SOHO State of the Art Updates & Next Questions: Intensive and Non-Intensive Approaches for Adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Nicholas J. Short , Hagop Kantarjian , Elias Jabbour

PII: S2152-2650(21)00361-X
DOI: https://doi.org/10.1016/j.clml.2021.08.003
Reference: CLML 1923

To appear in: *Clinical Lymphoma, Myeloma and Leukemia*

Received date: Jul 15, 2021
Revised date: Aug 9, 2021
Accepted date: Aug 16, 2021

Please cite this article as: Nicholas J. Short , Hagop Kantarjian , Elias Jabbour , SOHO State of the Art Updates & Next Questions: Intensive and Non-Intensive Approaches for Adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia, *Clinical Lymphoma, Myeloma and Leukemia* (2021), doi: https://doi.org/10.1016/j.clml.2021.08.003

SOHO State of the Art Updates & Next Questions: Intensive and Non-Intensive Approaches for Adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Intensive vs. Non-Intensive Approaches for Ph+ ALL

Nicholas J. Short, Hagop Kantarjian, Elias Jabbour

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX USA

Correspondence: Nicholas Short, MD, Department of Leukemia, Unit 428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA; e-mail: nshort@mdanderson.org

Keywords

chemotherapy, BCR-ABL, acute lymphoblastic leukemia, tyrosine kinase inhibitor, blinatumomab

Abstract

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) was historically considered to be a very poor-risk subtype of ALL. However, with the introduction of highly potent BCR-ABL tyrosine kinase inhibitors (TKIs), Ph+ ALL can now be considered relatively favorable-risk acute leukemia. Considering the high rates of measurable residual disease negativity and excellent long-term survival that has been achieved with regimens incorporating later-generation TKIs and particularly with ponatinib, lower-intensity and even chemotherapy-free regimens are now being evaluated for patients of all ages with Ph+ ALL. The very encouraging early results observed with blinatumomab-based, chemotherapy-free regimens challenge previous notions that all patients with Ph+ ALL should undergo allogeneic stem cell transplantation in first remission, as these regimens are capable of achieving deep and durable remissions without need for transplant in the vast majority of patients, particularly when combined with ponatinib. In this review, we discuss the evolving approach to the treatment of adults with newly diagnosed Ph+ ALL and the major principles that should guide therapy in this disease. We also review the rationale and data supporting the use of novel, chemotherapy-free regimens in Ph+ ALL and how these approaches may soon become new standards of care.

Introduction

Over the past 20 years, the outcomes of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) have dramatically improved, first with the addition of BCR-ABL tyrosine kinase inhibitors (TKIs) to chemotherapy backbones and, more recently, with the development of more potent later-generation TKIs.[1] In adults who are fit for intensive chemotherapy, most studies have evaluated TKIs in combination with intensive chemotherapy such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine) or similar regimens. However, with the development of more active, broader spectrum TKIs such as ponatinib and effective novel monoclonal antibody constructs such as blinatumomab, the role of intensive chemotherapy in treating patients with Ph+ ALL has been increasingly questioned. Several investigators are currently evaluating lower-intensity regimens in patients with Ph+ ALL of all ages in an effort to assess whether use of these novel agents may allow for de-intensification of therapy even for younger and fit patients. In this review, we summarize the evidence for frontline regimens in Ph+ ALL and specifically discuss the rationale and emerging data for non-intensive, chemotherapy-free regimens in this disease.

Principles of the Frontline Treatment of Ph+ ALL: Optimal Response and TKI Selection

Achievement of MRD negativity has been shown to be associated with superior disease-free survival (DFS) and overall survival (OS) in a meta-analysis of 39 publications on both children and adults with ALL, several of which included patients with Ph+ ALL.[2] In order to achieve cure in Ph+ ALL, it is imperative that patients achieve a complete molecular response (CMR), defined as the absence of detectable *BCR-ABL1* transcripts as assessed by real-time quantitative reverse-transcription polymerase chain reaction. Several studies have showed that this endpoint is associated with favorable outcomes, including in patients who do not undergo subsequent allogeneic hemopoietic stem cell transplantation (HSCT) in first remission.[3-5] In a retrospective study of patients with Ph+ ALL who received intensive chemotherapy

with hyper-CVAD plus a TKI and did not undergo HSCT in first remission, achievement of CMR within 3 months was associated a 4-year OS rate of 66% (versus 36% for those with lesser responses; P<0.001). In this analysis, CMR at 3 months was the only independent predictor of OS.[4] Given the favorable outcomes for patients who achieved CMR and did not undergo subsequent HSCT, these data suggest that HSCT may be safely deferred in first remission in patients who achieve this endpoint. This MRD-driven approach to consolidation therapy in Ph+ ALL is supported by consensus recommendations.[6] Early achievement of CMR is thus an important endpoint in evaluating new therapies for Ph+ ALL and may serve as an early indicator of regimens that are likely to lead to durable remissions and cure without need for HSCT.

Which BCR-ABL TKI is used in the frontline regimen is a major driver of both MRD negativity rates and long-term outcomes in Ph+ ALL. A key principle that has been observed across studies of various TKI-based regimens for Ph+ ALL is that later-generation TKIs are associated with increased molecular response rates and superior OS compared to earlier-generation TKIs.[7] A phase III randomized study of chemotherapy plus either imatinib or dasatinib was conducted in children with Ph+ ALL.[8] Notably, this study used a dasatinib dose of 80 mg/m^2 per day, a dose which provides enhanced penetration into the central nervous system (CNS)[9] and which was higher than the 60 mg/m^2 dose used in two previous pediatric studies.[10,11] The use of dasatinib was associated with a superior 4-year event-free survival (EFS) rate (71.0% versus 48.9%; P=0.005) and a superior 4-year OS rate (88.4% versus 69.2%; P=0.04).[8] The benefit to dasatinib treatment was driven by a decreased risk of relapse (4-year cumulative risk of relapse: 19.8% versus 34.4% with imatinib; P=0.01), including a lower rate of CNS relapses (2.7% versus 8.4%, respectively; P=0.06). These data provide the most robust evidence to date support the use of a later-generation TKI rather than imatinib in patients with Ph+ ALL. Unfortunately, there are no randomized data to guide TKI selection in adults with newly diagnosed Ph+ ALL, although a randomized

phase III study of reduced-intensity chemotherapy plus either imatinib or ponatinib in this population is ongoing (NCT03589326).

While superior to imatinib, a second-generation TKI such as dasatinib or nilotinib may not be adequate for many patients. T315I resistance mutations in the *ABL1* gene—which confer resistance to all first- and second-generation TKIs—have been reported in up to 75% of patients who relapse after treatment with a first- or second-generation TKI.[12,13] Using highly sensitivity next-generation sequencing based techniques, these mutations do not appear to be present at the time of treatment initiation and therefore baseline *ABL1* testing is unlikely to be useful in frontline TKI selection.[14] The dominant role that treatment-emergent T315I mutations play in driving relapse has led our group and other investigators to evaluate the role of ponatinib in the frontline setting. Data from these individual trials will be discussed in detail in later sections. However, importantly, these ponatinib-based regimens have been associated with superior rates of CMR compared to regimens using earlier-generation TKIs, which has translated to improved long-term outcomes. For example, the overall CMR rate with the hyper-CVAD plus ponatinib regimen was 86%, compared to 45-65% reported in studies with hyper-CVAD plus imatinib or dasatinib.[15-18] These deeper responses translated to superior 5-year OS for the hyper-CVAD plus ponatinib regimen (74% versus 40-50% with hyper-CVAD plus imatinib or dasatinib). The superior outcomes achieved with a ponatinib-based frontline regimen for Ph+ ALL is also supported by both a meta-analysis and a propensity-matched score analysis, both of which showed an OS benefit with use of ponatinib versus the use of earlier-generation TKIs.[19,20] Even among those who achieve CMR, there is evidence to suggest that treatment with ponatinib is superior to other TKIs. In a retrospective analysis of 84 patients who received hyper-CVAD plus a TKI and achieved 3-month CMR, use of ponatinib (rather than imatinib or dasatinib) was the only significant independent predictor of OS.[21]

Outcomes with Intensive Chemotherapy + TKI

Results from major clinical trials of various TKI-based regimens in newly diagnosed Ph+ ALL are shown in **Table 1**. The introduction of imatinib to standard chemotherapy improved outcomes compared to chemotherapy alone and resulted in complete remission (CR) rates of 95% and long-term OS rates of 35-45%.[15,22-24] As in the pre-TKI era, analyses of the impact of allogeneic HSCT in first remission from the imatinib era suggested a benefit to consolidative HSCT.[23] However, it is important to note that CMR rates <50% have been reported in most studies of imatinib-based regimens.[15,22,25,26] In a multicenter study of hyper-CVAD plus dasatinib in 94 adults ≤60 years of age, the 3-year OS was 69%.[27] Importantly, even with this second-generation TKI, allogeneic HSCT was associated with improvement of relapse-free survival (RFS) and OS compared with those who did not undergo HSCT in first remission (P=0.038 and 0.037, respectively). Notably, MRD data for this cohort have not been published, and therefore we do not know whether the impact of HSCT was impacted by MRD response, as has been suggested in some other studies.[4] In another study of intensive chemotherapy plus nilotinib, a 2-year OS rate of 72% was achieved, with 70% of patients undergoing HSCT in first remission.[28]

In the most recent update of the study of hyper-CVAD plus ponatinib for patients with newly diagnosed Ph+ ALL, 86 patients have been treated (median age: 46 years), 74% of whom achieved CMR at the 3-month time point and 86% of whom achieved CMR at some point over the course of therapy.[17,18] Due in part to the very high CMR rate, only 19 patients (22% of the entire cohort) underwent HSCT in first remission. With a median follow-up of 44 months, the 5-year OS rate was 74%, and in a landmark analysis, the 5-year OS rate among non-transplanted patients was 83%. Notably, only 3 patients relapsed while still on ponatinib, suggesting that ponatinib is highly effective at suppressing resistant clones. The toxicity of this regimen has also been manageable since instituting a risk-adapted dosing schedule of ponatinib in which patients receive 45mg on days 1-14 during induction, with decrease to

30mg once CR is achieved and again to 15mg once CMR is achieved. Acknowledging the challenges of cross-trial comparison of data from single-arm studies, both the CMR rates and long-term outcomes reported with the hyper-CVAD plus ponatinib regimen appear superior to those achieved with intensive chemotherapy plus an earlier-generation TKI. These results suggest that a ponatinib-based regimen can yield high rates of deep molecular remission, eliminating the need for HSCT for the vast majority of patients.

Outcomes with Lower-Intensity Chemotherapy and/or Corticosteroids + TKI

As the incidence of Ph+ ALL increases with age, many patients may be too old or frail to safely receive intensive chemotherapy. Therefore, several investigators have evaluated lower-intensity regimens in older patients with newly diagnosed Ph+ ALL. The EWALL-PH-01 study evaluated the combination of dasatinib with low-intensity chemotherapy in patients age >55 years of age.[13] While nearly all patients (96%) achieved CR, only 24% of patients achieved measurable residual disease (MRD) negativity, defined in this study as a 5-log reduction in *BCR-ABL1* transcript levels. The 5-year OS rate was 36%, reflecting poorer disease control with this lower-intensity regimen as compared to what has been achieved with intensive chemotherapy plus a TKI. The development of a T315I mutation in *ABL1*, which was detected in 75% of relapses, was the primary driver of resistance with this regimen. A study of low-intensity chemotherapy plus nilotinib in a similar population resulted in a CR rate of 94% and a 4-year OS rate of 47%.[29]

Regimens using only corticosteroid plus a TKI have also been explored. While these regimens are generally well-tolerated they are generally associated with short durations of response and suboptimal CMR rates (e.g. 4% with imatinib and 23% with dasatinib).[5,30,31] Given the established potency of ponatinib and its clinical activity against T315I mutations, ponatinib has also been explored in the

context of lower-intensity regimens. In the GIMEMA LAL1811 trial of older or unfit patients with newly diagnosed Ph+ ALL, ponatinib at a dose of 45mg daily was combined with corticosteroids in 44 patients.[32] CR was achieved in 95% of patients after 1 course of therapy. However, the CMR rate was only 46%, which translated to an estimated 2-year OS of 62%. Acknowledging that this study was conducted specifically in an older population, the depth of remission attained with this low-intensity regimen of ponatinib plus corticosteroids appears substantially lower than that achieved with hyper-CVAD plus ponatinib (46% versus 86%, respectively), providing evidence that treatment intensity may play an important role in achieving deep responses and long-term remissions in Ph+ ALL. However, as discussed in the following section, this benefit of intensive chemotherapy may not apply when more effective novel monoclonal antibodies such as blinatumomab are used.

Lower intensity therapies have also been studied in younger, fit patients with Ph+ ALL. For example, in the GIMEMA LAL1509 trial, the combination of dasatinib with prednisone was evaluated in younger patients (median age: 42 years).[5] Patients who did not achieve CMR by day 85 received subsequent chemotherapy, with or without HSCT, whereas those who achieved CMR continued with dasatinib alone. Using this risk-adapted treatment approach, the 3-year OS rate was 58%. However, only 18% of patients achieved CMR with TKI plus steroids alone and were therefore able to be spared chemotherapy and/or HSCT. Thus, while this approach could identify a subset of patients whose disease was highly sensitive to minimal therapy, the majority of patients required treatment intensification, including transplantation. In contrast, regimens capable of inducing very high rates of CMR can spare most patients the need for HSCT in first remission.

Outcomes with Blinatumomab + TKI

Blinatumomab has been shown to be highly effective in relapsed/refractory Ph+ ALL both as monotherapy and in combination with a TKI.[33,34] This has prompted the development of several clinical trials in the frontline setting evaluating blinatumomab in combination with a TKI. In the D-ALBA study, adults of any age with newly diagnosed Ph+ ALL were treated with a combination of corticosteroids and dasatinib for 85 days, followed by 2-5 cycles of blinatumomab consolidation, along with 12 doses of intrathecal chemotherapy. Sixty-three patients were treated with a median age of 54 years (range, 24-82 years). Among the 55 patients who received 2 cycles of blinatumomab, 60% achieved a molecular response at this time point (either CMR or positive non-quantifiable). Twenty-nine patients (46%) underwent HSCT. With a median follow-up of 28.8 months as of the most recent update, the 36-month DFS and OS rates were 71% and 80%, respectively. Overall, 9 patients relapsed, including 4 hematologic, 1 nodal, 3 isolated CNS, and 1 combined hematologic and CNS relapse. These results are encouraging and provide a proof-of-concept that chemotherapy-free blinatumomab plus TKI regimens are highly effective in Ph+ ALL. However, it remains unknown whether this regimen will be adequate to prevent the emergence of T315I mutations, which have historically been the dominant mechanism of relapse with dasatinib-based therapies. Furthermore, patients with *IKZF1* deletion alone or with *IKZF1* plus genotype both had relatively poor outcomes with dasatinib plus blinatumomab (36-month DFS rates of 55% and 41%, respectively), suggesting that alternative approaches may be required for these patients.

At MD Anderson, we have recently reported data from the combination of ponatinib plus blinatumomab in patients with Ph+ ALL.[36] In contrast to the D-ALBA regimen where patients receive nearly 3 months of single-agent dasatinib before blinatumomab is initiated, ponatinib and blinatumomab are started concomitantly. Patients receive up to 5 cycles of blinatumomab in combination with ponatinib 30mg daily in cycle 1, which is then decreased to 15mg daily once a CMR is achieved and then continued for 5 years as maintenance therapy. Patients also receive 12 doses of intrathecal chemotherapy as CNS

prophylaxis. A total of 35 patients have been treated (20 with newly diagnosed Ph+ ALL, 10 with relapsed/refractory Ph+ ALL, and 5 with chronic myeloid leukemia in lymphoid blast phase). The overall CR/CR with incomplete platelet recovery (CRp) rate for the entire cohort was 96%, and only 1 patient with relapsed/refractory Ph+ ALL who had previously received ponatinib did not respond. The overall CMR rates for the frontline and relapsed/refractory cohorts were 85% and 88%, respectively. With a median follow-up of 12 months, the estimated 2-year EFS and OS rates were 41% and 53%, respectively, in the relapsed/refractory cohort and were both 93% in the frontline population. Importantly, none of the newly diagnosed patients underwent HSCT in first remission and none has relapsed. These early data are encouraging, particularly in the newly diagnosed Ph+ ALL cohort, and suggest that ponatinib plus blinatumomab may serve as an effective chemotherapy-free, HSCT-sparing regimen in this population.

Conclusions

The treatment of Ph+ ALL is rapidly evolving. While historically Ph+ ALL was considered an aggressive and poor-risk subtype of ALL, outcomes in the modern era now surpass those of Ph-negative ALL. This has been driven largely by the development of newer, more potent TKIs as well as a better understanding of the impact of MRD on risk of relapse and how this information can inform decisions for HSCT. While studies using first- or second-generation TKIs have largely showed a benefit of HSCT in first remission, ponatinib-based regimens induce very high rates of CMR, and thus, most patients with Ph+ ALL who are treated with a frontline ponatinib-based approach can have excellent outcomes even when HSCT is not performed. The next step in the evolution of Ph+ ALL therapy has been the incorporation of blinatumomab into chemotherapy-free frontline regimens for patients of all ages. Studies of both dasatinib and ponatinib in combination with blinatumomab have yielded promising results. In particular, the combination of ponatinib plus blinatumomab may represent an HSCT-sparing regimen for patients with newly diagnosed Ph+ ALL, although longer follow-up is needed to confirm the durability of these

remissions. Given the multiple recent advances in the management of Ph+ ALL, we can reasonably envision a future in which what was once one of the most aggressive forms of leukemia is now considered nearly universally curable without either need for either chemotherapy or HSCT.

References

1. Samra B, Jabbour E, Ravandi F, Kantarjian H, Short NJ. Evolving therapy of adult acute lymphoblastic leukemia: state-of-the-art treatment and future directions. Journal of hematology & oncology 2020;13:70.
2. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA oncology 2017;3:e170580.
3. Ravandi F, Jorgensen JL, O'Brien SM, et al. Minimal residual disease assessed by multi-parameter flow cytometry is highly prognostic in adult patients with acute lymphoblastic leukaemia. British journal of haematology 2016;172:392-400.
4. Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016;128:504-7.
5. Chiaretti S, Vitale A, Elia L, et al. Multicenter Total Therapy Gimema LAL 1509 Protocol for De Novo Adult Ph+ Acute Lymphoblastic Leukemia (ALL) Patients. Updated Results and Refined Genetic-Based Prognostic Stratification. Blood 2015;126:81-.
6. Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. American journal of hematology 2019;94:257-65.
7. Short NJ, Kantarjian H, Jabbour E, Ravandi F. Which tyrosine kinase inhibitor should we use to treat Philadelphia chromosome-positive acute lymphoblastic leukemia? Best practice & research Clinical haematology 2017;30:193-200.
8. Shen S, Chen X, Cai J, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA oncology 2020;6:358-66.
9. Gong X, Li L, Wei H, et al. A Higher Dose of Dasatinib May Increase the Possibility of Crossing the Blood-Brain Barrier in the Treatment of Patients With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Clin Ther 2021.
10. Hunger SP, Saha V, Devidas M, et al. CA180-372: An International Collaborative Phase 2 Trial of Dasatinib and Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL). Blood 2017;130:98-.
11. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36:2306-14.
12. Ravandi F, Othus M, O'Brien SM, et al. US Intergroup Study of Chemotherapy Plus Dasatinib and Allogeneic Stem Cell Transplant in Philadelphia Chromosome Positive ALL. Blood Adv 2016;1:250-9.
13. Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128:774-82.
14. Short NJ, Kantarjian H, Kanagal-Shamanna R, et al. Ultra-accurate Duplex Sequencing for the assessment of pretreatment ABL1 kinase domain mutations in Ph+ ALL. Blood cancer journal 2020;10:61.

15. Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 2015;100:653-61.
16. Ravandi F, O'Brien SM, Cortes JE, 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;121:4158-64.
17. Jabbour E, Short NJ, Ravandi F, 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. The Lancet Haematology 2018;5:e618-e27.
18. Short NJ, Kantarjian HM, Ravandi F, et al. Long-Term Safety and Efficacy of Hyper-CVAD Plus Ponatinib As Frontline Therapy for Adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood 2019;134:283-.
19. 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;122:3650-6.
20. Jabbour E, DerSarkissian M, Duh MS, et al. Efficacy of Ponatinib Versus Earlier Generation Tyrosine Kinase Inhibitors for Front-line Treatment of Newly Diagnosed Philadelphia-positive Acute Lymphoblastic Leukemia. Clinical lymphoma, myeloma & leukemia 2018;18:257-65.
21. Sasaki K, Kantarjian HM, Short NJ, et al. Prognostic factors for progression in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia in complete molecular response within 3 months of therapy with tyrosine kinase inhibitors. Cancer 2021;127:2648-56.
22. Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al. Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2013;19:150-5.
23. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 2014;123:843-50.
24. Piccaluga PP, Paolini S, Martinelli G. Tyrosine kinase inhibitors for the treatment of Philadelphia chromosome-positive adult acute lymphoblastic leukemia. Cancer 2007;110:1178-86.
25. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:460-6.
26. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125:3711-9.
27. Ravandi F, Othus M, O'Brien S, et al. Multi-Center US Intergroup Study of Intensive Chemotherapy Plus Dasatinib Followed By Allogeneic Stem Cell Transplant in Patients with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Younger Than 60. Blood 2015;126:796-.
28. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood 2015;126:746-56.
29. Ottmann OG, Pfeifer H, Cayuela J-M, 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;132:31.
30. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic

leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-8.
31. Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521-8.
32. Martinelli G, Piciocchi A, Papayannidis C, et al. First Report of the Gimema LAL1811 Phase II Prospective Study of the Combination of Steroids with Ponatinib As Frontline Therapy of Elderly or Unfit Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood 2017;130:99-.
33. Martinelli G, Boissel N, Chevallier P, 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35:1795-802.
34. Assi R, Kantarjian H, Short NJ, et al. Safety and Efficacy of Blinatumomab in Combination With a Tyrosine Kinase Inhibitor for the Treatment of Relapsed Philadelphia Chromosome-positive Leukemia. Clinical lymphoma, myeloma & leukemia 2017;17:897-901.
35. Foà R, Bassan R, Vitale A, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. The New England journal of medicine 2020;383:1613-23.
36. Short NJ, Kantarjian HM, Konopleva M, et al. Combination of ponatinib and blinatumomab in Philadelphia chromosome-positive acute lymphoblastic leukemia: Early results from a phase II study. Journal of Clinical Oncology 2021;39:7001-.
37. Chiaretti S, Vitale A, Elia L, et al. Multicenter Total Therapy Gimema LAL 1509 Protocol for De Novo Adult Ph+ Acute Lymphoblastic Leukemia (ALL) Patients. Updated Results and Refined Genetic-Based Prognostic Stratification. Blood 2015;126:81.
38. Chalandon Y., Rousselot P., Cayuela J-M., et al. Nilotinib combined with lower-intensity chemotherapy for front-line treatment of younger adults with Ph-positive acute lymphoblastic leukemia: interim analysis of the GRAAPH-2014 trial. European Hematology Association. 2018;2:410.

Table 1: Frontline Trials of TKI-based Regimens in Ph+ ALL

TKI	N	Median age, years [range]	Overall CMR rate, %	HSCT rate, %	RFS rate, %	OS rate, %	Reference
Intensive Chemotherapy + TKI							
Imatinib	54	51 [17-84]	45	30	43 (5-year)	43 (5-year)	[15]
Imatinib	169	42 [16-64]	NR	72	50 (4-year)	38 (4-year)	[23]
Dasatinib	97	44 [20-60]	NR	42	62 (3-year)	69 (3-year)	[27]
Dasatinib	72	55 [21-80]	60	17	44 (5-year)	46 (5-year)	[16]
Nilotinib	90	47 [17-71]	86	70	72 (2-year)	72 (2-year)	[28]
Ponatinib	86	46 [21-80]	86	22	68 (5-year)	74 (5-year)	[17,18]

Low-Intensity Chemotherapy + TKI							
Imatinib	135	49 [18-59]	28	62	37 (5-year)	46 (5-year)	[26]
Dasatinib	71	69 [59-83]	24	10	28 (5-year)	36 (5-year)	[13]
Dasatinib	60	42 [19-60]	19	42	49 (3-year)	58 (3-year)	[37]
Nilotinib	79	65 [55-85]	58	16	42 (4-year)	47 (4-year)	[29]
Nilotinib	60	47 [18-59]	NR; MMR 80	52	85 (1-year)	96 (1-year)	[38]
Corticosteroids + TKI							
Imatinib	30	69 [61-83]	4	NR	48 (1-year)	74 (1-year)	[30]
Dasatinib	53	54 [24-77]	15	34	51 (2-year)	69 (2-year)	[31]
Ponatinib	42	69 [27-85]	46	NR	NR	62 (2-year)	[32]
Blinatumomab + TKI							
Dasatinib	63	55 [24-82]	81	19	71 (36-month)	80 (36-month)	
Ponatinib	20	62 [34-83]	85	0	93 (2-year)	93 (2-year)	[36]

TKI, tyrosine kinase inhibitor; CMR, complete molecular response; NR, not reported; MMR, major molecular response; HSCT, allogeneic stem cell transplant; RFS, relapse-free survival; OS, overall survival