



## Current management of Philadelphia chromosome positive ALL and the role of stem cell transplantation

Farhad Ravandi

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

Treatment of Philadelphia chromosome positive acute lymphoblastic leukemia exemplifies how the addition of potent targeted agents, directed at the molecular aberrations responsible for leukemic transformation, can overcome resistance mechanisms to traditional regimens and lead to improved outcomes. The introduction of *BCR-ABL1* targeted tyrosine kinase inhibitors (TKIs) has significantly improved the outcomes not only by allowing more patients to undergo allogeneic hematopoietic cell transplantation (alloHCT) but also by decreasing our reliance on this potentially toxic strategy, particularly in the less fit population. Long-term data using chemotherapy and TKI combinations demonstrate that a proportion of patients treated can achieve durable relapse-free survival without undergoing alloHCT. Furthermore, the availability of sensitive minimal residual disease monitoring assays may allow early detection of the patients who are more likely to relapse and who are likely candidates for early alloHCT. The emergence of more potent TKIs with significant activity against resistant mutations has allowed deintensification of chemotherapy regimens. Available data indicate that complete reliance on TKIs, alone or with minimal additional therapy, and elimination of more intensive chemotherapy or alloHCT is unlikely to achieve long term cure in most patients. However, introduction of other highly effective agents that can be combined with TKIs may allow further minimization of chemotherapy and alloHCT in the future, as we have witnessed in acute promyelocytic leukemia.

### Learning Objectives

- Understand how tyrosine kinase inhibitors (TKIs) have significantly improved outcomes in patients with Philadelphia chromosome positive acute lymphoblastic leukemia
- Learn why achieving complete molecular remission is an important predictor of outcome and should be the goal of all therapeutic strategies

### Role of tyrosine kinase inhibitors in frontline therapy

The introduction of tyrosine kinase inhibitors (TKIs) in the treatment of Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) has led to significant improvement in the outcomes of these patients.<sup>1</sup> This improvement has been attributed in part to the increased chance of undergoing an allogeneic hematopoietic cell transplantation (alloHCT), which was traditionally considered the standard and potentially curative treatment in this disease.<sup>2,3</sup> However, because of the lack of availability of a donor or ineligibility to undergo alloHCT due to age and comorbidity, a number of patients have been treated without an alloHCT, with combination chemotherapy and TKIs or autologous hematopoietic cell transplantation (autoHCT).<sup>4</sup> Long-term results of such studies suggest that it may be possible to cure some patients with this disease without an alloHCT and have raised questions about the universal necessity of this procedure in this disease.<sup>5,6</sup> Before the introduction of TKIs, it was clear that alloHCT performed in first complete remission (CR) did improve outcomes.<sup>7</sup> In

the UKMRCALLXII/ECOG2993 trial, among 267 patients with Ph+ ALL (median age 40, range 15-60 years), 82% achieved CR and 28% of patients in first CR underwent an alloHCT.<sup>7</sup> At 5-year follow-up, overall survival (OS) was 44% for sibling alloHCT, 36% for matched unrelated donor alloHCT, and 19% for chemotherapy alone.<sup>7</sup> After adjustment for age, white cell count, and exclusion of chemotherapy patients who died or relapsed before the median time to alloHCT, only relapse-free survival (RFS) remained significantly superior for the alloHCT group. This study clearly demonstrated the beneficial effect of alloHCT in this disease, as had been reported in other smaller previous studies.<sup>7</sup>

With the incorporation of imatinib in treatment regimens for Ph+ ALL, multiple groups have reported improved survival outcomes as compared with their historical experience with the same backbone chemotherapy regimens (Table 1).<sup>1</sup> Long-term follow-up of a single-institution study combining hyperfractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone (hyperCVAD) with imatinib reported a 5-year OS of 43% in an older cohort (median age 51, range 17-84 years), including 30% who underwent alloHCT.<sup>5</sup> A significant negative predictor of survival was age, with no significant improvement in median survival among patients who underwent alloHCT in first CR. However, although the difference was not statistically significant, probably because of small numbers, alloHCT seemed to be beneficial in patients <40 years old.<sup>5</sup> As a comparison, in a study of alloHCT in CR in the pre-imatinib era in 79 patients (median age 36, range 2-57 years), 10-year OS and event-free survival (EFS) were 54% and 48%, respectively.<sup>8</sup> These data

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Off-label drug use: Ponatinib and blinatumomab.

**Table 1. Published selected trials in Ph+ ALL**

Study	Age, y, median		Regimen	CMR rate	AlloHCT rate	RFS rate	OS rate
	N	[range]					
<b>Imatinib</b>							
Lee et al <sup>35</sup>	87	41 [16-71]	Intensive chemotherapy	66% (at remission)	68%	39% (5 y)	33% (5 y)
Yanada et al <sup>36</sup>	80	48 [15-63]	Intensive chemotherapy	50% (day 63)	49%	—	76% (1 y)
Vignetti et al <sup>18</sup>	29	69 [61-83]	Corticosteroids	4%	—	48% (1 y)	74% (1 y)
Bassan et al <sup>37</sup>	59	45 [20-66]	Intensive chemotherapy	—	72%	39% (5 y)	38% (5 y)
Fielding et al <sup>2</sup>	169	42 [16-64]	Intensive chemotherapy	—	72%	50% (4 y)	38% (4 y)
Daver et al <sup>5</sup>	54	51 [17-84]	Intensive chemotherapy	45% (overall)	30%	43% (5 y)	43% (5 y)
Chalandon et al <sup>21</sup>	133	45 [21-59]	Intensive chemotherapy	23% (2 cycles)	65%	—	46% (5 y)*
	135	49 [18-59]	Low-intensity chemotherapy	29% (2 cycles)	62%	—	46% (5 y)*
Wetzler et al <sup>33</sup>	34	45 [24-57]	Intensive chemotherapy	—	44%	46% (5 y)	51% (5 y)
<b>Dasatinib</b>							
Foà et al <sup>19</sup>	53	54 [24-77]	Corticosteroids	15% (day 85)	42%	22% (20 mo)	31% (20 mo)
Ravandi et al <sup>6</sup>	72	55 [21-80]	Intensive chemotherapy	65% (overall)	17%	44% (5 y)	46% (5 y)
Ravandi et al <sup>15</sup>	97	44 [20-60]	Intensive chemotherapy	—	42%	62% (3 y)	69% (3 y)
Rousselot et al <sup>20</sup>	71	69 [55-83]	Low-intensity chemotherapy	24% (consolidation)	10%	28% (5 y)	36% (5 y)
<b>Nilotinib</b>							
Kim et al <sup>14</sup>	90	47 [17-71]	Intensive chemotherapy	77% (3 mo)	63%	72% (2 y)	72% (2 y)
<b>Ponatinib</b>							
Jabbour et al <sup>28</sup>	37	51 [27-75]	Intensive chemotherapy	78% (overall)	24%	—	80% (2 y)

\*Pooled data.

suggest that the addition of imatinib or alloHCT in younger patients who are able to tolerate it can improve outcomes.

The question of how to best incorporate TKIs in the standard ALL chemotherapy regimens has also been examined by a number of studies. An early trial compared alternating and concurrent administration of imatinib with chemotherapy, and although both schedules had acceptable toxicity, the concurrent administration of imatinib with chemotherapy had greater antileukemic activity.<sup>9</sup> Fielding et al<sup>2</sup> introduced imatinib as a single-agent course administered after 2 induction courses (late imatinib) or during the second course of induction (early imatinib) in an update of the ULALLXII/ECOG2993 study. They reported significant improvement in CR rate (92% vs 82%, respectively,  $P = .004$ ) and 4-year OS (38% vs 22%, respectively,  $P = .003$ ) for imatinib-treated patients compared with the pre-imatinib era, and this improvement was more prominent in patients who received imatinib early.<sup>2</sup> They suggested that this improvement was due in part to imatinib therapy resulting in a higher number of patients undergoing alloHCT.<sup>2</sup>

The Children's Oncology Group administered increasing numbers of consecutive days of imatinib therapy to 5 cohorts of children with Ph+ ALL in order to assess toxicity.<sup>10</sup> The total imatinib exposure during the initial therapy for cohort 5 was 280 days, and the 3-year EFS for this cohort was 80.5% ± 11.2%, which was significantly better than that of their historical cohort.<sup>10</sup> Furthermore, there was no difference in 3-year EFS between patients in cohort 5 and patients who received an alloHCT from a sibling or alternative donor.<sup>10</sup> A follow-up report of this study further confirmed the good outcomes with imatinib plus chemotherapy, without an advantage for alloHCT, further underscoring the need for continuous TKI therapy.<sup>11</sup> Based on these data, the role of allogeneic stem cell transplantation in first CR has been reevaluated by several pediatric groups.

The development of second-generation TKIs such as nilotinib and dasatinib and the demonstration of their efficacy against resistance inducing *ABL1* kinase domain mutations led to their incorporation into chemotherapy regimens for Ph+ ALL (Table 1).<sup>12,13</sup> The investigator from the Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology reported on 90 patients (median age 47, range 17-71 years) treated with concurrent multi-agent chemotherapy and nilotinib.<sup>14</sup> After achieving CR, patients received either 5 courses of consolidation, followed by 2 years of maintenance with nilotinib, or alloHCT.<sup>14</sup> The CR rate was 91%, with a 2-year RFS of 72% among the 82 patients achieving CR; the 2-year OS was 72%.<sup>14</sup> Our group conducted a phase 2 trial combining the hyperCVAD regimen with dasatinib, which was given initially at 100 mg daily for the first 14 days of each cycle of induction, and consolidation chemotherapy.<sup>4</sup> Later, given the availability of more toxicity data and in order to maintain a continuous dosing strategy, dasatinib dosage and schedule were modified, and it was administered at 100 mg daily for the first 14 days of the first cycle and then at 70 mg daily continuously from cycle 2 onward.<sup>4</sup> Long-term follow-up in 72 patients (median age 55, range 21-80 years) showed a 5-year EFS and OS of 42% and 46%, respectively.<sup>6</sup> A similar phase 2 study was conducted by the South Western Oncology Group in a younger cohort of 94 patients (median age 44, range 20-60 years), with 41 undergoing alloHCT in first CR, followed by dasatinib maintenance after alloHCT.<sup>15</sup> The OS and EFS at 3 years were 69% and 62%, respectively, demonstrating the feasibility of this strategy in the multicenter setting. Of note, landmark analysis at 175 days from the time of CR (which was the longest time to alloHCT) showed a statistically superior advantage for RFS and OS ( $P = .038$  and  $P = .037$ , respectively) in favor of transplantation.<sup>15</sup>

These studies confirm the feasibility and efficacy of the addition of *BCR-ABL1* directed TKIs, including second-generation nilotinib and dasatinib, in the frontline therapy of patients with Ph+ ALL

and demonstrate that long-term leukemia-free survival is possible in patients who are unfit for allogeneic stem cell transplantation. However, resistance related to *ABL1* kinase domain mutations and other mechanisms such as deletion of *IKZF1* continue to result in relapse.<sup>16</sup> Preclinical studies have shown that concurrent cytotoxic chemotherapy can circumvent some of the mechanisms of resistance.<sup>17</sup> However, the potential toxicity of traditional ALL regimens, particularly in unfit patients, has led to efforts to reduce the intensity of chemotherapy.

### Deintensification of chemotherapy

Another approach that has been investigated largely by European groups is to use TKI alone or with steroids or minimal additional chemotherapy in the initial induction (Table 1). The Gruppo Italiano Malattie Ematologiche dell'Adulto group demonstrated that both imatinib and dasatinib can produce high hematological response rates (100%) with little or no associated mortality during the initial induction period. This approach is particularly attractive in older and infirm patients, where combined chemotherapy and TKI regimens are often associated with  $\leq 10\%$  mortality.<sup>6,14</sup> However, the reported trials have also demonstrated that without further consolidation with either chemotherapy, autoHCT, or alloHCT, the responses achieved are often of limited duration and associated with a high incidence of resistant *ABL1* mutations, particularly T315I. In the study by Vignetti et al,<sup>18</sup> all 29 patients (median age 69, range 61-83 years) evaluable for response who were treated with imatinib and steroids achieved a complete hematological remission, whereas only 1 of 27 patients achieved a complete molecular response. The median duration of response and median OS were 8 and 20 months, respectively.<sup>18</sup> More recently, Foà et al<sup>19</sup> treated 53 patients (median age 54, range 24-77 years) with dasatinib, steroids, and intrathecal methotrexate and reported a CR rate of 100%, with the majority achieving it after only 22 days of therapy and with no induction mortality. With a median follow-up of only 20 months, 43% of the patients relapsed, and relapses were more likely to occur in patients who received more limited postremission therapy.<sup>19</sup> Similarly, the European Working Group on Adult ALL treated 71 patients (median age 69, range 59-83 years) with dasatinib 140 mg daily, vincristine, dexamethasone, and intrathecal chemotherapy.<sup>20</sup> Patients in CR received dasatinib sequentially with asparaginase, methotrexate, and cytarabine for 6 months, followed by maintenance therapy with dasatinib and vincristine/dexamethasone for 18 months and dasatinib alone until relapse or death.<sup>20</sup> Almost all (96%) patients achieved CR, and the OS at 5 years was 36%. Among the 36 patients who relapsed, 24 were tested by Sanger sequencing for mutations, and 75% were positive for T315I.<sup>20</sup> Detection of T315I was associated with early relapse, and 10 patients were positive for the mutation before starting therapy, 8 of whom relapsed.

In a study by the Group for Research on Adult Lymphoblastic Leukemia, younger patients (median age 47, range 21-60 years) were randomly assigned to receive either hyperCVAD plus imatinib regimen or imatinib combined with low-intensity therapy with vincristine and dexamethasone.<sup>21</sup> Patients achieving CR in both arms would receive consolidation with methotrexate and cytarabine plus imatinib, and those with an available donor would proceed to an alloHCT. Patients achieving a major molecular response (MMR, defined as *BCR-ABL1/ABL1*  $\leq 0.1\%$  in the bone marrow) without an available donor could undergo autoHCT.<sup>21</sup> Although the CR rate was higher in the nonintensive arm (98% vs 91%,  $P = .006$ ) because of lower induction mortality (early death 0.7% vs 6.7%; 60-day mortality 2.2% vs 9.0%), the 5-year EFS and OS were not statistically different between the 2 arms (42.2% vs 32.1%,  $P = .13$  and 48.3% vs 43%,  $P = .37$ , respectively). The authors also examined the

role of alloHCT in CR and demonstrated that alloHCT in CR1 was associated with improved RFS and OS ( $P = .036$  and  $P = .02$ , respectively).<sup>21</sup> However, according to a donor vs no-donor analysis, having a donor was not associated with a significant improvement in RFS or OS.<sup>21</sup> Similarly, in a comparison of the outcomes of patients who achieved MMR after the second cycle and received either alloHCT or autoHCT, RFS and OS did not differ.<sup>21</sup> Therefore, this randomized study demonstrated that in younger patients with alloHCT as the goal, the outcomes were similar regardless of the intensity of the initial induction.

These reports clearly show that therapy with TKIs and corticosteroids or minimal chemotherapy is effective in achieving CR with minimal induction toxicity and mortality but is inadequate for long-term control of the disease unless it is followed by alloHCT, autoHCT, or consolidation chemotherapy. Therefore, in younger patients with an available sibling or matched unrelated donor destined to proceed to alloHCT, such nonintensive induction is appropriate. Of note, in the study by Chalandon et al,<sup>21</sup> the rate of MMR after cycle 2 of therapy was similar between the intensive and nonintensive arms at 66% and 64%, respectively (with the caveat that cycle 2 did contain high-dose cytarabine and methotrexate with imatinib and was the same in both arms).

### Predicting outcome by using MRD assessment

The availability of assays for minimal residual disease (MRD) monitoring has provided us with better tools to evaluate efficacy of the induction and consolidation courses to eradicate the leukemic clone.<sup>22</sup> Various assays including multiparameter flow cytometry (MFC) and polymerase chain reaction (PCR) for immunoglobulin and T-cell receptor gene rearrangements as well as PCR for *BCR-ABL1* fusion transcripts can be used, but clearly the latter is the established assay in Ph+ leukemias, including Ph+ ALL. The utility of MRD assessment in predicting outcome has been evident in early studies. In a Children's Oncology Group study, Schultz et al,<sup>10</sup> using MFC, demonstrated that an MRD level  $< 0.01\%$  after chemotherapy induction and before imatinib therapy was associated with greater RFS. However, this predictive value of flow MRD was nullified in patients who received continuous imatinib therapy for 280 days, demonstrating the efficacy of imatinib in this setting.<sup>10</sup>

We evaluated 76 patients (median age 54, range, 21-84 years) treated with hyperCVAD plus imatinib or hyperCVAD plus dasatinib. They achieved a CR after 1 induction course, did not undergo an alloHCT in first CR, and had  $\geq 1$  MRD assessment.<sup>23</sup> MRD monitoring was performed at the end of induction and every 3 months thereafter. Although there was no difference in survival by achievement of MMR (*BCR-ABL1/ABL1*  $\leq 0.1\%$  in the bone marrow) at CR, achieving MMR at 3, 6, 9, and 12 months was associated with improved OS.<sup>23</sup> Similarly, achieving an MFC-negative state at CR did not predict better survival but was associated with greater OS if achieved at 3 and 12 months.<sup>23</sup> In a follow-up study, we expanded the study population but restricted it to patients who had MRD data available both at CR and at 3 months, including patients treated with hyperCVAD plus imatinib, dasatinib, or ponatinib who did not undergo alloHCT in first CR.<sup>24</sup> Achieving complete molecular remission (CMR) at 3 months was better in predicting OS ( $P = .005$ ) and RFS ( $P = .002$ ) than MRD status at CR ( $P = .11$ , and  $P = .04$ , respectively).<sup>24</sup> Achieving CMR at 3 months compared with any response less than CMR (including MMR) was associated with a longer median OS (127 vs 38 months,  $P = .009$ ) and RFS (126 vs 18 months,  $P = .007$ ).<sup>24</sup> Only CMR at 3 months was prognostic for OS (hazard ratio [HR], 0.42; 95% confidence interval, 0.21-0.82;  $P = .01$ ) on multivariable analysis.<sup>24</sup>

**Table 2. Evolving therapeutic strategies in adult Ph+ ALL**

	Increasing age and comorbidity	MRD negative state	Available donor	Increased TKI efficacy
Chemotherapy	↓	↓	↓	↓
AlloHCT	↓	↓	↑	↓
AutoHCT	↑	↑	?	↑
TKIs	↑	↑	↑	↑
Novel therapies (antibodies, chimeric antigen receptor T-cells)	↑	↑	?	?

Traditional treatment of younger patients with Ph+ ALL with an available donor involved limited initial chemotherapy followed by alloHCT. With introduction of potent TKIs and particularly in older and more infirm patients, the role of chemotherapy and alloHCT has decreased. Several studies have confirmed the prognostic benefit of achieving CMR early in the course of therapy. With introduction of more potent TKIs and novel agents such as the bispecific antibody blinatumomab we may witness further reduction in the intensity of chemotherapy and elucidation of the role of alloHCT in this disease. The direction of arrows indicates the degree of reliance on the available modalities of therapy. “?” indicates lack of adequate data related to the interaction.

For RFS, only CMR at 3 months and presence of other cytogenetic abnormalities in addition to the Philadelphia chromosome were prognostic ( $P = .01$  and  $P = .03$ , respectively). Of note, among the 7 patients who did not achieve CMR at 3 months and remained alive and relapse free at long-term follow-up, all eventually achieved CMR, with a median time to CMR of 14 months (range 8-87 months).<sup>24</sup> This study confirms the value of achieving CMR at 3 months by using a TKI/chemotherapy regimen, an effect that appears to be independent of the TKI used.

The value of MRD by PCR for *BCR-ABL1* has also been demonstrated in the setting of alloHCT. Investigators from Korea treated 90 patients with Ph+ ALL (median age 47, range 17-71 years) with nilotinib combined with concurrent vincristine, prednisone, and daunorubicin.<sup>14</sup> Patients achieving CR received either 5 courses of consolidation with nilotinib and chemotherapy or alloHCT. MRD assessment was performed every 3 months from the time of achieving CR. CMR was assumed when the *BCR-ABL1/G6PDH* ratio was  $<1 \times 10^{-5}$  (MR5) and MMR when the ratio was  $\leq 1 \times 10^{-3}$  (MR3).<sup>14</sup> The overall CR rate was 91%, and 57 patients underwent alloHCT. At the time of CR, the MR5 was 56% and MR3 (including MR5) was 79%. Among the 70 patients evaluable at 3 months, the MR5 rate was 77% and MR3 (including MR5) was 87%. Among the patients who underwent alloHCT, the MR5 rate was 84% before they received the conditioning regimen.<sup>14</sup> Overall, 2-year RFS was affected by achieving MR3 or MR5 not at CR but at 3 months; patients failing to achieve MR3 at 3 months had a 9-fold higher risk of relapse ( $P = .004$ ) than those who achieved MR3.<sup>14</sup> Similarly, the estimated 2-year RFS was 80% and 33%, respectively, for those who did or did not achieve MR5 at 3 months ( $P < .001$ , HR 6.3).<sup>14</sup> Among the 57 patients who underwent alloHCT, significant predictors of 2-year RFS were failure to achieve MR3 (0% vs 83% for MR3 achievers; HR 19.8,  $P = .001$ ) and failure to achieve MR5 (49% vs 85% for MR5 achievers; HR, 3.8;  $P = .024$ ).<sup>14</sup> These data further suggest that even for patients who undergo alloHCT, reduction of disease burden before transplantation is associated with a significant improvement in outcome.

Although some studies have suggested differential outcomes for p210 versus p190 disease, the data are inconclusive, with some reports suggesting faster and deeper molecular response for patients harboring p190 transcripts.<sup>21,25</sup> Similarly, different groups have suggested different effects on disease-free survival and OS for the 2 transcript types.<sup>5,21,26</sup>

### Third-generation TKIs and other novel strategies

The presented data suggest that achieving CMR should be considered the goal of therapy in all patients with Ph+ ALL; it can be achieved by the introduction of more potent TKIs, which are able to overcome *ABL1*-resistant mutations, particularly T315I. In the study by Foà et al,<sup>19</sup> which used dasatinib and prednisone, all patients achieved CR, and postinduction treatment included TKI alone, TKI plus chemotherapy, and autoHCT or alloHCT. Relapse was more common in patients who continued low-intensity therapy or no further therapy (16 of 21 patients) compared with those who received TKI plus chemotherapy or autoHCT (5 of 14) or alloHCT (2 of 18).<sup>19</sup> Among the 17 patients who were analyzed for mutations at relapse, T315I was detected in 12, E255K in 1, and no mutations in 4.<sup>19</sup> In a recent update of hyperCVAD plus dasatinib, among 13 relapsed patients who underwent *ABL1* mutation analysis, 7 had mutations (4 T315I, 1 F359V, and 2 V299L).<sup>6</sup> In the study reported by the European Working Group on Adult ALL, which used dasatinib and low-intensity chemotherapy in older adults, among the 24 relapsed patients evaluated for mutations, 75% were T315I positive.<sup>20</sup> Allele-specific oligonucleotide PCR for the detection of *BCR-ABL1* was retrospectively performed on prospectively collected RNA samples in 43 patients, of whom 10 were positive for T315I before receiving any therapy; 8 relapsed, all with T315I.<sup>20</sup> Others have confirmed the presence of *ABL1* kinase domain mutations at diagnosis or early during therapy in most relapsed patients.<sup>26</sup> Therefore, it appears that resistance mutations, particularly T315I, are significant contributors to relapse and failure.

Ponatinib has been established as an effective TKI in heavily pre-treated patients with Ph+ leukemias. In the phase 2 trial of this agent in patients resistant or intolerant to second-generation TKIs, among the 32 patients with Ph+ ALL treated (including 22 patients with a T315I mutation), 41% had a major hematological response (median duration 3 months) and 47% had a major cytogenetic response (median duration 3.7 months).<sup>27</sup> Our group has reported on 37 patients (median age 51, range 27-75 years) treated with ponatinib combined with the hyperCVAD regimen.<sup>28</sup> Overall complete response, complete cytogenetic response, and CMR rates were 100%, 100%, and 78%, respectively, with 26% achieving CMR after 1 cycle of therapy.<sup>28</sup> With a median follow-up of 26 months, 78% were maintaining CR, with an estimated 2-year survival of 80%. The dose of ponatinib had to be reduced after occurrence of the well-described cardiovascular toxicity in the initial cohort, which has reduced this risk significantly in the subsequent patients enrolled.<sup>28</sup> Ongoing studies are evaluating the potential efficacy of ponatinib monotherapy in the frontline setting.

Other novel agents such as monoclonal antibodies may be incorporated in our armamentarium in the future. Topp et al<sup>29</sup> demonstrated the efficacy of the bispecific antibody blinatumomab in eradicating MRD in patients with B-lineage ALL, including 5 patients with Ph+ disease. Martinelli et al<sup>30</sup> recently reported on significant activity of blinatumomab in patients with relapsed and refractory Ph+ ALL. Among the 45 patients treated, 16 (36%) achieved CR or CR with partial hematological recovery during the first 2 cycles of therapy, including 4 of 10 patients with T315I mutation.<sup>30</sup> Combination of blinatumomab with TKIs in patients with relapsed Ph+ ALL is being evaluated in ongoing clinical trials. Other potentially effective strategies include antibody-drug conjugates such as inotuzumab ozogamicin and chimeric antigen receptor T-cell therapy.<sup>31,32</sup>

The role of autoHCT in Ph+ ALL continues to be investigated because of the feasibility of achieving deep molecular responses by using TKI-based regimens.<sup>21,33,34</sup> Several studies have demonstrated excellent efficacy of autoHCT, with outcomes at least equivalent to those of alloHCT, particularly in patients with reduced disease burden at the time of transplantation. In a long-term follow-up report of the GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia)-2003 study, OS rates were 50%, 33%, and 80% for patients treated with alloHCT, chemotherapy, or autoHCT, respectively.<sup>34</sup> In the study by Chalandon et al,<sup>21</sup> similar RFS and OS rates were reported for alloHCT and autoHCT among the patients achieving MMR (an eligibility criterion for autoHCT). Ongoing trials are investigating the potential role of autoHCT by using more potent TKIs and monoclonal antibodies, able to produce deeper molecular responses.

In summary, treatment modalities for patients with Ph+ ALL are expanding (Table 2). With the introduction of more potent TKIs effective against resistance inducing *ABL1* kinase mutations in the frontline setting, more patients achieve CMR earlier in the course of therapy. This improvement has been associated with higher likelihood of achieving long-term RFS and OS. It has also led to deintensification of initial chemotherapy, with decreased early treatment-related mortality, particularly in older adults. Novel agents such as monoclonal antibodies will probably complement these strategies, leading to improved response rates and duration. The potential for these combined strategies to deintensify chemotherapy (particularly for older adults and the unfit) and to improve the responses, including the depth of molecular response, will need to be investigated to further clarify the eventual role of intensive chemotherapy and alloHCT in treating patients with Ph+ ALL. These questions will be elucidated by ongoing clinical trials.

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## Correspondence

Farhad Ravandi, Department of Leukemia, Unit 428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; e-mail: fravandi@mdanderson.org.

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