REVIEW ARTICLE

Ph-Positive Acute Lymphoblastic Leukemia — 25 Years of Progress

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In the past 25 years — from 2000 to 2024 — we have witnessed a revolution in the management, treatment, and outcome of what used to be the most lethal hematologic cancer: Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL). This progress is an illuminating example of how a better understanding of the biology of a disease, the implementation of targeted treatment directed toward the underlying genetic defect, accurate molecular monitoring of the depth of response to treatment, and most recently, the addition of immunotherapy have provided a cure in most affected patients.

Ph-positive ALL is the most common genetic subgroup of ALL in adults, with an incidence that increases with age, whereas it is rare in children.[1,2] Until the end of the 20th century, before the advent of tyrosine kinase inhibitors (TKIs), the prognosis for affected children[3] and adults[4-6] was dismal. The only curative option was allogeneic stem-cell transplantation, which could be carried out in only a minority of patients. Both in chronic myeloid leukemia (CML) and in Ph-positive ALL, the Philadelphia chromosome derives from a translocation between chromosomes 9 and 22 that gives rise to the *BCR::ABL1* fusion gene and to a constitutively active ABL1 tyrosine kinase oncoprotein.[7-9] In the late 1990s, it was shown that inhibitors of the ABL kinase blocked in vitro proliferation of *BCR::ABL1* leukemic cell lines derived from CML and also from Ph-positive ALL, as well as proliferation of primary ALL blasts.[10-12] The results obtained with TKIs in patients with CML,[13,14] coupled with the in vitro studies, opened the way to investigate the role of TKIs in the management of Ph-positive ALL.

In this article, we discuss how TKIs have been used to treat Ph-positive ALL since the early 2000s, how their use as frontline treatment has radically changed our approach to the disease, how the clinical responses and rates of minimal or measurable residual disease (MRD) negativity have progressively increased over the years, and how long-term survival has markedly improved. Finally, we discuss how the recent addition of immunotherapy to frontline management has further improved the depth of response and long-term outcome. These results have opened the possibility of curing the most fatal hematologic cancer without systemic chemotherapy and allogeneic transplantation. Results have improved to the extent that cessation of treatment (treatment-free remission), which is widely used for CML, is also being considered for Ph-positive ALL.

How TKIs Have Changed Frontline Treatment of Ph-Positive ALL

In 2001, Druker et al.[15] reported that patients with relapsed or refractory Ph-positive ALL, as well as those with CML in blast crisis, had a response to the first TKI, imatinib (STI571). Similar results were described in 2002 by Ottmann et al.[16] The use of TKIs was extended to the frontline treatment of patients with Ph-positive ALL, and in the past 25 years, these agents have revolutionized the management

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CME

KEY POINTS

PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

- Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL) is the most common genetic ALL subgroup in adulthood, with a prevalence that increases with age. In patients over the age of 50 years, Ph-positive disease accounts for about 50% of cases of B-lineage ALL.
- Before the advent of tyrosine kinase inhibitors (TKIs), Ph-positive ALL was the hematologic cancer with the worst outcome. Only the few patients who could undergo allogeneic stem-cell transplantation had a chance of long-term survival.
- Initially, TKIs were added to conventional intensive chemotherapy. Since this approach had notable toxic effects, reduced-intensity chemotherapy programs, plus TKIs, were used, an approach resulting in improved responses and outcomes, with fewer toxic effects.
- In the year 2000, the GIMEMA cooperative study group started using a TKI plus glucocorticoids for induction without systemic chemotherapy. First-, second-, and third-generation TKIs have been used over the years. These studies have shown the feasibility of this approach, with hematologic complete responses in 94 to 100% of adults, irrespective of age, and with limited toxic effects.
- The addition of the bispecific monoclonal antibody blinatumomab (an anti-CD19 and anti-CD3 antibody) in consolidation therapy has further improved molecular response and survival.
- As for all forms of ALL, a sustained molecular MRD negativity in the bone marrow should be the primary goal of frontline treatment.
- The combination of TKI (targeted treatment) and blinatumomab (immunotherapy) is associated with long-term survival of 75 to 80%, with many patients never receiving systemic chemotherapy or undergoing transplantation.

and outcomes of the disease. The more recent contribution to this success has been the addition of immunotherapy — namely, the bispecific monoclonal antibody blinatumomab — to TKI treatment.

Imatinib was the first TKI to be added to the intensive chemotherapeutic frontline regimens that were standard at the time. This addition consistently led to better responses and outcomes, but the improvement was undermined by an increase in toxic effects, including a higher incidence of deaths during induction.[17-19] This was also the experience of the GIMEMA cooperative group (Gruppo Italiano Malattie Ematologiche dell'Adulto) in Italy, which amended the LAL0904 protocol to make it a sequential treatment, with imatinib followed by intensive chemotherapy.[20] Similar results were subsequently observed when the second- and third-generation TKIs dasatinib and ponatinib were combined as frontline treatment with intensive chemotherapy.[21-25] These findings prompted other groups to modify frontline treatment by combining imatinib and dasatinib with lower-intensity chemotherapy or, in the case of ponatinib, by using a lower dose of the TKI in combination with chemotherapy.[24,25] This milder approach had equally good clinical results and fewer toxic effects.[26-28] The timeline for the use of TKIs with intensive or lower-dose chemotherapy is shown in Figure 1.

Starting in the year 2000, GIMEMA took a different approach by pioneering the use of TKI-based induction treatment without systemic chemotherapy. At a later stage, with the advent of immunotherapy, chemotherapy was also omitted in consolidation therapy. The various GIMEMA protocols that were developed in the 25 years that followed the introduction of this strategy are listed in Table 1.

In the late 1990s, a study of frontline treatment for older adults with Ph-positive ALL, which involved induction therapy with imatinib alone plus glucocorticoids, without systemic chemotherapy, was designed (protocol LAL0201-B).[30] The study was restricted to older patients for ethical reasons, since chemotherapy was to be systematically omitted for the treatment of the most aggressive leukemia. Before the advent of TKIs, many older patients with Ph-positive ALL were offered only palliative treatment, given the toxic effects of chemotherapy and the dismal prognosis. The LAL0201-B protocol for patients over the age of 60 years was approved by all the ethics committees at participating centers and opened to recruitment in 2000.[30]

After 1 week of treatment with glucocorticoids, during which the presence or absence of *BCR::ABL1* was centrally determined, the patients (age range, 61 to 89 years) received imatinib at a dose of 800 mg daily, plus continued glucocorti-

coids for 45 days. All the patients had a complete hematologic remission. No major toxic effects occurred, and the care of many of the patients was largely managed on an outpatient basis. The median overall survival was 20 months. Similarly, Ottmann et al.[39] reported that in older patients, imatinib-based induction therapy was more effective and less toxic than chemotherapy. These studies represented a proof of concept that Ph-positive ALL could be successfully managed in induction without chemotherapy. The only chemotherapy administered was for central nervous system (CNS) prophylaxis.

On the basis of these findings, GIMEMA designed a subsequent frontline study (LAL1205)[31] to evaluate dasatinib, a second-generation TKI that can overcome resistance to imatinib in vitro[40,41] and in vivo.[42] All patients with Ph-positive ALL who were at least 18 years of age, with no upper age limit, were eligible for the study. Patients received dasatinib induction therapy for 84 days, combined with glucocorticoids for the first 32 days.[31] Postremission therapy was left open. All patients had a hematologic complete remission. At 20 months, overall survival was 69.2% and disease-free survival was 51.1%. A significant difference in disease-free survival was observed between patients with *BCR::ABL1* levels that were less than 10^{-3} at day 22 and patients with higher levels during induction therapy. A T315I *ABL1* mutation was detected in 12 of 17 patients with relapsed disease. This study showed, first, that TKI-based, chemotherapy-free induction was doable in all adults, irrespective of their age; second, that it was safe and effective; third, that the degree of early molecular response was a prognostic factor; and finally, that with the use of dasatinib, most samples from patients with relapsed disease carried the T315I mutation, which confers resistance to the TKI.[31]

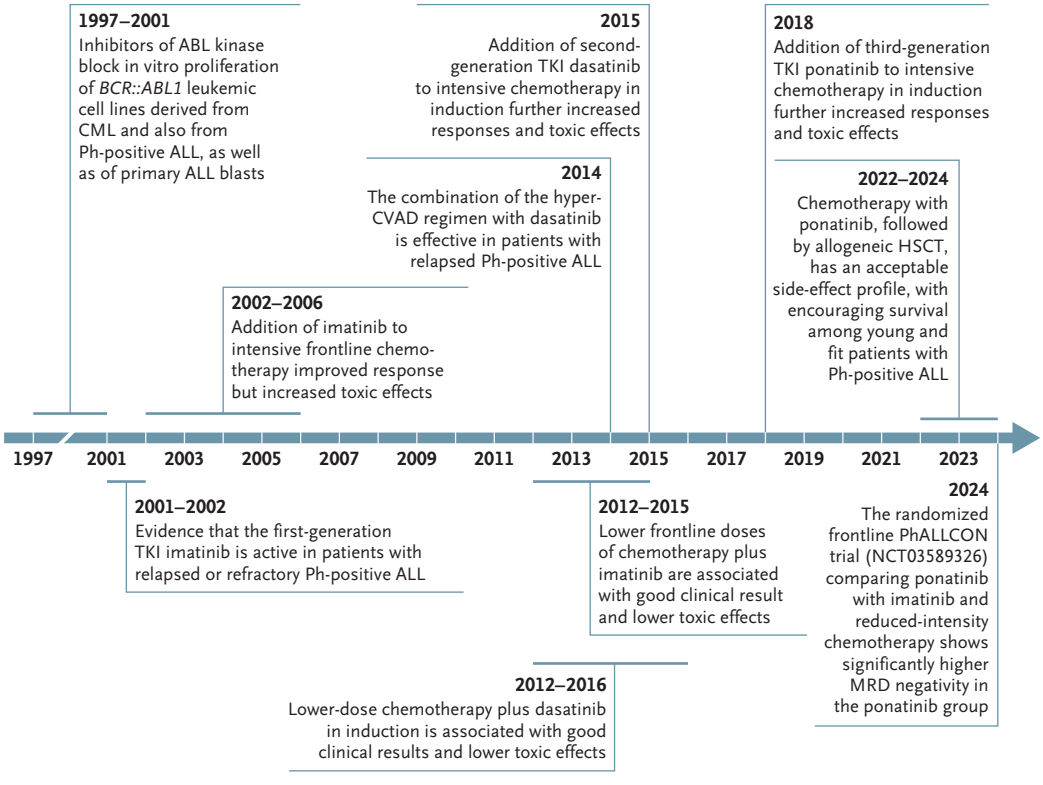

Figure 1. Timeline for Studies of Frontline TKIs plus Intensive or Lower-Dose Chemotherapy in Adults with Ph-Positive ALL, 1997–2024.[10-12,15-29]

ALL denotes acute lymphoblastic leukemia; CML chronic myeloid leukemia; CVAD cyclophosphamide, vincristine sulfate, doxorubicin, dexamethasone, methotrexate, and cytarabine; HSCT hematopoietic stem-cell transplantation; TKI tyrosine kinase inhibitor; MRD minimal or measurable residual disease; and Ph Philadelphia chromosome.

Table 1. The GIMEMA Frontline Strategy without Chemotherapy from 2000 to 2025 in Patients with Ph-Positive ALL.*

Study Protocol	Age	Induction Therapy	Complete Remission
	yr		*% of patients*
LAL0201-B[30]	>60	Imatinib	100
LAL1205[31]	>18	Dasatinib	100
LAL0904, 3rd amendment[20]	16–60	Imatinib followed by chemotherapy (with or without HSCT)	96
LAL1408[32]	>60 or unfit	Nilotinib and imatinib	94
LAL1509[33]	18–60	Dasatinib and total therapy†	97
LAL1811[34]	>60 or unfit	Ponatinib	95
LAL2116[35,36]	>18	Dasatinib plus blinatumomab	98
ALL2820[37,38]	>18	Ponatinib plus blinatumomab	95

* Starting in 2000, tyrosine kinase inhibitors (TKIs) (plus glucocorticoids) were used without chemotherapy for induction therapy. Starting in 2017 (protocols LAL2116 and ALL2820), the bispecific monoclonal antibody blinatumomab was added as consolidation therapy, always without chemotherapy. Patients who were not candidates for chemotherapy or allogeneic hematopoietic stem-cell transplantation (HSCT) were classified as "unfit." ALL denotes acute lymphoblastic leukemia, GIMEMA Gruppo Italiano Malattie Ematologiche dell'Adulto, and Ph Philadelphia chromosome.
† Dasatinib and glucocorticoids were given in the induction phase, followed by chemotherapy and transplantation in patients who did not have a complete molecular response.

A total therapy study (LAL1509) was subsequently conducted, with dasatinib plus glucocorticoids in the induction phase, followed by chemotherapy and transplantation in patients who did not have a complete molecular response. Long-term follow-up showed 5-year overall survival of 56.3% and disease-free survival of 47.2%.[33] Again, patients with early molecular responses had the best outcome, and the presence of additional copy number aberrations — *IKZF1* associated with *CDKN2A/B*, *PAX5* deletions (so-called *IKZF1*^{plus} Ph-positive ALL), or both — was the most important unfavorable prognostic factor.

A GIMEMA study involving patients over the age of 60 years who were not candidates for chemotherapy and transplantation showed the feasibility of an induction protocol based on the rotation of two TKIs, nilotinib and imatinib (LAL1408).[32] After 6 weeks, the percentage of patients with hematologic complete remission was 94%, with an overall survival at 2 years of 64%.

After the development of ponatinib, a third-generation TKI with activity against the T315I mutation,[43] GIMEMA conducted the frontline LAL1811 study with ponatinib alone (45 mg per day for 48 weeks) plus glucocorticoids in older patients and patients who were ineligible for systemic chemotherapy.[34] The primary end point (a complete hematologic remission at 24 weeks) was reached in 86.4% of the patients, with a complete molecular response in 40.9% at 24 weeks. At the time of the report, the median duration of a complete molecular remission was 11.6 months. During treatment, cardiac adverse events occurred in 29.5% of the patients and vascular adverse events occurred in 27.3% of the patients. The study showed the feasibility of using ponatinib plus glucocorticoids alone in older patients and those who are not candidates for systemic chemotherapy, but dose reductions (in 43.2% of the patients), treatment interruptions (in 43.2%), and discontinuation of treatment (in 27.3%) indicated that an up-front reduced dose of ponatinib should be considered.

Taken together, the GIMEMA studies carried out since 2000 that used a first-, second-, or third-generation TKI plus glucocorticoids in the induction phase and intrathecal CNS prophylaxis, without systemic chemotherapy, showed that between 94 and 100% of adults with Ph-positive ALL, irrespective of age, had complete hematologic remission and limited toxic effects (Table 1). After induction therapy with dasatinib or ponatinib alone (plus glucocorticoids), 30 to 40% of patients also had a molecular response.[31,33,34] These studies showed that with the frontline use

of targeted treatment directed against the founding genetic lesion of Ph-positive ALL (*BCR::ABL1*), patients could be spared the toxic effects of systemic chemotherapy. However, the rates of molecular response at the end of the induction phase remained higher when chemotherapy was added to the TKI during induction.

ADDITIONAL ROLE OF BLINATUMOMAB

A further step forward is represented by the development of the bispecific monoclonal antibody blinatumomab,[44] which targets CD19 — present on virtually all B-lineage ALLs — and the T-cell antigen CD3.[45] An immunotherapeutic strategy involving blinatumomab aims to activate the patient's T cells against CD19+ leukemic cells. The role of this agent in the management of relapsed or refractory B-lineage ALL[46] was conclusively shown by the phase 3 TOWER study, which compared blinatumomab with standard therapy.[47] The study results led to the approval of blinatumomab for patients with relapsed or refractory B-lineage ALL. The evidence that the antibody was also active against MRD-positive cells[48] led to its approval for the treatment of MRD-positive B-lineage ALL, making blinatumomab the first agent approved for the treatment of MRD in any cancer.

This was the background that led to the design of the GIMEMA LAL2116 frontline protocol (D-ALBA) for all adults, with no upper age limit, in which a step forward was pursued by the addition of a consolidation phase with blinatumomab (up to five cycles) after induction with dasatinib plus glucocorticoids.[35] A complete hematologic response was observed in 98% of patients, and 29% had a molecular response at the end of induction (day 85).[48] After two cycles of blinatumomab, the percentage of patients with a molecular response (the primary end point) increased to 60% and increased further after additional blinatumomab cycles. At a median follow-up of 18 months, overall survival was 95% and disease-free survival was 88%. This study showed that a frontline protocol of chemotherapy-free induction with dasatinib and consolidation with blinatumomab, based on a targeted signaling and immunotherapeutic strategy, was associated with high percentages of molecular response and survival, with few toxic effects of grade 3 or higher, in adults of all ages with Ph-positive ALL.[35]

In view of the possibility that leukemia-driven genetic alterations in CML may be targeted by the immune system in association with a clinical response,[49] immunologic monitoring was carried out in patients who received dasatinib and blinatumomab without undergoing systemic chemotherapy. These studies showed a marked proliferation of immunocompetent T cells, natural killer T cells, and natural killer cells, which was more pronounced after repeated cycles of blinatumomab.[35,50] This host immune activation was also observed in older patients. Lymphocyte changes in patients with ALL who were treated with blinatumomab had already been suggested.[51] Regulatory T (Treg) cells, which can have marked immunosuppressive effects,[52] were reduced after treatment with dasatinib and blinatumomab.[35,50] The percentage of Treg cells has been correlated with the outcome in patients with ALL who receive blinatumomab, with significantly fewer Treg cells in patients with a response than in those without a response.[53] A higher proportion of effector memory CD8 T-cell subsets has been found in patients receiving blinatumomab as maintenance therapy after undergoing allogeneic transplantation.[54] It has also been suggested that blinatumomab may differentially influence the blood and marrow immune cell antigen repertoire, with potential clinical implications.[55]

Earlier studies of treatment for CML showed that dasatinib induced host immune activation, which was documented by a marked lymphocytosis, an increase in large granular lymphocytes, mobilization of cytotoxic cells, and clonal expansion of T cells and natural killer cells.[56-59] It is thus conceivable that in Ph-positive ALL, the frontline combination of dasatinib and blinatumomab has the added effect of activating the host immune system without the potential immunosuppressive effects of chemotherapy. This possibility is supported by the progressive enhancement observed after repeated cycles of blinatumomab.

The effectiveness of blinatumomab in combination with dasatinib and glucocorticoids as frontline treatment has also been reported by Advani et al.[60] in older patients with Ph-positive ALL. The recently published long-term follow-up

of the dasatinib–blinatumomab D-ALBA protocol showed that at a median follow-up of 53 months, disease-free survival was 75.8%, overall survival was 80.7%, and event-free survival was 74.6%.[36] No events were recorded for the patients who had an early molecular response. A significantly worse outcome was observed in the patients with *IKZF1*^{plus} ALL. With 93.1% of the patients having a molecular response after dasatinib–blinatumomab treatment, half the patients never received chemotherapy or underwent transplantation, and they continued to receive treatment with only a TKI; all the patients who continued to receive only a TKI except one remain in long-term complete hematologic remission. Allogeneic transplantation was performed during the first remission mainly in patients with persistent MRD, and 83.3% of those patients are in continuous complete hematologic remission.[36]

The final analysis of the D-ALBA study showed that a chemotherapy-free induction–consolidation regimen based on targeted signaling (dasatinib) and immunotherapy (blinatumomab) was effective in inducing durable long-term hematologic and molecular responses in adults of all ages with Ph-positive ALL, paving the way for a new era in the management of the disease.[36] The possibility of not performing an allogeneic transplantation in patients with rapid clearance of MRD was also suggested by Sasaki et al.[61]

Targeted frontline treatment for adults who have Ph-positive ALL, with no upper age limit, is also being pursued by the MD Anderson Cancer Center, with the use of ponatinib in combination with blinatumomab.[62] In a recent update,[63] the authors reported high percentages of patients with molecular MRD negativity and estimated 3-year overall survival of 91% and event-free survival of 77%. The combined treatment was associated with some toxic effects. Only 63% of the eligible patients started the protocol; three patients discontinued blinatumomab, and nine patients discontinued ponatinib. In addition, when they started the protocol, 35% of the patients were already in complete hematologic remission after one or two courses of chemotherapy, which may have contributed to the subsequent toxic effects.

The studies of induction therapy and, more recently, consolidation therapy without systemic chemotherapy that have been conducted from 2000 to 2024 are summarized in Figure 2.

OPEN ISSUES AND WHERE WE ARE GOING

The studies described above show how the management and outcome of Ph-positive ALL have radically changed in the past 25 years with the advent and frontline use of TKIs. This progress suggests that all adults with ALL, irrespective of their age, should be tested at presentation for the presence of *BCR::ABL1* and that a TKI should always be used. On the basis of the data obtained more recently with blinatumomab, the use of a second- or third-generation TKI, followed by blinatumomab, has opened a new era in the treatment of Ph-positive ALL, an indication that for a proportion of patients, targeted treatment alone (dasatinib or ponatinib plus blinatumomab) is sufficient to control the disease.[34,63]

We still do not know the precise number of patients who can be spared systemic chemotherapy and transplantation with this combined approach. This question is being conclusively addressed by the GIMEMA ALL2820 phase 3 trial, which has recently completed enrollment and is evaluating treatment with ponatinib followed by blinatumomab as compared with imatinib plus chemotherapy.[37,38] Transplantation is planned only for patients who are positive for MRD, have an *IKZF1*^{plus} profile at presentation, or both. So far, only 10% of patients in the experimental group have undergone transplantation.[38]

These observations underscore once again that the end point of frontline treatment should be the achievement of sustained molecular MRD negativity, as previously reported for all patients with ALL.[64] The high percentages of patients with Ph-positive ALL who had a documented molecular response after receiving a TKI (dasatinib or ponatinib) and blinatumomab are highly rewarding. Additional issues include, first, access to MRD-monitoring facilities; second, further refinement of MRD technologies; and third, the timing for obtaining approval for the use of blinatumomab in MRD-negative patients with Ph-positive ALL.

In the United States, the ECOG-ACRIN (Eastern Cooperative Oncology Group–American College of Radiology Imaging Network) EA9181 phase 3 trial (ClinicalTrials.gov number, NCT04530565) is comparing intensive chemotherapy, glucocorticoids, and a TKI (dasatinib or ponatinib) with the same treatment plus blinatumomab. The trial is open for enrollment, and completion is expected in 2028.

Monitoring of MRD is largely carried out by quantifying *BCR::ABL1*, the founding lesion in Ph-positive ALL. Some cases with a very low signal are reported as "positive not quantifiable" or "positive below quantitative range." MRD monitoring may be refined with the use of the more sensitive droplet digital polymerase-chain-reaction (ddPCR) technique[65-67] or by means of next-generation sequencing.[68] Ph-positive ALL can also be monitored with the use of lymphoid-specific immunoglobulin/T-cell receptor (*IG/TR*) gene markers, and the prognostic role of *IG/TR* MRD in adult Ph-positive ALL has recently been documented.[69,70] In the GIMEMA ALL2820 trial, MRD is monitored by means of real-time quantitative PCR and ddPCR with the use of both *BCR::ABL1* and *IG/TR*. Analyses of the data should clarify the relative strengths of these MRD monitoring strategies.

In patients with Ph-negative B-lineage ALL and no MRD after intensive frontline treatment, consolidation therapy with blinatumomab plus chemotherapy has significantly improved survival, as compared with chemotherapy alone.[71] This finding led to the recent (June 2024) Food and Drug Administration (FDA) approval of blinatumomab for consolidation treatment in patients with CD19+, Ph-negative, B-lineage ALL, even in those who are negative for MRD. Approval of blinatumomab for the frontline treatment of Ph-positive ALL is thus eagerly awaited. In its absence, most patients worldwide are still being treated with a TKI plus reduced-dose chemotherapy, followed when possible by allogeneic transplantation, which is a much more invasive approach, particularly for older patients. Figure 3A shows the recommended approach to management of Ph-positive ALL when the required laboratory testing, at

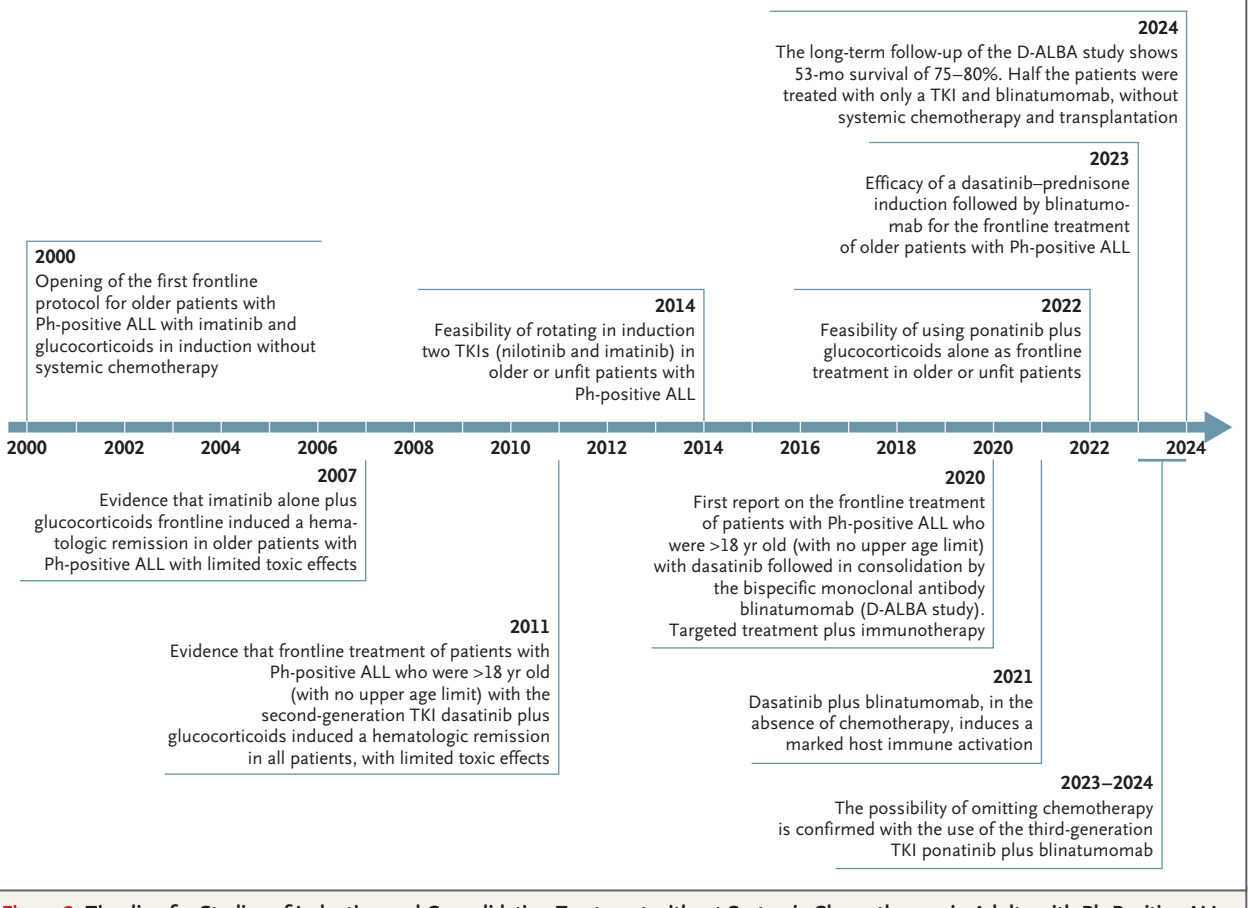

Figure 2. Timeline for Studies of Induction and Consolidation Treatment without Systemic Chemotherapy in Adults with Ph-Positive ALL, 2000–2024.[30-38,60,62,63]

diagnosis and during clinical follow-up, as well as TKIs and blinatumomab, are all available. Figure 3B shows the approach in the real-life setting when one or more of the above components of management are not available.

Long-term follow-up in the D-ALBA study shows that today, using frontline induction with dasatinib, followed by consolidation with blinatumomab, we can expect survival of 75 to 80% among adults of all ages with Ph-positive ALL.[36] The percentage of patients with relapsed disease has decreased dramatically. Extramedullary relapses, particularly in the CNS, have been reported[36,63] and have led to intensified intrathecal prophylaxis. Genetic predictors of CNS localization are also being sought.[72]

Another open question is the choice of TKI. Preclinical studies have shown that the second-generation TKI, dasatinib, is more potent than imatinib and that the third-generation TKI, ponatinib, is superior to dasatinib. A significantly higher proportion of patients with no MRD was observed in the ponatinib group in the randomized PhALLCON trial comparing ponatinib with imatinib, plus reduced-intensity chemotherapy, as frontline treatment.[29] Approximately 30% of patients have no molecular evidence of MRD after induction treatment with dasatinib alone plus glucocorticoids,[31,33] and the percentage of patients with MRD negativity increases to approximately 45% with ponatinib and glucocorticoids.[34,38] As discussed above, the dasatinib–blinatumomab combination induces a marked host immune activation, which increases after further cycles of blinatumomab.[35,50] This appears to be less evident with the ponatinib–blinatumomab combination.[73]

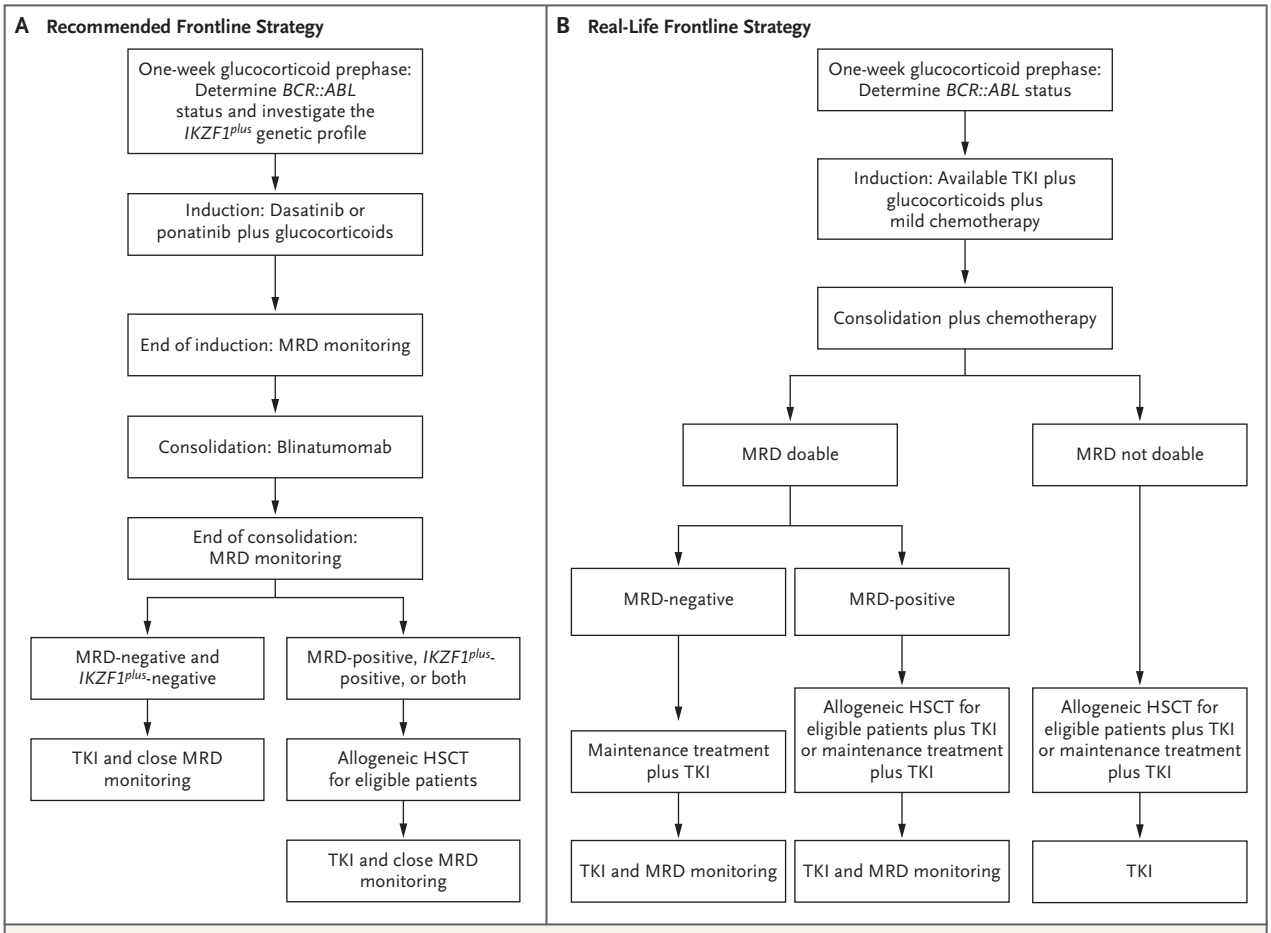

Figure 3. Recommended and Real-Life Strategies for Frontline Treatment in Adults of All Ages with Ph-Positive ALL.

Panel A shows the frontline strategy that is recommended when all the required components of frontline treatment are available. Panel B shows the strategy in real-life scenarios when one or more of the components of the recommended strategy are not available.

Long-term follow-up of the ALL2820 protocol will clarify whether the greater immune activation associated with dasatinib–blinatumomab will be counterbalanced by the lower incidence of *ABL1* mutations and fewer relapses with the ponatinib–blinatumomab combination.

Another third-generation TKI, olverembatinib, is effective in patients with CML and the T315I mutation.[74] Alone or in combination with other drugs, olverembatinib has shown activity in relapsed or refractory Ph-positive ALL, including activity in patients with the T315I mutation,[75-77] and olverembatinib-based regimens have recently been used as frontline therapy in patients with Ph-positive ALL.[78] More studies are needed to clarify the exact role of this new TKI in comparison with the other TKIs and to define its safety profile.

On the basis of a phase 3 trial,[79] the FDA has recently granted accelerated approval of asciminib, a first-in-class specific allosteric inhibitor of *BCR::ABL1*, for the treatment of newly diagnosed CML. In combination with dasatinib, this new TKI, which has a different site of binding to *BCR::ABL1*, may also have a role in the frontline management of Ph-positive ALL.[80] However, the data have not shown that asciminib is superior to second-generation TKIs. Chimeric antigen receptor T-cell therapy has so far not been widely applied to Ph-positive ALL.

Twenty-five years of advances in the management of Ph-positive ALL have led to consideration of the possibility of stopping treatment, an unthinkable option until now. Treatment-free remission is a goal for many patients with CML.[81,82] The first data on stopping treatment have been reported in retrospective analyses of patients with Ph-positive ALL who were treated with chemotherapy and a TKI,[83] as well as those treated with a TKI plus reduced-dose chemotherapy or with a TKI alone,[84] which suggests that a fixed duration of treatment may also become a reality for patients with Ph-positive ALL.

The possible overlap between CML in lymphoid blast crisis and Ph-positive ALL has been a long-lasting debate. In the presence of a p210 transcript — the hallmark of CML but also present in a proportion of Ph-positive ALL cases — it is difficult to distinguish between the two conditions.[85] Ph-positive ALL may be more heterogeneous than expected. Subtypes with distinct transcriptomic and genomic profiles, which correlate with multilineage or lymphoid-only *BCR::ABL1* involvement, have been identified.[86,87] In the most recent International Consensus Classification of Myeloid Neoplasms and Acute Leukemias,[88] Ph-positive ALL is subcategorized as lymphoid-only involvement or multilineage involvement. Although this difference is of biologic interest and deserves further investigation, the response

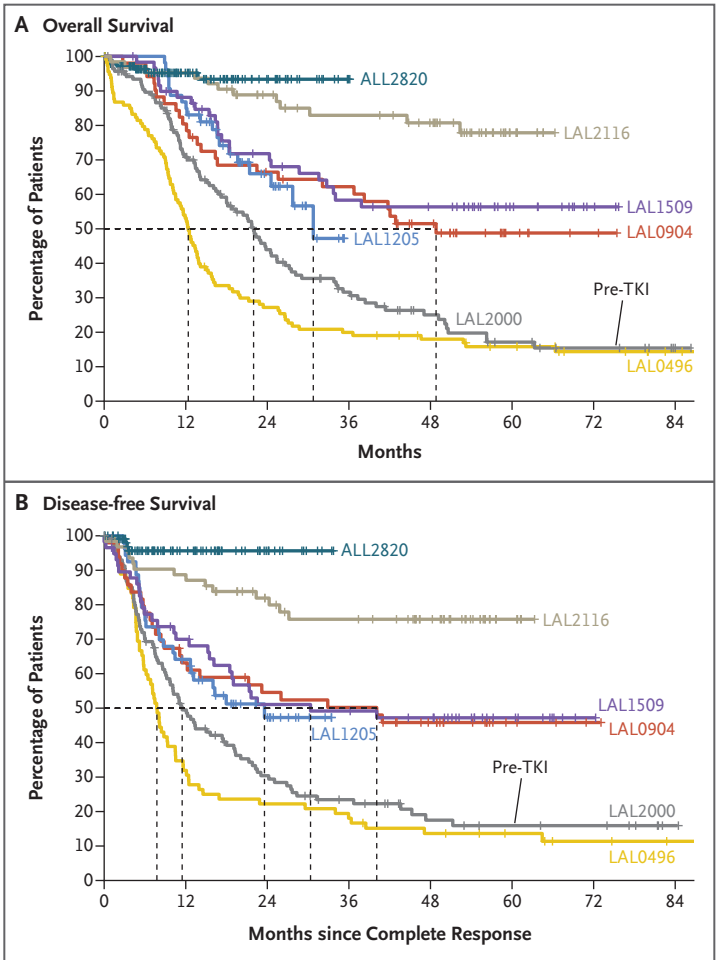

Figure 4. Overall and Disease-free Survival among Adults with Ph-Positive ALL Treated with or without TKIs in the GIMEMA Trials.

Shown are overall and disease-free survival for all GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) trials from 2000 to 2024 that included adults with Ph-positive ALL. The ALL2820 trial enrolled 158 adults 18 years of age or older, with no upper age limit.[37,38] The LAL2116 trial enrolled 63 adults 18 years of age or older, with no upper age limit.[35,36] The LAL1509 trial enrolled 60 adults 18 to 60 years of age.[33] The LAL0904 trial enrolled 51 adults 18 to 60 years of age.[20] The LAL1205 trial enrolled 53 adults 18 years of age or older, with no upper age limit.[31] The LAL0496 and LAL2000 trials were conducted before the advent of TKIs and included adults 18 to 60 years of age; 139 patients were enrolled in the LAL0496 trial and 115 in the LAL2000 trial (unpublished data).

to treatment appears to be similar in the two subtypes.

CONCLUSIONS

In the year 2000, a TKI without chemotherapy was introduced for the frontline treatment of older adults with Ph-positive ALL,[30] which gave rise to a new era in the management of this disease. If every piece of the puzzle is in place — early diagnosis, TKI and blinatumomab availability, and MRD monitoring — today, 25 years later, we can expect to cure most adults with Ph-positive ALL, irrespective of age. Efforts to do so should ensure that all these components are widely available, including availability in middle- and low-income countries. A subcutaneous formulation of blinatumomab is under active investigation, with very encouraging early results.[89] We can thus expect that soon most patients with Ph-positive ALL will be treated with an oral TKI plus subcutaneous blinatumomab.[90] These past 25 years have witnessed a true revolution in the management and outcome of what used to be the most lethal hematologic cancer, as illustrated by the increases in overall and disease-free survival shown in Figure 4.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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REFERENCES

1. Burmeister T, Schwartz S, Bartram CR, et al. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. Blood 2008;112:918-9.
2. Chiaretti S, Vitale A, Cazzaniga G, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica 2013;98:1702-10.
3. Aricò M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome–positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998-1006.
4. Dombret H, Gabert J, Boiron J-M, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia — results of the prospective multicenter LALA-94 trial. Blood 2002;100:2357-66.
5. Mancini M, Scappaticci D, Cimino G, et al. A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): analysis of the GIMEMA 0496 protocol. Blood 2005;105:3434-41.
6. Fielding AK, Rowe JM, Richards SM, 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;113:4489-96.
7. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. J Natl Cancer Inst 1960; 25:85-109.
8. Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973;243:290-3.
9. Stam K, Heisterkamp N, Grosveld G, et al. Evidence of a new chimeric *bcr/c-abl* mRNA in patients with chronic myelocytic leukemia and the Philadelphia chromosome. N Engl J Med 1985;313:1429-33.
10. Gambacorti-Passerini C, le Coutre P, Mologni L, et al. Inhibition of the ABL kinase activity blocks the proliferation of BCR/ABL+ leukemic cells and induces apoptosis. Blood Cells Mol Dis 1997;23: 380-94.
11. Beran M, Cao X, Estrov Z, et al. Selective inhibition of cell proliferation and BCR-ABL phosphorylation in acute lymphoblastic leukemia cells expressing Mr 190,000 BCR-ABL protein by a tyrosine kinase inhibitor (CGP-57148). Clin Cancer Res 1998;4:1661-72.
12. Nakajima A, Tauchi T, Ohyashiki K. ABL-specific tyrosine kinase inhibitor, STI571 in vitro, affects Ph-positive acute lymphoblastic leukemia and chronic myelogenous leukemia in blastic crisis. Leukemia 2001;15:989-90.
13. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001; 344:1031-7.
14. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM-L. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol 2016;34:2851-7.
15. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001; 344:1038-42.
16. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002;100:1965-71.
17. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood 2006;108:1469-77.
18. 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. J Clin Oncol 2006;24:460-6.
19. de Labarthe A, Rousselot P, Huguet-Rigal F, et al. Imatinib combined with

induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. Blood 2007;109:1408-13.
20. Chiaretti S, Vitale A, Vignetti M, et al. A sequential approach with imatinib, chemotherapy and transplant for adult Ph+ acute lymphoblastic leukemia: final results of the GIMEMA LAL 0904 study. Haematologica 2016;101:1544-52.
21. Benjamini O, Dumlao TL, Kantarjian H, et al. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. Am J Hematol 2014; 89:282-7.
22. 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.
23. 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. Lancet Haematol 2018;5(12):e618-e627.
24. Ribera J-M, García-Calduch O, Ribera J, et al. Ponatinib, chemotherapy, and transplant in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood Adv 2022;6:5395-402.
25. Ribera J-M, Morgades M, Ribera J, et al. Ponalfil trial for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: long-term results. Hemasphere 2024;8(4):e67.
26. Ribera J-M, García O, Montesinos P, et al. Treatment of young patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia using increased dose of imatinib and deintensified chemotherapy before allogeneic stem cell transplantation. Br J Haematol 2012;159:78-81.
27. 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.
28. Rousselot P, Coudé MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128:774-82.
29. 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;331:1814-23.
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. Foà 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, Papayannidis C, Piciocchi A, et al. Extremely high rate of complete hematological response of elderly Ph+ acute lymphoblastic leukemia (ALL) patients by innovative sequential use of nilotinib and imatinib: a GIMEMA protocol LAL 1408. Cancer Res 2014;74;Suppl: 5552. abstract (https://doi.org/10.1158/1538-7445.AM2014-5552).
33. Chiaretti S, Ansuinelli M, Vitale 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; 106:1828-38.
34. Martinelli G, Papayannidis C, Piciocchi A, et al. INCB84344-201: ponatinib and steroids in frontline therapy for unfit patients with Ph+ acute lymphoblastic leukemia. Blood Adv 2022;6:1742-53.
35. Foà R, Bassan R, Vitale A, et al. Dasatinib–blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med 2020;383:1613-23.
36. Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol 2024;42:881-5.
37. Chiaretti S, Leoncin M, Elia L, et al. Comparison between dasatinib-blinatumomab vs ponatinib blinatumomab chemo-free strategy for newly diagnosed Ph+ acute lymphoblastic leukemia patients: preliminary results of the GIMEMA ALLL2820 trial. Blood 2023;142:Suppl 1:4249. abstract.
38. Chiaretti S, Leoncin M, Elia L, 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:Suppl 1:835. abstract.
39. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer 2007;109:2068-76.
40. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305:399-401.
41. O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res 2005;65: 4500-5.
42. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. N Engl J Med 2006;354:2531-41.
43. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 2009;16:401-12.
44. Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. Science 2008;321:974-7.
45. Topp MS, Kufer P, Gökbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011;29:2493-8.
46. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16:57-66.
47. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47.
48. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131:1522-31.
49. Cai A, Keskin DB, DeLuca DS, et al. Mutated *BCR-ABL* generates immunogenic T-cell epitopes in CML patients. Clin Cancer Res 2012;18:5761-72.
50. Puzzolo MC, Radice G, Peragine N, et al. Host immune system modulation in Ph+ acute lymphoblastic leukemia patients treated with dasatinib and blinatumomab. Blood 2021;138:2290-3.
51. Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. Blood 2012;119: 6226-33.
52. Wan YY. Regulatory T cells: immune suppression and beyond. Cell Mol Immunol 2010;7:204-10.
53. Duell J, Dittrich M, Bedke T, et al. Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. Leukemia 2017;31:2181-90.
54. Gaballa MR, Banerjee P, Milton DR, et al. Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage acute lymphoblastic leukemia. Blood 2022;139:1908-19.
55. Ocadlikova D, Lussana F, Fracchiolla N, et al. Blinatumomab differentially modulates peripheral blood and bone marrow immune cell repertoire: a Campus ALL study. Br J Haematol 2023;203:637-50.

56. Mustjoki S, Ekblom M, Arstila TP, et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. Leukemia 2009;23:1398-405.
57. Kim DH, Kamel-Reid S, Chang H, et al. Natural killer or natural killer/T cell lineage large granular lymphocytosis associated with dasatinib therapy for Philadelphia chromosome positive leukemia. Haematologica 2009;94:135-9.
58. Kreutzman A, Juvonen V, Kairisto V, et al. Mono/oligoclonal T and NK cells are common in chronic myeloid leukemia patients at diagnosis and expand during dasatinib therapy. Blood 2010;116:772-82.
59. Schiffer CA, Cortes JE, Hochhaus A, et al. Lymphocytosis after treatment with dasatinib in chronic myeloid leukemia: effects on response and toxicity. Cancer 2016;122:1398-407.
60. Advani AS, Moseley A, O'Dwyer KM, et al. Dasatinib/prednisone induction followed by blinatumomab/dasatinib in Ph+ acute lymphoblastic leukemia. Blood Adv 2023;7:1279-85.
61. 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.
62. 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.
63. Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. J Clin Oncol 2024;42:4246-51.
64. 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 Oncol 2017;3(7):e170580.
65. Ansuinelli M, Della Starza I, Lauretti A, et al. Applicability of droplet digital polymerase chain reaction for minimal residual disease monitoring in Philadelphia-positive acute lymphoblastic leukaemia. Hematol Oncol 2021;39:680-6.
66. Schwinghammer C, Koopmann J, Chitadze G, Karawajew L, Brüggemann M, Eckert C. A new view on minimal residual disease quantification in acute lymphoblastic leukemia using droplet digital PCR. J Mol Diagn 2022;24:856-66.
67. van der Velden VHJ, Dombrink I, Alten J, et al. Analysis of measurable residual disease by IG/TR gene rearrangements: quality assurance and updated EuroMRD guidelines. Leukemia 2024;38:1315-22.
68. Short NJ, Jabbour E, Macaron W, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: prognostic impact and correlation with RT-PCR for BCR::ABL1. Am J Hematol 2023;98:1196-203.
69. Kim R, Chalandon Y, Rousselot P, et al. Significance of measurable residual disease in adult Philadelphia chromosome-positive ALL: a GRAAPH-2014 study. J Clin Oncol 2024;42:3140-50.
70. Short NJ, Jabbour E, Kantarjian H. SOHO state of the art updates and next questions, measurable residual disease in Philadelphia chromosome-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2024;24:427-32.
71. Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. N Engl J Med 2024;391:320-33.
72. Sapienza MR, Chiaretti S, Cardinali D, et al. A five-gene signature may associate with central nervous system dissemination in adult acute lymphoblastic leukemia. Hematol Oncol 2023;41:789-91.
73. Ansuinelli M, De Propris MS, Puzzolo MC, et al. Immunomodulatory effect of dasatinib plus blinatumomab versus ponatinib plus blinatumomab in newly diagnosed Ph^+ acute lymphoblastic leukemia patients. Blood 2024;144:Suppl 1:838. abstract.
74. Jiang Q, Li Z, Qin Y, et al. Olverembatinib (HQP1351), a well-tolerated and effective tyrosine kinase inhibitor for patients with T315I-mutated chronic myeloid leukemia: results of an open-label, multicenter phase 1/2 trial. J Hematol Oncol 2022;15:113.
75. Fan S, Wang L, Lu Y, Li Z. Olverembatinib combined with blinatumomab in treating T315I-mutated Philadelphia chromosome-positive acute lymphoblastic leukemia: two-case report. Ann Hematol 2024;103:525-32.
76. Liu W, Wang C, Ouyang W, et al. Efficacy and safety of olverembatinib in adult BCR::ABL1-positive ALL with T315I mutation or relapsed/refractory disease. Br J Haematol 2024;205:2228-33.
77. Tang H, Jia W, Jia S, et al. A new chemotherapy-free regimen of olverembatinib in combination with venetoclax and dexamethasone for newly diagnosed Ph+ acute lymphoblastic leukemia: preliminary outcomes of a prospective study. Am J Hematol 2024;99:1177-9.
78. Zhu Y, Huang J, Wang Y, et al. Olverembatinib treatment in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Hematol 2024;103:4643-8.
79. Hochhaus A, Wang J, Kim D-W, et al. Asciminib in newly diagnosed chronic myeloid leukemia. N Engl J Med 2024;391:885-98.
80. Luskin MR, Murakami MA, Keating J, et al. Asciminib plus dasatinib and prednisone for Philadelphia chromosome-positive acute leukemia. Blood 2025;145:577-89.
81. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020;34:966-84.
82. Deininger MW, Shah NP, Altman JK, et al. Chronic myeloid leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2020;18:1385-415.
83. Samra B, Kantarjian HM, Sasaki K, et al. Discontinuation of maintenance tyrosine kinase inhibitors in Philadelphia chromosome-positive acute lymphoblastic leukemia outside of transplant. Acta Haematol 2021;144:285-92.
84. Dragani M, Ansuinelli M, Papayannidis C, et al. Tyrosine kinase inhibitor discontinuation in non-allografted Philadelphia-positive acute lymphoblastic leukemia patients: a Campus ALL real-life study. Haematologica 2025 January 9 (Epub ahead of print).
85. Anastasi J, Feng J, Dickstein JI, et al. Lineage involvement by BCR/ABL in Ph+ lymphoblastic leukemias: chronic myelogenous leukemia presenting in lymphoid blast vs Ph+ acute lymphoblastic leukemia. Leukemia 1996;10:795-802.
86. Kim JC, Chan-Seng-Yue M, Ge S, et al. Transcriptomic classes of BCR-ABL1 lymphoblastic leukemia. Nat Genet 2023;55:1186-97.
87. Bastian L, Beder T, Barz MJ, et al. Developmental trajectories and cooperating genomic events define molecular subtypes of BCR::ABL1-positive ALL. Blood 2024;143:1391-8.
88. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-28.
89. Jabbour E, Zugmaier G, Agrawal V, et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. Am J Hematol 2024;99:586-95.
90. Luskin MR. Ph+ ALL: new approaches for upfront therapy. Hematology Am Soc Hematol Educ Program 2024;2024:78-85.