute (DFCI) pediatric-like regimen[5] and, less commonly, the CALGB 10403 regimen[4] are the most frequently used for AYA patients. For older adults (>50–60 years), no

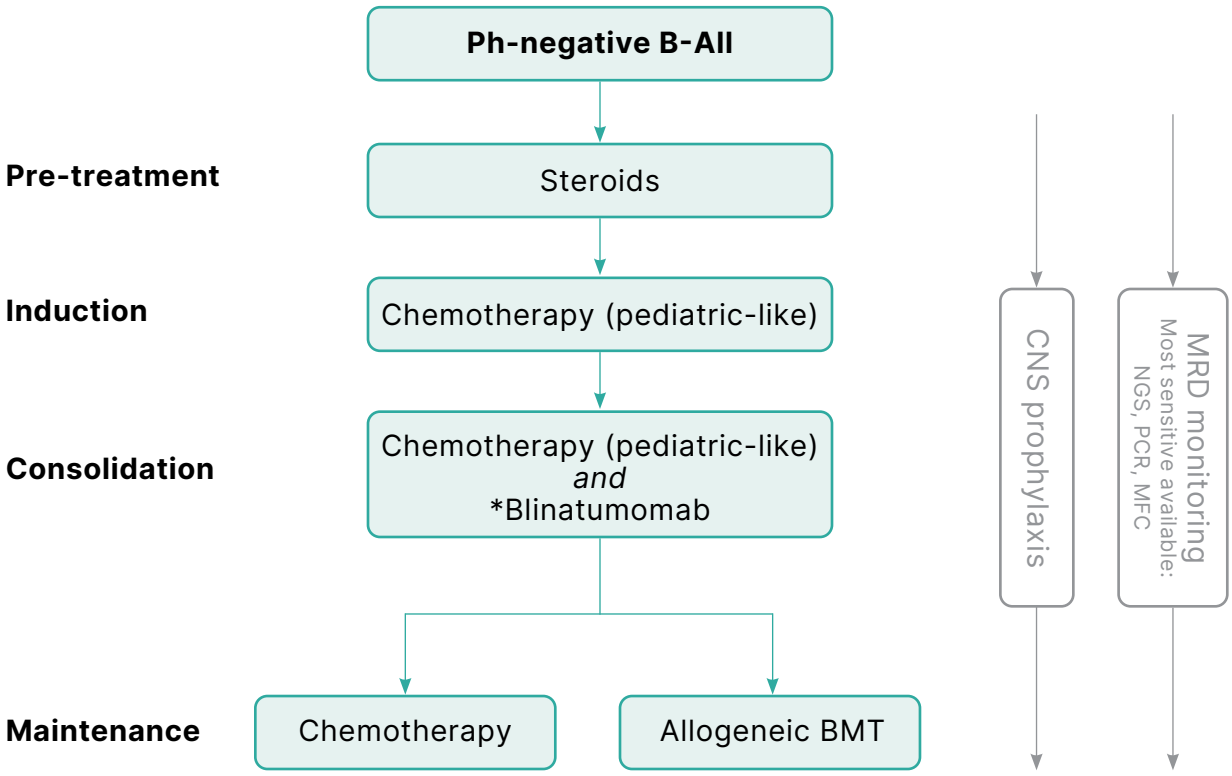

Figure 1. How I Treat *BCR::ABL1*-negative B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **MFC:** multiparametric flow cytometry; **MRD:** measurable residual disease; **NGS:** next-generation sequencing; **PCR:** polymerase chain reaction.

* If available

standardized approach exists across Canadian centres. Some experienced centres use age-adjusted DFCI-based protocols, supported by data from the Princess Margaret Cancer Centre, where Philadelphia chromosome (Ph)-negative ALL patients aged 60–79 years had a 5-year overall survival (OS) of 40%.[14] Age-adjusted hyperCVAD is another acceptable approach.[15] In elderly patients (>75 years) or those with significant comorbidities or reduced fitness, palliative strategies—such as steroids, vincristine, intrathecal therapy, and maintenance with mercaptopurine and methotrexate—are often employed.

Blinatumomab, a bispecific CD19-CD3 T-cell engager, has demonstrated safety and efficacy in treating MRD ($\geq 10^{-3}$)[16] and relapsed/refractory (R/R) BCR::ABL1-negative B-ALL,[17] prompting interest in its use as consolidation in front-line therapy for MRD-negative patients. The ECOG-ACRIN 1910 trial, a randomized phase 3 study in patients aged 30–70 years, compared 4 cycles of blinatumomab plus consolidation chemotherapy to chemotherapy alone in those achieving MRD-negative remission (<0.01%) after induction and intensification.[18] Blinatumomab significantly improved 3-year relapse-free survival (RFS) (80% vs. 64%) and OS (85% vs. 68%) over chemotherapy alone and has since become the standard of care as part of consolidation therapy in *BCR::ABL1*-negative B-ALL, regardless of MRD status, where available.

Blinatumomab is currently under reimbursement review by the Canadian Drug Agency for use in adult *BCR::ABL1*-negative B-ALL as consolidation in the frontline with multiphase chemotherapy. While not yet publicly funded, a patient assistance program is available in Canada to support access regardless of MRD status.

The Canadian Leukemia Study Group (CLSG) recently developed the CLSG ALL 1 protocol,

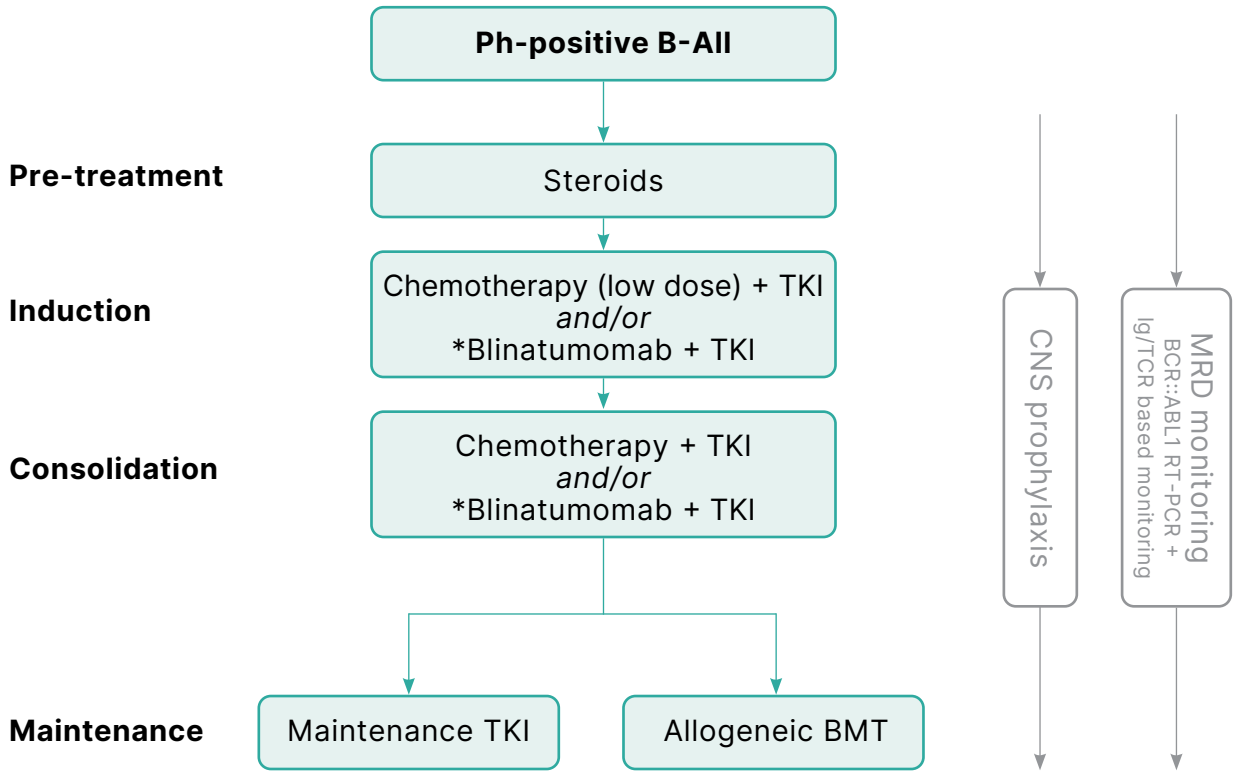

Figure 2. How I Treat *BCR::ABL1*-positive B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **Ig/TCR:** immunoglobulin/T cell receptor; **MRD:** measurable residual disease; **RT-PCR:** reverse-transcription polymerase chain reaction; **TKI:** tyrosine kinase inhibitor.

* If available

integrating blinatumomab into consolidation based on a modified Princess Margaret-DFCI regimen. CLSG ALL 1 includes four MRD-independent cycles of post-induction blinatumomab and aims to reduce chemotherapy exposure, steroid use, and overall treatment duration. Key modifications include reducing intensification to seven cycles across all age groups, eliminating methotrexate from intensification, and shortening maintenance to 18 cycles. Regular MRD assessments are recommended to validate the CLSG ALL 1 approach, clarify the role of transplant, and inform future treatment refinements. My approach to the upfront treatment of *BCR::ABL1*-negative ALL is shown in **Figure 1**.

Front-line Treatment of *BCR::ABL1*-positive B-ALL

Ph-positive B-ALL, the most common genetic subtype of B-ALL, occurs in 25%–30% of cases, with incidence increasing with age.[19] It arises from the t(9;22) translocation, resulting in BCR-ABL1 oncoprotein expression and constitutive kinase activation. Previously associated with poor survival, the introduction of tyrosine kinase inhibitors (TKIs) and sensitive MRD monitoring has markedly improved outcomes.

BCR::ABL1-positive ALL exhibits reduced chemosensitivity with remissions often being short-lived even in patients achieving a complete response (CR).[20,21] Historically, allo-HSCT was recommended for all eligible patients with suitable donors, though long-term survival rates remained low.[22,23] The introduction of TKIs has transformed treatment, with imatinib combined with low-dose chemotherapy inducing CR rates exceeding 95%, reducing induction-related mortality, and achieving survival outcomes comparable to standard induction therapy.[24,25] Second-generation TKIs (e.g. dasatinib, nilotinib) have further improved efficacy and proven safe in combination with chemotherapy.[26-30] Though indirect comparisons suggest these agents may be superior to imatinib, no front-line randomized trials have established a definitive standard. The only randomized data come from a pediatric study (median age 7.8 years), where dasatinib combined with intensive chemotherapy significantly improved 4-year event-free survival (EFS; 71.0% vs. 48.9%) and OS (88.4% vs. 69.2%) while reducing the 4-year cumulative risk of isolated CNS relapse (2.7% vs. 8.4%) compared to imatinib.[31]

The acquisition of the T315I mutation is a key mechanism of relapse in patients treated with first- and second-generation TKIs, driving interest in the front-line use of ponatinib, a third-generation TKI with activity against *ABL1* mutations including T315I.[32-34] The recent PhALLCON trial randomized newly diagnosed patients with Ph+ ALL to ponatinib versus imatinib with reduced-intensity chemotherapy, demonstrating significantly higher MRD-negative CR (≤0.01% BCR::ABL1) rates with ponatinib (34.4% vs. 16.7%) and a trend toward improved EFS.[35] Long-term survival data are awaited to determine whether these findings translate into a survival benefit. Based on current evidence, second- or third-generation TKIs are preferred for front-line therapy, though imatinib remains a reasonable option where access to newer agents is limited. Finally, dual *BCR::ABL1* inhibition with asciminib—an allosteric *BCR::ABL1* inhibitor targeting a distinct site from ATP-competitive TKIs—and dasatinib has shown promise in a phase 1 study. However, further research is needed to determine the safety and efficacy of dual TKI therapy relative to current standard treatments.[36]

Given the success of blinatumomab in MRD eradication[16] and treatment of low-level disease in R/R B-ALL,[37] there was interest in evaluating its role as a consolidation therapy in *BCR::ABL1*-positive B-ALL. The GIMEMA LAL2116 (D-ALBA) study evaluated dasatinib and prednisone induction followed by 2 to 5 cycles of blinatumomab consolidation in newly diagnosed Ph-positive B-ALL.[38] Nearly all patients (98%) achieved complete hematologic response after chemotherapy-free induction, with 29% achieving molecular remission (MR), defined as undetectable or non-quantifiable *BCR::ABL1*. MR rates increased to 60% and over 80% after 2 and 4 cycles of blinatumomab, respectively. Similarly, ponatinib, when used either concurrently[39,40] or sequentially[41] with blinatumomab, has demonstrated safety and efficacy, leading to high rates of deep molecular responses. While CNS prophylaxis is a standard component of ALL therapy, particular attention is needed in chemotherapy-free regimens, as CNS relapse remains a common pattern of disease recurrence. Further, patients with the IKZF1Plus genotype (*IKZF1* deletion alongside deletions in *CDKN2A/B* and/or *PAX5*) remain at high risk of relapse.[40] Notably, blinatumomab is not currently available in Canada outside of clinical trials for front-line *BCR::ABL1*-positive ALL. My approach to

the upfront treatment of *BCR::ABL1*-positive ALL is shown in **Figure 2**.

Additional Considerations: CNS Prophylaxis

There is a paucity of data on CNS-directed therapy in adult ALL, leading to variability in clinical practice. The first lumbar puncture (LP) is typically performed at the time of the first scheduled intrathecal (IT) chemotherapy unless neurological symptoms warrant earlier evaluation. Whether LP should be delayed until circulating blasts clear remains debated due to the theoretical risk of CSF contamination.

Adult ALL regimens include CNS-penetrating systemic agents (e.g., dexamethasone, pegaspargase, methotrexate, 6-mercaptopurine, cytarabine, dasatinib) alongside IT chemotherapy for prophylaxis. Standard regimens for CNS-negative patients historically include 8–12 IT treatments, but with the incorporation of immunotherapies (e.g., blinatumomab) and reduced-intensity chemotherapy, CNS prophylaxis has become increasingly important. Modern regimens now incorporate upwards of 15 IT treatments. Adherence to established treatment protocols for CNS-directed prophylaxis is essential to ensure adequate protection against CNS relapse. Notably, most adult protocols do not include radiotherapy for patients without CNS involvement at diagnosis.

Indications for Transplant in First Complete Remission

Allo-HSCT remains a critical therapeutic strategy for high-risk ALL, particularly when standard chemotherapy alone is unlikely to provide durable disease control.[42] Advances in targeted therapies and MRD-driven treatment strategies have improved survival rates, and indications for allo-HSCT in first complete remission (CR1) continue to evolve, balancing the risk of relapse against transplant-related morbidity and mortality.

BCR::ABL1-negative B-ALL

Among Ph-negative B-ALL subtypes, Ph-like, *KMT2A*-rearranged (*KMT2A*-r) ALL and those with complex karyotype remain particularly challenging due to high relapse rates and poor responses to conventional chemotherapy. Ph-like ALL, defined by a gene expression profile similar to Ph-positive ALL but lacking *BCR::ABL1*,[43,44] is associated with inferior survival outcomes with chemotherapy alone. However, routine identification of Ph-like ALL remains limited in many centres due to the lack of widely available, standardized diagnostic assays. Data from GIMEMA,[45,46] MD Anderson,[43] and City of Hope[47] suggest that allo-HSSCT improves outcomes, particularly in MRD-positive patients, with post-transplant survival rates comparable to other Ph-negative subtypes. Further, a recent U.S. multicentre study found that, despite higher induction failure in Ph-like ALL, progression-free survival (PFS) and OS after allo-HCT in CR1 were similar to other Ph-negative subtypes.[48]

Similarly, *KMT2A*-r ALL has historically carried a poor prognosis, though data from MD Anderson[49] and the GRAALL[50] support the benefit of allo-HSCT in this subgroup. However, emerging evidence suggests that a subset of *KMT2A*-r patients with early MRD-negativity and favourable molecular features may achieve durable remissions without transplant.[51] Complex karyotype (≥5 abnormalities) and low hypodiploidy (30–39 chromosomes)[52] are both high-risk cytogenetic abnormalities and should prompt early referral for allo-HSCT.

As targeted therapies,[53,54] immunotherapies,[18] and refined MRD-based risk stratification[55] continue to advance, the role of allo-HSCT in these subtypes may evolve. For now, it remains a key consideration for eligible patients in CR1.

BCR::ABL1-positive B-ALL

The role of allo-HSCT in *BCR::ABL1*-positive ALL has evolved significantly. Before the introduction of TKIs, transplant was the standard of care for all eligible patients, supported by donor versus no-donor analyses demonstrating superior outcomes.[20,23] In the TKI era, studies have continued to support the benefit of consolidative allo-HSCT with first or second-generation TKIs;[29,56-58] however, these studies did not routinely incorporate MRD-guided risk stratification into transplant decisions.

Recent evidence suggests that patients achieving early, deep remissions with TKI-based therapy may safely forgo allo-HSCT. Prospective trials of imatinib-[24] and nilotinib-based[59] regimens found no survival advantage for transplant in MRD-negative patients. Similarly, a U.S. multicentre study reported no OS benefit for allo-HSCT in patients achieving complete molecular remission (CMR) within 90 days of diagnosis, as higher non-relapse mortality (NRM) offset lower relapse rates in those undergoing transplant.[60] Although

not yet routinely available in Canada for front-line therapy, ponatinib has shown efficacy in inducing deep and durable remissions without allo-HSCT. A single-centre study of ponatinib and hyperCVAD reported CMR rates exceeding 80%,[32] with only 23% of patients undergoing allo-HSCT in CR1 and a 6-year OS of 87% in those not transplanted.[32,61]

The necessity of transplant is further challenged by the emergence of highly effective low-intensity or chemotherapy-free regimens incorporating blinatumomab. The GIMEMA LAL2116 (D-ALBA) trial, which combined dasatinib with blinatumomab, reported a 98% CR rate, with the majority achieving MRD-negative remissions.[38,62] Sustained remissions were observed in nearly all MRD-negative patients without transplant, whereas MRD-positive patients undergoing allo-HSCT experienced low transplant-related mortality. Ponatinib combined with blinatumomab may further improve these outcomes, as an MD Anderson study of concurrent ponatinib and blinatumomab reported next-generation sequencing (NGS)-MRD negativity in 98% of patients, with only 3% requiring transplant and a 3-year OS of 91%.[39,40] An interim analysis of the GIMEMA ALL2820 trial, a follow-up to LAL2116 in which dasatinib was replaced with ponatinib, demonstrated similarly impressive results.[41] Although the median follow-up was just over 6 months, the estimated 12-month disease-free survival and OS were 95.6% and 94.9%, respectively. Transplant allocation was based on the presence of the *IKZF1*plus genotype and MRD persistence, with only 12% of patients undergoing allo-HSCT. The GRAAPH-2024 study (NCT06860269) aims to clarify the role of transplant by randomizing patients in CMR after treatment with ponatinib, blinatumomab, and low-intensity chemotherapy to either allo-HSCT or continued TKI-based therapy.

Measurable Residual Disease

MRD is a key predictor of relapse and a critical determinant in transplant decisions for both Ph-negative and Ph-positive ALL, often outweighing traditional clinical and genetic risk factors.[63-66] Across multiple risk stratification models, MRD is the most consistent factor guiding allo-HCT in CR1,[67] with transplant offering a survival advantage in MRD-positive patients.[68,69] The necessity of allo-HSCT in MRD-negative high-risk patients remains uncertain, particular when highly sensitive methods of MRD detection (NGS-MRD) are used. In BCR-ABL1-positive ALL, reverse transcription-polymerase chain reaction (RT-PCR) for *BCR::ABL1*, though widely used, is less sensitive and correlates poorly with immunoglobulin (Ig)/ T cell receptor (TCR) PCR and NGS-based MRD.[70,71] NGS-MRD can identify patients with a "CML-like" profile, where residual *BCR::ABL1* transcripts do not necessarily indicate active disease.[71] Given the limited access to NGS-MRD in Canada, the most sensitive assay available should be used for *BCR::ABL1*-negative ALL, while in *BCR::ABL1*-positive ALL, quantitative PCR for both p190 and p210 ABL1 transcripts, ideally alongside Ig/TCR-based assays, is recommended to guide transplant decisions. Ongoing evaluation of MRD dynamics and treatment-specific thresholds remains crucial as front-line therapies evolve.

Conclusion

Despite significant advances in B-ALL treatment, challenges persist, particularly the absence of standardized guidelines and disparities in access to novel agents such as blinatumomab and ponatinib. The expanding role of targeted and immunotherapies, including chimeric antigen receptor (CAR)-T cell therapies and next-generation TKIs, is reshaping treatment paradigms and necessitating a reassessment of transplant indications. Moving forward, harmonizing treatment strategies and refining risk-adapted approaches will be crucial to optimizing outcomes across diverse clinical settings.

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References

1. Gökbuget N, Boissel N, Chiaretti S, Dombret H, Doubek M, Fielding A, et al. Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024;143(19):1891-902.
2. Stock W, La M, Sanford B, Bloomfield CD, Vardiman JW, Gaynon P, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112(5):1646-54.
3. Boissel N, Auclerc MF, Lhéritier V, Perel Y, Thomas X, Leblanc T, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol. 2003;21(5):774-80.

4. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. Blood. 2019;133(14):1548-59.
5. DeAngelo DJ, Stevenson KE, Dahlberg SE, Silverman LB, Couban S, Supko JG, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia. 2015;29(3):526-34.
6. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009;27(6):911-8.
7. Huguet F, Chevret S, Leguay T, Thomas X, Boissel N, Escoffre-Barbe M, et al. Intensified Therapy of Acute Lymphoblastic Leukemia in Adults: Report of the Randomized GRAALL-2005 Clinical Trial. J Clin Oncol. 2018;36(24):2514-23.
8. Ribera JM, Oriol A, Sanz MA, Tormo M, Fernández-Abellán P, del Potro E, et al. Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Español de Tratamiento en Hematología pediatric-based protocol ALL-96. J Clin Oncol. 2008;26(11):1843-9.
9. Rytting ME, Jabbour EJ, Jorgensen JL, Ravandi F, Franklin AR, Kadia TM, et al. Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin-Frankfurt-Münster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen. Am J Hematol. 2016;91(8):819-23.
10. Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, et al. Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia. 2018;32(3):606-15.
11. Ram R, Wolach O, Vidal L, Gafter-Gvili A, Shpilberg O, Raanani P. Adolescents and young adults with acute lymphoblastic leukemia have a better outcome when treated with pediatric-inspired regimens: systematic review and meta-analysis. Am J Hematol. 2012;87(5):472-8.
12. Siegel SE, Stock W, Johnson RH, Advani A, Muffly L, Douer D, et al. Pediatric-Inspired Treatment Regimens for Adolescents and Young Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Review. JAMA Oncol. 2018;4(5):725-34.
13. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004;101(12):2788-801.
14. Martell MP, Atenafu EG, Minden MD, Schuh AC, Yee KW, Schimmer AD, et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. Br J Haematol. 2013;163(4):458-64.
15. Rausch CR, Jabbour EJ, Kantarjian HM, Kadia TM. Optimizing the use of the hyperCVAD regimen: Clinical vignettes and practical management. Cancer. 2020;126(6):1152-60.
16. Gökbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522-31.
17. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017;376(9):836-47.
18. Litzow MR, Sun Z, Mattison RJ, Paietta EM, Roberts KG, Zhang Y, et al. Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2024;391(4):320-33.
19. Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV. Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. Leukemia. 1991;5(3):196-9.
20. Dombret H, Gabert J, Boiron JM, Rigal-Huguet F, Blaise D, Thomas X, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia--results of the prospective multicenter LALA-94 trial. Blood. 2002;100(7):2357-66.
21. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A Collaborative Study of the Group Français de Cytogénétique Hématologique. Blood. 1996;87(8):3135-42.
22. Gleissner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Janssen JW, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood. 2002;99(5):1536-43.
23. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. 2009;113(19):4489-96.
24. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-9.
25. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer. 2007;109(10):2068-76.
26. Ottmann OG, Pfeifer H, Cayuela J-M, Spiekermann K, Jung W, Beck J, et al. Nilotinib (Tasigna®) and Low Intensity Chemotherapy for First-Line Treatment of Elderly Patients with BCR-ABL1-Positive Acute Lymphoblastic Leukemia: Final Results of a Prospective Multicenter Trial (EWALL-PH02). Blood. 2018;132(Supplement 1):31-.
27. Chalandon Y, Rousselot P, Chevret S, Cayuela JM, Kim R, Huguet F, et al. Nilotinib with or without cytarabine for Philadelphia-positive acute lymphoblastic leukemia. Blood. 2024;143(23):2363-72.
28. Chiaretti S, Ansuinelli M, Vitale A, Elia L, Matarazzo M, Piciocchi A, et al. A multicenter total therapy strategy for de novo adult Philadelphia chromosome positive acute lymphoblastic leukemia patients: final results of the GIMEMA LAL1509 protocol. Haematologica. 2021;106(7):1828-38.
29. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC, et al. US Intergroup Study of Chemotherapy Plus Dasatinib and Allogeneic Stem Cell Transplant in Philadelphia Chromosome Positive ALL. Blood Adv. 2016;1(3):250-9.
30. Ravandi F, O'Brien SM, Cortes JE, Thomas DM, Garris R, Faderl S, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer. 2015;121(23):4158-64.
31. Shen S, Chen X, Cai J, Yu J, Gao J, Hu S, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol. 2020;6(3):358-66.
32. Kantarjian H, Short NJ, Jain N, Sasaki K, Huang X, Haddad FG, 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.
33. Ribera JM, García-Calduch O, Ribera J, Montesinos P, Cano-Ferri I, Martínez P, et al. Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Adv. 2022;6(18):5395-402.
34. Martinelli G, Papayannidis C, Piciocchi A, Robustelli V, Soverini S, Terragna C, et al. INCB84344-201: Ponatinib and steroids in frontline therapy for unfit patients with Ph+ acute lymphoblastic leukemia. Blood Adv. 2022;6(6):1742-53.
35. Jabbour E, Kantarjian HM, Aldoss I, Montesinos P, Leonard JT, Gómez-Almaguer D, et al. Ponatinib vs Imatinib in Frontline Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. Jama. 2024;331(21):1814-23.
36. Luskin MR, Murakami MA, Keating J, Flamand Y, Winer ES, Garcia JS, et al. Asciminib plus dasatinib and prednisone for Philadelphia chromosome-positive acute leukemia. Blood. 2025;145(6):577-89.
37. Martinelli G, Boissel N, Chevallier P, Ottmann O, Gökbuget N, Topp MS, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017;35(16):1795-802.
38. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo MC, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2020;383(17):1613-23.

39. Jabbour E, Short NJ, Jain N, Huang X, Montalban-Bravo G, Banerjee P, 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.
40. Kantarjian H, Short NJ, Haddad FG, Jain N, Huang X, Montalban-Bravo G, et al. Results of the Simultaneous Combination of Ponatinib and Blinatumomab in Philadelphia Chromosome-Positive ALL. J Clin Oncol. 2024;42(36):4246-51.
41. Chiaretti S, Leoncin M, Elia L, Soddu S, Piciocchi A, Matarazzo M, et al. Efficacy and Toxicity of Frontline Ponatinib Plus Blinatumomab for Adult Ph+ ALL Patients of All Ages. Intermediate Analysis of the Gimema ALL2820. Blood. 2024;144(Supplement 1):835-.
42. Marcoux C, Kebriaei P. Transplant in ALL: who, when, and how? Hematology Am Soc Hematol Educ Program. 2024;2024(1):93-101.
43. Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Chen K, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood. 2017;129(5):572-81.
44. Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. J Clin Oncol. 2017;35(4):394-401.
45. Chiaretti S, Messina M, Della Starza I, Piciocchi A, Cafforio L, Cavalli M, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. Haematologica. 2021;106(6):1559-68.
46. Koller P, Saliba RM, Ledesma C, Rondon G, Popat U, Alousi A, et al. Outcomes in patients with CRLF2 overexpressed acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2021;56(7):1746-9.
47. Aldoss I, Yang D, Tomasian V, Mokhtari S, Jackson R, Gu Z, et al. Outcomes of allogeneic hematopoietic cell transplantation in adults with fusions associated with Ph-like ALL. Blood Adv. 2022;6(17):4936-48.
48. Rahman ZA, Othman T, Saliba RM, Vanegas YAM, Mohty R, Ledesma C, et al. A Multicenter Analysis of Allogeneic Transplant Outcomes in Adults with Philadelphia-Like B-Cell Acute Lymphoblastic Leukemia in First Complete Remission. Transplant Cell Ther. 2024;30(12):1197-205.
49. Richard-Carpentier G, Kantarjian HM, Tang G, Yin CC, Khoury JD, Issa GC, et al. Outcomes of acute lymphoblastic leukemia with KMT2A (MLL) rearrangement: the MD Anderson experience. Blood Adv. 2021;5(23):5415-9.
50. Lafage-Pochitaloff M, Baranger L, Hunault M, Cuccuini W, Lefebvre C, Bidet A, et al. Impact of cytogenetic abnormalities in adults with Ph-negative B-cell precursor acute lymphoblastic leukemia. Blood. 2017;130(16):1832-44.
51. Kim R, Bergugnat H, Pastoret C, Pasquier F, Raffoux E, Larcher L, et al. Genetic alterations and MRD refine risk assessment for KMT2A-rearranged B-cell precursor ALL in adults: a GRAALL study. Blood. 2023;142(21):1806-17.
52. Moorman AV, Barretta E, Butler ER, Ward EJ, Twentyman K, Kirkwood AA, et al. Prognostic impact of chromosomal abnormalities and copy number alterations in adult B-cell precursor acute lymphoblastic leukaemia: a UKALL14 study. Leukemia. 2022;36(3):625-36.
53. Jabbour E, Searle E, Abdul-Hay M, Abedin S, Aldoss I, Alfonso Piérola A, et al. A First-in-Human Phase 1 Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Adult Patients with Relapsed/Refractory Acute Leukemia Harboring KMT2A or NPM1 Alterations. Blood. 2023;142:57.
54. Aldoss I, Issa GC, Thirman M, DiPersio J, Arellano M, Blachly JS, et al. Revumenib Monotherapy in Patients with Relapsed/Refractory KMT2Ar Acute Leukemia: Topline Efficacy and Safety Results from the Pivotal Augment-101 Phase 2 Study. Blood. 2023;142(Supplement 2):LBA-5-LBA-.
55. Burmeister T, Ströh AS, Kehden B, Trautmann H, Meyer C, Marschalek R, et al. Measurable residual disease quantification in adult patients with KMT2A-rearranged acute lymphoblastic leukemia. Leukemia. 2024;38(7):1600-3.
56. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-9.
57. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746-56.
58. Wieduwilt MJ, Yin J, Wetzler M, Uy GL, Powell BL, Kolitz JE, et al. Dasatinib and dexamethasone followed by hematopoietic cell transplantation for adults with Ph-positive ALL. Blood Adv. 2021;5(22):4691-700.
59. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746-56.
60. Ghobadi A, Slade M, Kantarjian H, Alvarenga J, Aldoss I, Mohammed KA, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. Blood. 2022;140(20):2101-12.
61. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol. 2018;5(12):e618-e27.
62. Foà R, Bassan R, Elia L, Piciocchi A, Soddu S, Messina M, et al. Long-Term Results of the Dasatinib-Blinatumomab Protocol for Adult Philadelphia-Positive ALL. J Clin Oncol. 2024;42(8):881-5.
63. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008;111(12):5477-85.
64. Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica. 2019;104(10):2028-39.
65. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017;3(7):e170580.
66. Ribera JM, Oriol A, Morgades M, Montesinos P, Sarrà J, González-Campos J, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. J Clin Oncol. 2014;32(15):1595-604.
67. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2019;54(6):798-809.
68. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120(9):1868-76.
69. Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125(16):2486-96; quiz 586.
70. Cazzaniga G, De Lorenzo P, Alten J, Röttgers S, Hancock J, Saha V, et al. Predictive value of minimal residual disease in Philadelphia-chromosome-positive acute lymphoblastic leukemia treated with imatinib in the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukemia, based on immunoglobulin/T-cell receptor and BCR/ABL1 methodologies. Haematologica. 2018;103(1):107-15.
71. Short NJ, Jabbour E, Macaron W, Ravandi F, Jain N, Kanagal-Shamanna R, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: Prognostic impact and correlation with RT-PCR for BCR::ABL1. Am J Hematol. 2023;98(8):1196-203.