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Dasatinib/prednisone induction followed by blinatumomab/dasatinib in Ph$^+$ acute lymphoblastic leukemia

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Key Points

- The combination of dasatinib and blinatumomab has impressive overall survival and disease-free survival in older patients with Ph$^+$ ALL.
- Dasatinib/blinatumomab is well tolerated in older patients with Ph$^+$ ALL.

Novel treatment strategies are needed for the treatment of Philadelphia chromosome–positive (Ph$^+$) acute lymphoblastic leukemia (ALL) in older patients. This trial evaluated the feasibility and outcomes with the anti-CD19 bispecific T-cell–engaging antibody, blinatumomab, in combination with dasatinib and steroids. Patients 65 years of age or older with Ph$^+$ or Ph-like ALL (with dasatinib-sensitive fusions/mutations) were eligible and could be newly diagnosed or relapsed/refractory. Induction therapy consisted of dasatinib/prednisone. Patients not achieving response by day 56 proceeded to blinatumomab reinduction therapy. Patients achieving response with induction or reinduction therapy proceeded to blinatumomab/dasatinib postremission therapy for 3 cycles followed by dasatinib/prednisone maintenance. All patients received central nervous system prophylaxis with intrathecal methotrexate for a total of 8 doses. Response was assessed at days 28, 56, and 84 and at additional time points based on response parameters. Measurable residual disease was assessed centrally by 8-color flow cytometry at day 28. A total of 24 eligible patients with newly diagnosed Ph$^+$ ALL were enrolled with a median age of 73 years (range, 65-87 years). This combination was safe and feasible. With a median of 2.7 years of follow-up, 3-year overall survival and disease-free survival were 87% (95% confidence interval [CI], 64-96) and 77% (95% CI, 54-90), respectively. Although longer follow-up is needed, these results are encouraging, and future trials are building on this backbone regimen. This trial was registered at www.clinicaltrials.gov as #NCT02143414.

Introduction

Tyrosine kinase inhibitors (TKIs) have improved the outcomes of patients with Philadelphia chromosome–positive (Ph$^+$) acute lymphoblastic leukemia (ALL). Many older patients are not good candidates for intensive chemotherapy and are treated with TKIs plus corticosteroids or low-intensity

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The policies and procedures for requesting SWOG Cancer Research Network data are available at https://www.swog.org/sites/default/files/docs/2019-12/Policy43_0.pdf.

Data are available on request from the corresponding author, Anjali S. Advani (advania@ccf.org).

The full-text version of this article contains a data supplement.

chemotherapy. Although the remission rates with this approach have been high, the median disease-free survival (DFS) has been short. In the GIMEMA LAL1205 protocol, patients were treated with dasatinib, steroids, and intrathecal therapy.[1] All patients achieved a complete hematologic remission, but DFS was only 51% at 20 months. Therefore, novel treatment strategies are clearly needed. Blinatumomab, an anti-CD19 bispecific T-cell engager antibody, has significant activity in B-cell ALL (B-ALL) and has been approved by the Food and Drug Administration (FDA) for the treatment of relapsed/refractory B-ALL and measurable residual disease (MRD)–positive B-ALL.[2,3] This trial evaluated the feasibility of combining the TKI dasatinib with prednisone and blinatumomab in older patients with newly diagnosed Ph^+ and Ph-like ALL.

Methods

This trial (NCT02143414 on www.clinicaltrials.gov) was activated through the National Clinical Trials Network in January 2015 and closed to accrual in April 2021. The primary objective was to assess the feasibility (safety) of this regimen. Secondary objectives included (1) estimating DFS and overall survival (OS) and (2) estimating the rate of MRD negativity. An Investigational New Drug application was approved by the FDA, and the protocol was approved by a central institutional review board. All patients provided informed consent. Eligibility criteria were as follows: age ≥ 65 years; Ph^+ or Ph-like ALL (with dasatinib-sensitive fusions or mutations), newly diagnosed or relapsed/refractory, no evidence of central nervous system (CNS) disease, no history or presence of clinically relevant CNS pathology, no active pericardial or pleural effusion, cardiac ejection fraction ≥ 45%, and adequate organ function. Adequate organ function was defined as creatinine ≤ 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤3.0 × institutional upper limits of normal (IULN), total bilirubin ≤2 × IULN, and alkaline phosphatase ≤2.5 × IULN. Cytogenetic and molecular testing were performed. An absolute peripheral blast count <25 000/uL at the time of the first infusion of blinatumomab was required. Prephase dexamethasone (10-20 mg/m^2 per day) for 3 to 5 days was given to patients with bone marrow blasts ≥50%, peripheral blood blasts 15 000/uL or higher, or elevated lactate dehydrogenase.

Treatment

The treatment schema is outlined in Figure 1. The full protocol is attached in the supplementary materials. For induction, patients received dasatinib 140 mg/d orally on days 1 to 56 along with prednisone 60 mg/m^2 per day orally on days 1 to 24. Patients achieving complete remission (CR) or CR with incomplete count recovery (CRi) (day 28 or day 56) continued dasatinib until day 84 followed by 3 cycles of postremission therapy (PRT) with blinatumomab/dasatinib. Patients not achieving CR or CRi by day 56 received reinduction with blinatumomab. Response was assessed at day 35 of blinatumomab. Patients not achieving CR/CRi could receive a second cycle of blinatumomab. This was followed by 3 cycles of PRT with blinatumomab/dasatinib. Dasatinib was administered at a dose of 70 mg/d when given in combination with blinatumomab, given the potential concerns for myelosuppression with the combination. During initial reinduction, blinatumomab was administered at a dose of 9 μg/d on days 1 to 7 and 28 μg/d on days 8 to 28. For additional reinduction and PRT, blinatumomab was administered at a dose of 28 μg/d on days 1 to 28. Patients received dexamethasone 20 mg IV 1 hour before the start of blinatumomab for each cycle and before day 8 of cycle 1 when the blinatumomab dose was escalated. Maintenance therapy consisted

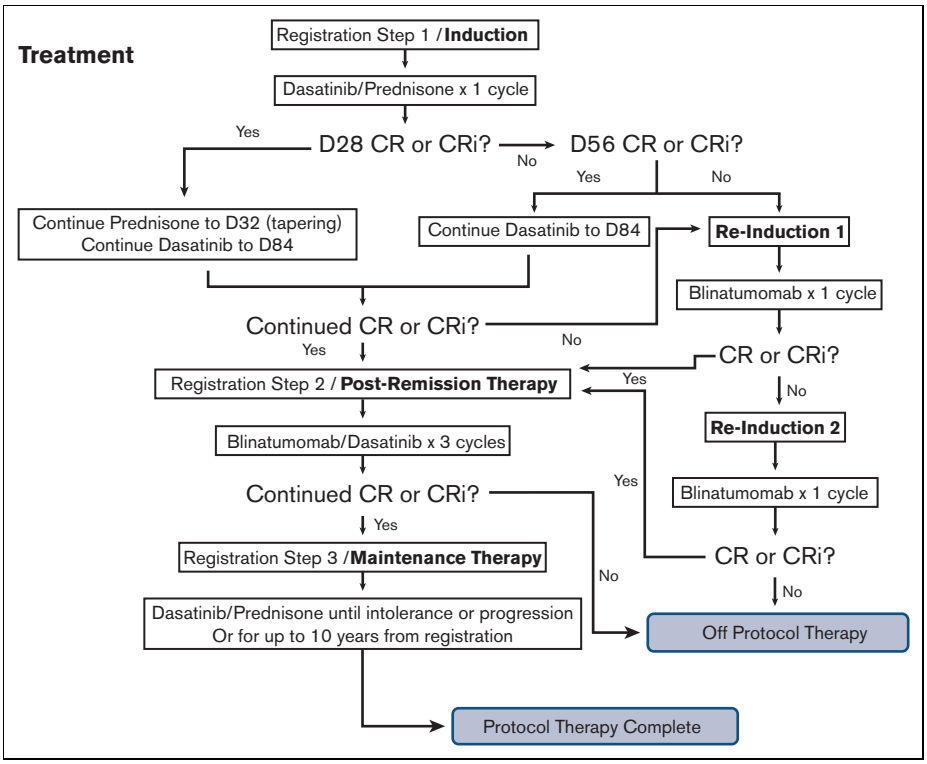

Figure 1. Treatment schema.

of prednisone 60 mg/m^2 per day × 5 days every 28 days for a total of 18 cycles along with dasatinib 140 mg orally daily indefinitely. CNS prophylaxis included intrathecal (IT) methotrexate every 4 to 6 weeks × 8 doses. IT methotrexate was given at least 2 days apart from blinatumomab. Dose modifications are outlined in the full protocol.

Response and outcomes

Response was assessed at days 28, 56, and 84, and additional time points were dependent on response. MRD testing was assessed centrally by 8-color flow cytometry at the University of Washington at day 28.[4] MRD negativity was defined as <0.01%, based on the sensitivity of this method. CR was defined as <5% marrow blasts with no evidence of extramedullary disease and recovery of counts (absolute neutrophil count [ANC], >1000/UI; platelet count >100 000/uL). CRi was defined same as CR but with ANC ≤ 1000/uL and/or platelets ≤ 100 000/uL. Relapse was defined as follows: (1) appearance of leukemic blasts in the peripheral blood, (2) appearance of extramedullary disease, or (3) ≥5% blasts in the bone marrow not attributable to another cause (ie, recovery of normal cells following chemotherapy-induced aplasia). OS was measured from the day of registration of trial until the date of death, with patients last known to be alive censored at their date of last contact. DFS was measured from the date of CR/CRi until relapse or death, with patients last known to be alive and relapse-free censored at their date of last contact. Toxicities were graded according to National Cancer Institute (NCI) CTCAE version 4.0.

Statistics

The sample size was selected through negotiation with the NCI and not based on specific statistical parameters or properties. There was concern that a larger sample size would not be feasible initially because of accrual concerns before the trial opened. The study opened with the maximum number of patients the NCI would approve with the goal of gaining as much information as possible through the trial. Accrual was better than anticipated; therefore, we requested an amendment to the sample size and proposed a more rigorous design. The NCI was willing to approve a fixed number of additional patients with no change to objectives and statistics. A total of 9 eligible patients receiving PRT and evaluable for dose-limiting toxicities (DLTs) were to be evaluated before enrolling additional patients. For the patients to be considered evaluable for DLTs, they had to be eligible and either experience a DLT during cycle 1 of PRT or receive at least 75% of the prescribed dose of blinatumomab for cycle 1 of PRT. DLTs were defined as ≥ grade 3 nonhematologic toxicities with the exception of nausea, vomiting, or diarrhea (if manageable with supportive care measures) or grade 4 neutropenia lasting >42 days with possible relationship to dasatinib or blinatumomab. If the regimen was considered safe, 8 additional eligible and evaluable patients would be enrolled.

Results

Because of rapid unexpected accrual patterns, 16 patients enrolled before accrual was paused to assess feasibility and safety. The over accrual to the initial cohort was due to 2 factors: (1) the long period between initial registration and the start of PRT with blinatumomab and (2) the 2-week notice given to sites before closing the study. Patients who did not receive at least 75% of the prescribed dose of blinatumomab during their first cycle of PRT were not considered "evaluable" for DLT. A total of 12 patients were evaluable for DLT of whom 4 experienced the following DLTs: grade 3 dyspnea and gastrointestinal pain (n = 1), grade 3 hypertension (n = 1), grade 3 dyspnea (n = 1), and grade 3 hyperglycemia (n = 1). These adverse events were deemed acceptable following NCI and FDA review, and the study reopened to accrual.

Table 1. Patient characteristics (n = 24)

Median age	**73 y (range, 65-87 y)**
Newly diagnosed, (%)	N = 24 (100)
Ph$^+$ (%)	N = 24 (100)
Patients with additional cytogenetic abnormalities (%)	79
Gender, n (%)	8 male (33)
Race, n (%)	
Asian	2 (8)
Black	1 (4)
White	18 (75)
Unknown	3 (13)
Hispanic ethnicity, n (%)	
Hispanic	3 (13)
Not Hispanic	18 (75)
Unknown	3 (13)
Median baseline white blood cell count	7500 (7.5 × 1000) (range, 1.3-123.3)
Median bone marrow blast percentage (%)	89 (range, 30-100)

Patient characteristics

A total of 24 eligible patients were accrued (Table 1). The median age was 73 years (range, 65-87 years). All patients had newly diagnosed Ph$^+$ ALL. Additional cytogenetic abnormalities were found in 79% of the Ph$^+$ patients. There were 8 (33%) male patients; median baseline white blood cell count was 7500 (7.5 × 1000) (range, 1.3-123.3) at registration; and median bone marrow blast count percentage was 89% (range, 30-100).

Toxicities

DLTs during PRT with dasatinib/blinatumomab are noted above. During induction, 2 patients experienced treatment-related nonhematologic grade 4 toxicities. No grade 4 or higher treatment-related nonhematologic toxicities occurred during PRT or maintenance. Table 2 captures all hematologic and nonhematologic toxicities during PRT thought to be possibly related to treatment.

Dose modifications of dasatinib

A total of 19 patients had dose modification of dasatinib because of adverse events during the course of treatment. Modifications occurred in 9 patients during induction, 13 patients during PRT, and 11 patients during maintenance. The most common causes for dose modification during the various phases of therapy were pulmonary, cardiac, infection (during induction); neutropenia and pulmonary (during PRT); and pulmonary (during maintenance).

Table 2. PRT adverse events possibly related to treatment

Adverse events (n = number of patients)	Postremission nonhematologic events (grade) ≤2	3	4	5	Total
ALT increased	17	1	0	0	18
AST increased	17	1	0	0	18
Agitation	17	1	0	0	18
Confusion	16	2	0	0	18
Dyspnea	15	3	0	0	18
Encephalopathy	17	1	0	0	18
Gastrointestinal pain	17	1	0	0	18
Hyperglycemia	16	2	0	0	18
Hypertension	16	2	0	0	18
Hypocalcemia	17	1	0	0	18
Infections/infestations-Other	16	2	0	0	18
Pericardial effusion	17	1	0	0	18
Max grade any AE	7	11	0	0	18

Adverse events	Postremission hematologic events ≤2	3	4	5	Total
Anemia	17	0	1	0	18
Lymphocyte count decreased	12	3	3	0	18
Neutrophil count decreased	8	3	7	0	18
White blood cell decreased	17	1	0	0	18
Max grade any AE	5	3	10	0	18

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Max, maximum.

Response/outcomes

The Consolidated Standards of Reporting Trials diagram of the patients is shown in Figure 2. Of the 24 patients, 22 (92%) achieved a CR during dasatinib and prednisone induction therapy. The other 2 patients died during induction (days 1-84) and did not receive blinatumomab. Causes of death during induction were acute respiratory distress syndrome unrelated to treatment with possible contribution from adverse effects of prednisone, prior influenza, aspiration, and urinary tract infection (1 patient) and disease progression (1 patient). Of patients achieving CR, 14 patients had the p190 transcript, and 6 patients had the p210 transcript. The transcript type is unknown in the remaining 2 patients. MRD data were available for 16 patients who achieved CR. Of 16 patients, 6 patients (38%) were MRD negative by flow cytometry at day 28. Most sites also monitored patients molecularly with peripheral blood or bone marrow BCR::ABL1. Of 19 patients analyzed, 17 patients (89%) were in a major or complete molecular remission at some time point after treatment, with at least 12 of these patients achieving complete molecular remission. Only limited numbers of patients have available data to assess the response to blinatumomab-based PRT because flow MRD per protocol was only measured at days 28 and 56 (with only 2 patients having data at day 56) and because BCR::ABL1 PCR was not mandated per protocol. Of 7 patients with detectable transcript at the end of induction, 5 patients (71%) achieved complete molecular response after blinatumomab-based PRT. Four patients

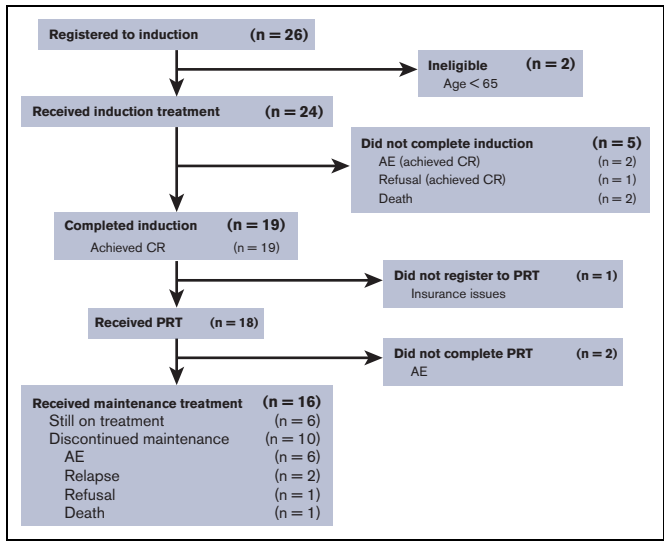

Figure 2. Consolidated Standards of Reporting Trials diagram. AE, adverse event.

who achieved CR did not receive PRT (2 because of adverse events, 1 to receive transplant, and 1 because of insurance issues). Six patients remain on maintenance. Reasons for treatment discontinuation during the various phases of therapy are outlined in Table 3. Treatment was discontinued by 10 patients because of the following adverse events: pleural effusion (n = 4), pulmonary hypertension (n = 1), rash (n = 1), pericardial effusion (n = 1), cytomegalovirus pneumonitis (n = 1), hypoxia and edema (n = 1), and edema (n = 1). The median follow-up for patients who are alive is 2.7 years. As of 18 July 2022, the median OS had not been reached and the median DFS was 5.3 years (95% confidence interval [CI], 3.0-NA [the upper confidence limit was not reached]). Kaplan-Meier 3-year estimates of OS and DFS are 87% (95% CI, 64-96) and 77% (95% CI, 54-90), respectively (Figure 3).

Relapse characteristics

At the time of relapse, 2 patients had CNS disease. Of the 7 relapses, 4 patients were CD19$^+$ and 3 patients had T315I mutations. Of the 7 relapses, 5 occurred in patients who came off therapy for causes other than relapse. Of these, 3 patients never received blinatumomab, and all 3 patients had systemic relapses.

Discussion

Historically, the outcomes of adults with Ph$^+$ ALL have been poor. However, this has improved significantly with the advent of TKI-based therapy. The median age of patients with Ph$^+$ ALL is 56 years, which further complicates treatment.[5] Many patients are not good candidates for intensive chemotherapy or allogeneic transplant. The remission rate with TKI/steroid-based therapy is excellent[1]; however, remission duration has been short with combinations such as dasatinib/steroids. A significant percentage of these patients relapse with resistance mutations.[1] Given the concern for T315I mutations, studies have been conducted with ponatinib (which has specific activity against these mutations) and steroids[6]; however, longer follow-up is needed to determine the durability of these results. In addition, given ponatinib's risk of cardiovascular events, it may not be a good option for many older patients.[7]

Table 3. Reasons for treatment discontinuation

Induction	Induction: *N* = number of patients
Completed planned treatment	19
Died while on treatment	2
Off because of refusal	1
Off because of side effects	2
All	24
Postremission	**Postremission: *N* = number of patients**
Completed planned treatment	16
Off because of side effects	2
All	18
Maintenance	**Maintenance: *N* = number of patients**
Died while on treatment	1
On protocol treatment	6
Off because of progression/relapse	2
Off because of refusal	1
Off because of side effects	6
All	16

The anti-CD19 bispecific antibody, blinatumomab, has demonstrated significant activity in Ph^+ and Ph^- B-ALL and has been generally well tolerated. In cohort 1 of this trial (SWOG 1318),[8] patients who had Ph^- B-ALL were treated with blinatumomab for induction and PRT. The median age in this cohort was 75 years, and there were no deaths in the first 28 days. This points to the excellent tolerability of blinatumomab in the older patient population. The Ph^+ cohort of this study aimed to evaluate blinatumomab as PRT (instead of chemotherapy) with the hopes that this approach may lead to a chemotherapy-free regimen with good tolerability and outcomes. This initial trial was a feasibility study to assess the safety of the dasatinib/blinatumomab combination. Although DLTs were noted, these toxicities were not different from what have been observed with dasatinib and steroids alone; therefore, this combination was deemed feasible.

The outcomes in this study were excellent with a 3-year DFS and OS of 77% and 87%, respectively. This is similar to what was observed in the D-ALBA study (blinatumomab and dasatinib).[9] However, in this latter trial, a higher percentage of patients proceeded to allogeneic transplant (vs only 1 patient in this trial) and that trial included younger patients (youngest patient 24 years and median age 54 years vs youngest patient in this trial was 65 years and the median age of 73 years). In addition, the consolidation therapy was left to the discretion of the investigator. Our data suggest that outcomes with this regimen may be excellent without allogeneic transplant, particularly in an older patient population. However, follow-up remains short and longer follow-up will be needed to determine the duration of response in the absence of allogeneic transplantation. It is not clear whether blinatumomab will overcome the development of resistance mutations typically seen with dasatinib/prednisone alone. However, some T315I mutations were noted at relapse, suggesting that other TKIs (asciminib, ponatinib) or additional sequencing of novel therapies (inotuzumab) may be needed. In addition, it is unclear whether there would be differences in outcome with other genetic mutations as assessed by next-generation sequencing. The latter were not checked at the time of this trial. IKZF1 deletions have been associated with decreased DFS. In the D-ALBA trial, patients with IKZF1 deletions plus additional genetic aberrations (CDKN2A or CDKN2B, PAX5, or both) had a lower DFS.[9] Thus, it is possible that this would be applicable in our trial given the similar backbone regimen.

Given the concern for tyrosine kinase resistance mutations, other trials have taken a similar approach but used ponatinib with blinatumomab. This approach has demonstrated good results in Ph^+ relapsed/refractory ALL.[10] Short et al have evaluated this approach in patients newly diagnosed with Ph^+ ALL as well.[11] With a median follow-up of 9 months, the estimated 2-year EFS and OS for the newly diagnosed cohort is 95%, which is impressive. However, patients were selected (they could not have uncontrolled cardiovascular disease), and the median age was significantly younger than our trial (60 years). In addition, although the percentage of toxicity was low, 2 patients did have to discontinue treatment because of known ponatinib toxicities (1 deep vein thrombosis and 1 stroke). It is also unclear whether ponatinib is needed to help prevent the development of resistance mutations with the addition of blinatumomab. Foa et al were able to demonstrate that ABL mutations were detected in 6 patients who had increased MRD during

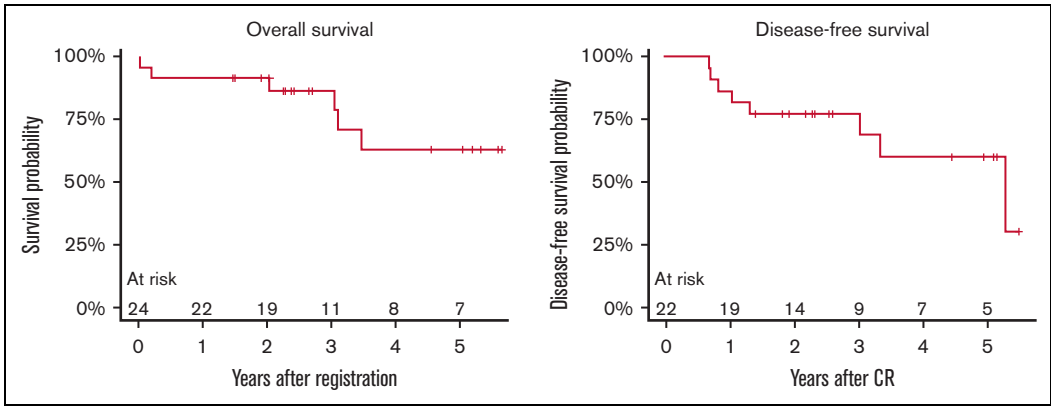

Figure 3. Outcomes: disease-free and overall survival.

induction therapy, and all these mutations were cleared by blinatumomab.[9] An ongoing trial (NCT03739814) is evaluating ponatinib, steroids, blinatumomab, and the anti-CD22 antibody–drug conjugate inotuzumab ozogamicin in Ph^+ ALL with sequencing of therapy.

This study had limitations given its small size and lack of serial molecular measurements. In addition, although the results were excellent, 10 patients discontinued treatment because of side effects, demonstrating that even with dasatinib, patients can have significant toxicity, and further dose adjustments of the TKI therapy may be needed for older patients. Other novel TKIs, such as asciminib, are also being studied in this disease.[12,13] However, the combination of dasatinib and blinatumomab in this older patient population was clearly safe and active. Longer follow-up will be needed to determine the durability of these results. Whether this approach, which does not include transplantation, results in durable remissions will be particularly important for younger patients who are often offered transplant in first CR. It will also be important to examine patterns and mechanisms of relapse with this treatment approach and to explore other novel combination regimens which are "chemotherapy-free" in both younger and older patients with Ph^+ ALL.

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Authorship

Contribution: A.S.A., K.M.O., and M.W. conceived and designed the study, provided the study materials or patients, and were involved with collection and assembly of data, data analysis, and data interpretation; A.M., B.L.W., J.P., M.O., and H.P.E. conceived and designed the study and were involved with collection and assembly of data, data analysis, and data interpretation; J.L.L. was responsible for collection and assembly of data; D.J., G.Y., E.L.A., A.T.G., and S.M.O. provided study material or patients and were responsible for collection and assembly of data; M.L., R.M.S., and E.S. were responsible for concept and design and collection and assembly of data; A.S.A., K.M.O., A.M., and M.O. have directed, accessed, and verified the underlying data reported in the manuscript; and all authors were involved in manuscript writing as well as final approval of manuscript, had full access to data, and are accountable for all aspects of the work.

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