

# Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia in Adults: Current Treatments and Future Perspectives

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**Abstract:** Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) accounts for approximately one-fourth of cases of adult ALL. It typically presents with an aggressive clinical course, responds poorly to standard chemotherapy, and carries a high risk for relapse. The landscape of Ph+ ALL therapy has changed favorably since the development of tyrosine kinase inhibitors (TKIs). With the successful incorporation of TKIs into chemotherapy regimens, remissions occur more frequently and patients live longer. Imatinib was the first TKI that targeted the BCR-ABL1 oncoprotein in Ph+ ALL. Since then, nilotinib, dasatinib, bosutinib, and ponatinib have been developed. Despite the significant progress that has been made in inducing remission, frequent relapses remain a challenge, especially among those with resistant *BCR-ABL1* mutations. Still, the therapeutic armamentarium of ALL therapy is expanding at a breathtaking pace today compared with a decade ago. Novel drugs, such as potent later-generation TKIs, antibody-drug conjugates, bispecific monoclonal antibodies, and chimeric antigen receptor T-cell therapies, are being developed and investigated in patients with Ph+ ALL. In this review, we summarize the current treatment options for Ph+ ALL and highlight the therapies that may become the standard of care in the near future.

## Introduction

Acute lymphoblastic leukemia (ALL) is an aggressive form of leukemia characterized by malignant lymphocytes in the bone marrow. ALL comprises a heterogeneous group of diseases with different morphologic, cytogenetic, and molecular subgroups, some of which carry significant therapeutic implications. The Philadelphia chromosome (Ph), which results from a reciprocal translocation between chromosomes 9 and 22 (t[9;22][q34;q11]) and fusion of the *ABL* proto-

### Keywords

Acute lymphoblastic leukemia, BCR-ABL1, Philadelphia chromosome–positive, tyrosine kinase inhibitor

**Table 1.** Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Only

Clinical Trial (year)	N	Median Age, [range]	Chemotherapy	CR, %	SCT in CR1, %	OS, %
Gotz (1992) <sup>53</sup>	25	44 [21-74]	BFM	76	8	6 at 40 mo
Larson (1995) <sup>54</sup>	30	32 [16-80]	CALGB	70	NA	16 at 36 mo
Thomas (2001) <sup>6</sup>	51	35 [14-89] <sup>a</sup>	LALA	NA	16	10 at 60 mo
Gleissner (2002) <sup>55</sup>	175	45 [15-65]	GMALL	68	NA	15 at 36 mo
Takeuchi (2002) <sup>3</sup>	51	31 [15-59] <sup>a</sup>	JALSG	51	NA	5 at 72 mo
Kantarjian (2004) <sup>4</sup>	48	40 [15-92] <sup>a</sup>	HyperCVAD	92	23	12 at 60 mo
Pullarkat (2008) <sup>5</sup>	36	47 [17-64]	SWOG	67	NA	8 at 60 mo

ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munich protocol; CALGB, Cancer and Leukemia Group B; CR, complete remission; GMALL, German Multicenter Study Group for Adult ALL; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate; JALSG, Japan Adult Leukemia Study Group; LALA, Leucémie Aiguë Lymphoblastique chez l'Adulte; mo, months; N, number of patients; NA, not available; OS, overall survival; Ph+, Philadelphia chromosome-positive; SCT in CR1, stem cell transplant in first CR; SWOG, Southwest Oncology Group

<sup>a</sup>Age for the whole study cohort, including patients with Ph-negative ALL.

oncogene from chromosome 9 to the *BCR* sequences on chromosome 22, accounts for approximately 25% of adult ALL cases and close to 50% of cases in older adults.<sup>1</sup> Among adult patients, approximately 25% have a p210 breakpoint and 75% have a p190 breakpoint in the *BCR* locus.<sup>2</sup> The fusion product, the BCR-ABL1 oncoprotein, contributes to proliferation and tumor growth by altering multiple signaling pathways. Ph-positive (Ph+) ALL typically presents with an aggressive clinical course, responds poorly to standard chemotherapy, and carries a high risk for relapse. The landscape of Ph+ ALL therapy has changed since the introduction of tyrosine kinase inhibitors (TKIs) into clinical practice. Imatinib was the first TKI tested in Ph+ ALL, and since then dasatinib (Sprycel, Bristol-Myers Squibb), nilotinib (Tasigna, Novartis), bosutinib (Bosulif, Pfizer), and ponatinib (Iclusig, Ariad) have been investigated. Herein, we provide a comprehensive review of the studies that have assessed the role of chemotherapy and TKIs in the management of Ph+ ALL and highlight the potential benefit of the newer-generation TKIs.

### Treatment of Ph+ ALL Before the Tyrosine Kinase Inhibitor Era

Patients with Ph+ ALL have an inferior outcome when treated with chemotherapy alone (Table 1). Most chemotherapy regimens induce a complete response (CR) in just two-thirds of patients. The 5-year overall survival (OS) rate is dismal, ranging from 8% to 12%. In one study, 229 patients (median age, 31 years [range, 15-59]) with newly diagnosed ALL received induction therapy with doxorubicin, vincristine, L-asparaginase, cyclophosphamide, and prednisone.<sup>3</sup> The CR rate was 51% in patients

with Ph+ ALL and 83% in patients with and Ph-negative (Ph-) ALL. Correspondingly, the 6-year OS rate in the patients with Ph+ ALL was inferior to that in the patients with Ph- ALL—5% vs 39%. Chemotherapy consisting of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate (hyperCVAD) was one of the regimens that induced a high CR rate in Ph+ ALL. In a study conducted at the MD Anderson Cancer Center, the CR rate was 92% among 48 patients with newly diagnosed Ph+ ALL treated with hyperCVAD.<sup>4</sup> However, owing to a high relapse rate and treatment-related deaths, the 5-year OS rate was still poor, at just 12%. This is comparable to the survival rates published in other clinical trials that tested different chemotherapy regimens.<sup>5,6</sup>

### Treatment of Ph+ ALL With Tyrosine Kinase Inhibitors

#### First-Generation Tyrosine Kinase Inhibitor: Imatinib

Imatinib mesylate blocks the adenosine triphosphate (ATP) binding site of the BCR-ABL1 oncoprotein and prevents the activation of downstream pathways that provide proliferation and survival signals.<sup>7</sup> In initial studies, imatinib as a single agent had limited efficacy in Ph+ ALL.<sup>8</sup> In combination with chemotherapy, however, imatinib has yielded remarkable responses in the frontline treatment of Ph+ ALL (Table 2). Different imatinib dosing schedules have been investigated, such as concurrent dosing (given simultaneously with chemotherapy) and sequential dosing (alternating with chemotherapy). Owing to a lack of safety data regarding combination treatment with imatinib plus chemotherapy, initial frontline studies explored the

**Table 2.** Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy and a TKI

Clinical Trial (year)	N	Median Age, [range]	Chemo-therapy	TKI, mg/d	CR, %	CMR, %	SCT in CR1, %	OS, %
<b>Imatinib</b>								
Yanada (2006) <sup>56</sup>	80	48 [15-63]	JALSG ALL202	IM 600	96	26 at CR	49	76 at 12 mo
Wassmann (2006) <sup>9</sup>	45	41 [19-63]	GMALL	IM 400	96	27 at CR	80	43 at 24 mo
Fielding (2014) <sup>10</sup>	175	42 [16-64]	UKALLXII/ ECOG2993	IM 400-600	92	NA	46	38 at 48 mo
Chalandon (2015) <sup>13</sup>	135	49 [18-59]	Low-int induction	IM 800	98	29 at ~3 mo	74	48 at 60 mo
	133	45 [21-59]	High-int induction	IM 800	91	23 at ~3 mo	79	43 at 60 mo
Bassan (2010) <sup>57</sup>	59	45 [20-66]	NILG	IM 600	92	40 at ~3 mo	72	38 at 60 mo
Daver (2015) <sup>11</sup>	54	51 [17-84]	HyperCVAD	IM 400-800	93	45 at ~3 mo	30	43 at 60 mo
De Labarthe (2007) <sup>58</sup>	45	45 [16-59]	GRAAPH 2003	IM 600-800	96	NA	49	51 at 18 mo
Lim (2015) <sup>12</sup>	87	41 [16-71]	Multiagent chemo	IM 600	94	NA	64	33 at 60 mo
<b>Nilotinib</b>								
Kim (2015) <sup>23</sup>	90	47 [17-71]	Multiagent chemo	NIL 800	91	77 at ~3 mo	63	72 at 24 mo
<b>Dasatinib</b>								
Foa (2011) <sup>31</sup>	53	54 [24-76]	Prednisone	DAS 100-140	93	22 at CR	NA	69 at 20 mo
Ravandi (2015) <sup>30</sup>	72	55 [21-80]	HyperCVAD	DAS 100	96	65 at ~3 mo	17	46 at 60 mo
Ravandi (2016) <sup>59</sup>	94	44 [20-60]	HyperCVAD	DAS 70-100	88	NA	47	69 at 36 mo
<b>Ponatinib</b>								
Jabbour (2015) <sup>36,37</sup>	64	48 [21-80]	HyperCVAD	PON 30-45	100	77 at ~3 mo	16	78 at 36 mo

ALL, acute lymphoblastic leukemia; CR, complete remission; CMR, complete molecular response rate at CR or after approximately 3 months of therapy; d, day; DAS, dasatinib; ECOG, Eastern Cooperative Oncology Group; GMALL, German Multicenter Study Group for Adult ALL; GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate; IM, imatinib; int, intensity; JALSG, Japan Adult Leukemia Study Group; mo, months; N, number of patients; NA, not available; NIL, nilotinib; NILG, Northern Italy Leukemia Group; OS, overall survival; Ph+, Philadelphia chromosome-positive; PON, ponatinib; SCT in CR1, stem cell transplant in first CR; TKI, tyrosine kinase inhibitor; UKALLXII, United Kingdom ALL XII.

sequential use of imatinib, or else imatinib was introduced later in treatment. Direct comparisons of concurrent vs sequential use or early vs late use of imatinib suggested no significant difference in toxicity.<sup>9,10</sup>

In the first frontline study of the hyperCVAD/ imatinib combination, imatinib was administered at a dose of 400 mg once daily on days 1 to 14 of the induction/consolidation cycles and of 600 mg daily continuously during the maintenance phase.<sup>11</sup> Cell count

recovery and the incidence of adverse events were similar to those with hyperCVAD alone. Subsequently, the study was expanded to evaluate higher imatinib doses: 600 mg once daily on days 1 to 14 of the induction/consolidation cycles and 800 mg daily continuously during maintenance. Given the excellent tolerance among the first 35 patients, the imatinib dose was further increased to 600 mg once daily on days 1 to 14 of induction, 600 mg daily continuously starting from the

first consolidation cycle, and 800 mg daily continuously throughout maintenance.

As more clinical experience was gained, most other studies adopted the earlier and continuous use of imatinib with chemotherapy. Multiple studies investigated imatinib schedules ranging from daily doses of 400 to 800 mg. However, there is no clear consensus regarding any specific dose owing to a lack of head-to-head comparisons. What is more important is that the imatinib dose intensity be maintained throughout the treatment; relapse was more likely to occur in the patients whose imatinib intake was interrupted.<sup>12</sup>

The optimal chemotherapy regimen to be administered with TKIs remains unknown. Ideally, patients should be enrolled and treated in a clinical trial. In the absence of a clinical trial, chemotherapy should be chosen according to the patient's performance status, age, and underlying comorbidities, the drug side effect profiles, and the physician's experience with administering the regimen. A variety of multiagent combination chemotherapy regimens have shown equally favorable CR and OS rates (Table 2). The GRAAPH 2005 study is the only randomized clinical trial to have compared 2 different chemotherapy regimens that included imatinib in patients with Ph+ ALL.<sup>13</sup> A total of 268 patients (median age, 47 years [range, 18-59]) were randomly assigned to receive induction with a reduced-intensity or high-intensity regimen. Arm A received the reduced-intensity regimen, which consisted of 800 mg of imatinib daily on days 1 to 28, vincristine, and dexamethasone. Arm B received the high-intensity regimen, which consisted of 800 mg of imatinib daily on days 1 to 14, cyclophosphamide, doxorubicin, vincristine, and dexamethasone. Of note, the 2 arms received identical consolidation therapy, and imatinib was given on days 1 to 14 of each cycle. The CR rates were 98% and 91% for arms A and B, respectively ( $P=.006$ ), and the 5-year OS rates were 48% and 43% for arms A and B, respectively ( $P=.37$ ). Patients in arm A were less likely to die early (death during cycle 1 or 2) than those in arm B—1% vs 7%, respectively ( $P=.01$ ). Fewer early deaths accounted for the higher CR rate in arm A.

With chemotherapy alone, the prognosis for older patients who have Ph+ ALL is dismal. The concurrent use of TKIs with reduced-intensity chemotherapy or corticosteroids achieves higher CR rates and improves outcomes, similar to those in younger adults (Table 3). In one study, 30 patients with a median age of 69 years (range, 61-83) were treated with imatinib and prednisone; the CR rate and 2-year OS rate were 100% and 50%, respectively.<sup>14</sup> In a similar clinical trial, 28 patients with a median age of 66 years (range, 54-79) were treated with age-adjusted chemotherapy and imatinib; the CR rate and 2-year OS rate were 96% and 42%, respectively.<sup>15</sup>

Despite significant progress with the use of imatinib, a considerable number of patients with Ph+ ALL still relapse. It has become evident that imatinib is not sufficient to eradicate leukemia because of the emergence of resistance mechanisms, including amplification of the *BCR-ABL1* gene, cellular efflux of imatinib and its metabolites, insufficient drug concentrations in extramedullary sites, and the development of mutations within ABL kinase or the ATP binding site of BCR-ABL1.<sup>16-20</sup> Because of frequent relapses due to imatinib resistance, chemotherapy and imatinib combinations have not obviated the need for allogeneic stem cell transplant (ASCT) in patients with Ph+ ALL.

### **Second-Generation Tyrosine Kinase Inhibitors**

**Nilotinib.** Nilotinib is a second-generation TKI with greater selectivity and potency than those of imatinib for BCR-ABL1.<sup>21</sup> In a phase 2 study in which most participants had imatinib-refractory Ph+ ALL (N=44), nilotinib monotherapy induced a CR rate of 24%.<sup>22</sup> Later, a phase 2 study from Korea investigated a nilotinib and a multiagent chemotherapy combination in patients (N=90) with newly diagnosed Ph+ ALL (Table 2). The CR rate and 2-year OS rate were 91% and 72%, respectively.<sup>23</sup> Of these patients, 63% underwent ASCT in first CR (CR1). The achievement of a deep molecular remission was associated with similar favorable survival rates in the patients who did and those who did not receive ASCT. Among patients with a BCR-ABL1 ratio of less than  $10^{-5}$  at 3 months, the estimated 2-year disease-free survival (DFS) rates were 78% for the ASCT recipients and 64% for the non-ASCT recipients.

The European Working Group on Adult ALL (EWALL) investigated an age-adjusted, low-intensity chemotherapy regimen plus nilotinib in elderly patients with newly diagnosed Ph+ ALL.<sup>24</sup> Of the 47 patients (median age, 65 years [range, 55-85]) who received induction, 87% achieved a CR. With a median follow-up of 8.5 months, the 2-year OS rate was 67%. The final results of this study are pending.

Although nilotinib is a very potent TKI, it cannot overcome mutations such as Y253H, E255V, and T315I.<sup>25</sup> Multiple clinical trials are ongoing to further clarify the role of nilotinib in Ph+ ALL (NCT01914484, NCT02611492, NCT01620216, and NCT02253277). At present, however, it has not yet been approved for this indication.

**Bosutinib.** Bosutinib is a dual SRC/ABL inhibitor with a potency up to 200-fold greater than that of imatinib. Owing to the minimal inhibitory effect of c-KIT and platelet-derived growth factor receptor, bosutinib has a better safety profile than those of other TKIs.<sup>26</sup> In particular, the incidence of treatment-related vascular and cardiac

**Table 3.** Outcomes of Older Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy and a TKI

Clinical Trial (year)	N	Age, median [Range]	Chemotherapy	TKI, mg/d	CR, %	SCT in CR1, %	OS, %
Ottmann (2007) <sup>15</sup>	28	66 [54-79]	GMALL	IM 400	96	0	42 at 24 mo
Vignetti (2007) <sup>14</sup>	30	69 [61-83]	Prednisone	IM 800	100	0	50 at 24 mo
Delannoy (2006) <sup>60</sup>	29	66 [58-78]	GRALL-AFR09	IM 600	72	0	66 at 12 mo
Rousselot (2016) <sup>32</sup>	71	69 [59-83]	EWALL-Ph-01	DAS 100-140	96	10	36 at 60 mo
Ottmann (2014) <sup>24</sup>	47	65 [55-85]	EWALL-Ph-02	NIL 800	87	20	67 at 24 mo

ALL, acute lymphoblastic leukemia; CR, complete remission; d, day; DAS, dasatinib; EWALL, European Working Group on Adult ALL; GMALL, German Multicenter Study Group for Adult ALL; GRALL, Group for Research on Adult ALL; IM, imatinib; mo, months; NIL, nilotinib; OS, overall survival; Ph+, Philadelphia chromosome-positive; SCT in CR1, stem cell transplant in first CR; TKI, tyrosine kinase inhibitor.

adverse events is low during long-term bosutinib therapy.<sup>27</sup> The clinical potential of bosutinib in combination with inotuzumab ozogamicin in both frontline and salvage Ph+ ALL therapy in elderly patients is currently under investigation in a pilot clinical trial (NCT02311998).

**Dasatinib.** Dasatinib is a potent inhibitor of the BCR-ABL1 and SRC family kinases, including the mutant BCR-ABL proteins identified in imatinib-resistant patients.<sup>28</sup> Except for T315I, the mutations that are known to cause insensitivity to imatinib do not affect sensitivity to dasatinib. In a phase 2 study, 36 patients with imatinib-resistant Ph+ ALL received single-agent dasatinib (70 mg twice daily), and 58% achieved complete cytogenetic remission.<sup>29</sup>

The role of dasatinib has been investigated in several frontline studies using different chemotherapy backbone regimens (Table 2). In the final results of a clinical trial by Ravandi and colleagues, in which 50 mg of dasatinib twice daily was combined with hyperCVAD in 72 patients (median age, 55 years [range, 21-80]) with newly diagnosed Ph+ ALL, 96% of the patients achieved a CR, and the 5-year OS rate was 46%.<sup>30</sup> Overall, 12 patients (17%) underwent ASCT in CR1, and 7 patients died of transplant-related complications. Although the numbers of patients were small, patients 40 years of age or older did not benefit from undergoing ASCT in CR1. The 5-year OS rate was above 40% in the patients (n=49) who did not undergo ASCT in CR1, compared with less than 20% in the patients (n=9) who underwent ASCT in CR1 ( $P=.02$ ). In total, 22 patients (31%) relapsed, and 8 of these patients experienced an isolated central nervous system relapse. Among 13 patients with relapse who were tested for an *ABL* mutation, 7 (54%) had mutations: 4 with T315I, 2 with V299L, and 1 with F359V.

An inability to achieve deep molecular remission and the development of T315I mutations in dasatinib-treated patients are associated with progressive disease. In

the GIMEMA study, 53 patients (median age, 54 years [range, 24-76]) with newly diagnosed Ph+ ALL received dasatinib and prednisone as induction therapy.<sup>31</sup> A CR was achieved by 93% of the patients, and the OS rate was 69% at 20 months. A BCR-ABL ratio below  $10^{-3}$  on day 22 of induction was associated with superior DFS at 15 months: 80% vs 43% ( $P=.03$ ). At last follow-up, 23 patients had relapsed. A T315I mutation was detected in 12 of the 17 patients (71%) who underwent sequencing.

In another frontline study, 71 elderly patients (median age, 69 years [range, 59-83]) with Ph+ ALL underwent induction with dasatinib, dexamethasone, and vincristine, and 96% achieved a CR (Table 3).<sup>32</sup> The 5-year DFS and OS rates were 54% and 36%, respectively. Sanger sequencing was available for 24 patients with relapse, and 18 (75%) were found to have the T315I mutation. Retrospective *BCR-ABL1* T315I allele-specific oligonucleotide (ASO) real-time quantitative polymerase chain reaction (RQ-PCR) was performed on the pretreatment samples of 43 patients, of whom 10 (23%) tested positive for the T315I mutation. Relapse occurred in 8 of the patients with the T315I mutation, and 2 died in CR. Overall, in both frontline studies, the T315I mutation was a frequent cause of relapse in dasatinib-treated patients with Ph+ ALL.

### **Third-Generation Tyrosine Kinase Inhibitor: Ponatinib**

The emergence of T315I gatekeeper residue mutations poses a significant challenge for the treatment of Ph+ leukemias. The development of novel drugs that overcome these resistant mutations can push Ph+ ALL therapy one step closer to a potential cure. Ponatinib, a pan-BCR-ABL1 inhibitor, is active against the T315I mutation.<sup>33</sup> Ponatinib is 520 times more potent than imatinib in inhibiting native ABL.<sup>34</sup> It also has potent activity against other kinases, such as fibroblast growth factor receptor, vascular endothelial growth factor receptor, SRC, KIT, and

FLT3.<sup>34</sup> In a phase 2 study, patients who had Ph+ leukemias with the T315I mutation or resistance to dasatinib or nilotinib, or who could not tolerate dasatinib or nilotinib, received ponatinib as salvage therapy. Of 32 patients with Ph+ ALL, 27 (84%) had disease resistant to dasatinib or nilotinib. A total of 15 of the 32 patients (47%) achieved a major cytogenetic response with single-agent ponatinib.<sup>35</sup>

The results with other TKIs indicated that the addition of chemotherapy to ponatinib would be likely to induce superior results. In a pilot phase 2 study, 64 patients (median age, 48 years [range, 21-80]) with newly diagnosed Ph+ ALL underwent induction with ponatinib and hyperCVAD combinations (Table 2).<sup>36,37</sup> The CR rate was 100%, and 78% of the patients were alive at 3 years. Overall, 77% achieved a complete molecular remission, and the DFS rate was 79% at 3 years. In total, only 7 patients relapsed (11%). There were 10 patients (16%) who underwent ASCT in CR1. The median OS was similar regardless of whether patients were censored at the time of ASCT. The most notable adverse effect of ponatinib was cardiovascular; 3 patients had a myocardial infarction and 4 patients had other thrombotic events. A total of 10 deaths occurred, of which 2 were attributed to ponatinib. With the recognition of ponatinib-related vascular events, the protocol was amended; the ponatinib dose was reduced from 45 to 30 mg daily and was further reduced to 15 mg daily upon achievement of a complete molecular response. This study is ongoing, and additional studies are investigating the role of ponatinib as a single agent or in combination (NCT01641107 and NCT01620216).

### Treatment of Ph+ ALL With Monoclonal Antibodies and Immunotherapy

Cell surface antigens, such as CD19, CD20, and CD22, are commonly expressed in B-cell ALL. The addition of rituximab (Rituxan, Genentech/Biogen Idec), a monoclonal antibody against CD20, to chemotherapy has improved OS in patients with CD20+ ALL. In a recent study, 209 patients with newly diagnosed CD20+ B-cell ALL were randomly assigned to receive chemotherapy with or without rituximab.<sup>38</sup> The CR rates were similar in the arms with and without rituximab—90% and 88%, respectively. However, rituximab improved the 2-year event-free survival rate from 52% to 65% ( $P=.04$ ) and the 2-year OS rate from 63% to 74% ( $P=.02$ ) after the data had been censored for ASCT. Importantly, the overall incidence of severe adverse events was similar in each of the 2 groups. Newer CD20-targeted monoclonal antibodies, such as ofatumumab (Arzerra, Novartis) and obinutuzumab (Gazyva, Genentech), are under investigation in patients with CD20+ ALL.

Blinatumomab (Blinicyto, Amgen), an anti-CD19 bispecific T-cell engager, enables CD3+ cytotoxic T cells to recognize CD19+ leukemic cells. It was initially developed to eradicate minimal residual disease (MRD) in ALL and was later studied further in the salvage setting.<sup>39-42</sup> In a phase 2 study, single-agent blinatumomab was administered to 45 patients (median age, 55 years [range, 23-78]) with relapsed or refractory Ph+ ALL. All patients had been exposed to prior TKI therapies, including ponatinib (51%). The CR rate was 36% during the first 2 cycles, and 88% of the responders achieved negativity for MRD. Of 10 patients with a T315I mutation, 4 achieved a CR. Blinatumomab allowed 44% of the responders to undergo ASCT. In a retrospective chart review, high response rates were reported in a small number of patients with multiply refractory Ph+ leukemias who received blinatumomab and ponatinib.<sup>43</sup> Overall, the complete molecular response rate was 75% (9 of 12) in this heavily treated population. The activity of blinatumomab is being further investigated in combination with dasatinib or ponatinib in 2 different phase 2 clinical trials for patients with Ph+ ALL (NCT02143414 and NCT03263572).

Inotuzumab ozogamicin (Besponsa, Pfizer) is an antibody-drug conjugate in which an anti-CD22 antibody is attached to calicheamicin, a potent DNA-binding cytotoxic agent.<sup>44</sup> It was recently approved for patients with relapsed or refractory B-cell ALL on the basis of results of the INO-VATE clinical trial, in which 208 patients were randomly assigned to receive single-agent inotuzumab ozogamicin or standard-of-care chemotherapy.<sup>45</sup> The CR rate was 81% in the inotuzumab ozogamicin group and 29% in the standard chemotherapy group. The DFS and OS were better for patients treated with inotuzumab ozogamicin than for those treated with standard-of-care chemotherapy: 5 vs 1.8 months and 7.7 vs 6.7 months, respectively. The concurrent use of inotuzumab ozogamicin and a TKI appears to be a reasonable strategy to follow in patients with Ph+ ALL, especially those who are older or ineligible to receive intensive chemotherapy. In an interim report of a phase 1/2 trial, 14 patients (median age, 62 years [range, 19-74]) with multiply refractory Ph+ ALL were treated with a combination of bosutinib and inotuzumab, and 11 achieved a CR (79%). Of the 11 responders, 10 (91%) achieved a complete cytogenetic remission and 8 (73%) achieved MRD negativity by flow cytometry.<sup>46</sup> This study is ongoing and actively enrolling patients.

CD19-directed chimeric antigen receptor (CAR) T cells have been shown to induce sustained remission in patients with multiply refractory ALL. CARs are genetically engineered receptors in which an anti-CD19 single-chain variable segment is fused to intracellular signaling domains of the T-cell receptor, so that cytotoxic T lymphocytes are directed to the cells expressing

this antigen.<sup>47</sup> In a phase 1/2 clinical trial, 30 pediatric patients with relapsed or refractory ALL received CAR T cells directed against CD19.<sup>48</sup> After a single infusion, 27 patients (90%) achieved a CR, and the 6-month OS rate was 78%. Now that tisagenlecleucel (Kymriah, Novartis), a CD19-directed autologous CAR T-cell therapy, has been approved for patients younger than 25 years with relapsed B-cell ALL, clinical trials investigating CAR T cells in adult patients are opening (NCT02614066).<sup>49</sup> Innovative combinations of CAR T cells and monoclonal antibodies may further improve outcomes and allow patients to avoid treatment intensification with modalities such as ASCT.

### Minimal Residual Disease

In pediatric ALL, the detection of MRD after induction indicates that treatment intensification is needed.<sup>50</sup> However, the role of MRD assessment remains unidentified in adult patients with ALL. The prognostic significance of MRD supersedes that of almost all conventional risk factors in ALL, but it still has no predictive value. Multicolor flow cytometry, RQ-PCR for immunoglobulin H, T-cell receptor and gene fusions, and next-generation sequencing are potential laboratory techniques for detecting MRD. Although an ideal MRD assessment strategy remains under investigation, close monitoring for MRD early during treatment may help to identify patients with an anticipated favorable outcome. In studies of patients who received frontline hyperCVAD plus a TKI but did not receive ASCT in CR1, those who achieved a deep molecular remission had superior long-term survival.<sup>51,52</sup> In a study by Chalandon and colleagues, OS rates were similar in patients with newly diagnosed Ph+ ALL who achieved a major molecular response regardless of whether they received ASCT or autologous SCT as consolidation.<sup>13</sup> In another study, patients with a complete molecular remission (defined as the absence of BCR-ABL1 by RT-PCR) after 3 months of therapy had a 4-year OS rate of 66% despite not receiving ASCT in CR1.<sup>52</sup> The encouraging outcomes for this subgroup highlight the question of whether ASCT in CR1 can be avoided in these patients. Definitive conclusions cannot be reached, however, without a prospective MRD-based risk stratification clinical trial.

### Conclusion

The combination of chemotherapy with potent TKIs, such as ponatinib, has increased CR rates to up to 100% and has improved long-term OS from a low of 10% to more than 70% in patients with Ph+ ALL. Even among elderly patients, CR rates with age-adjusted chemotherapy and TKI combinations have increased to as

much as 100%, and the 5-year OS has exceeded 30% in some studies. Currently, ASCT is the standard of care for most of the eligible patients with Ph+ ALL. However, a fraction of patients still fare poorly owing to the toxicity of the induction regimens, progressive disease, or morbidities associated with ASCT. Innovative clinical trial designs combining lower-intensity chemotherapy with novel drugs, such as antibody-drug conjugates, bispecific monoclonal antibodies, potent TKIs, and CAR-T cells, may allow deeper and long-lasting remissions and so obviate the need for ASCT.

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