

Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study

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Published at jco.org on March 29, 2017.

Clinical trial information: NCT02000427.

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0732-183X/17/3516w-1795w/\$20.00

ABSTRACT

Purpose

Few therapeutic options are available for patients with Philadelphia chromosome–positive (Ph⁺) B-precursor acute lymphoblastic leukemia (ALL) who progress after failure of tyrosine kinase inhibitor (TKI) –based therapy. Here, we evaluated the efficacy and tolerability of blinatumomab in patients with relapsed or refractory Ph⁺ ALL.

Patients and Methods

This open-label phase II study enrolled adults with Ph⁺ ALL who had relapsed after or were refractory to at least one second-generation or later TKI or were intolerant to second-generation or later TKIs and intolerant or refractory to imatinib. Blinatumomab was administered in 28-day cycles by continuous intravenous infusion. The primary end point was complete remission (CR) or CR with partial hematologic recovery (CRh) during the first two cycles. Major secondary end points included minimal residual disease response, rate of allogeneic hematopoietic stem-cell transplantation, relapse-free survival, overall survival, and adverse events (AEs).

Results

Of 45 patients, 16 (36%; 95% CI, 22% to 51%) achieved CR/CRh during the first two cycles, including four of 10 patients with the T315I mutation; 88% of CR/CRh responders achieved a complete minimal residual disease response. Seven responders (44%) proceeded to allogeneic hematopoietic stem-cell transplantation, including 55% (six of 11) of transplantation-naïve responders. Median relapse-free survival and overall survival were 6.7 and 7.1 months, respectively. The most frequent AEs were pyrexia (58%), febrile neutropenia (40%), and headache (31%). Three patients had cytokine release syndrome (all grade 1 or 2), and three patients had grade 3 neurologic events, one of which (aphasia) required temporary treatment interruption. There were no grade 4 or 5 neurologic events.

Conclusion

Single-agent blinatumomab showed antileukemia activity in high-risk patients with Ph⁺ ALL who had relapsed or were refractory to TKIs. AEs were consistent with previous experience in Ph⁺ ALL.

J Clin Oncol 35:1795-1802. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Philadelphia chromosome–positive (Ph⁺) acute lymphoblastic leukemia (ALL) constitutes approximately 25% of adult B-precursor ALL and is characterized by a reciprocal t(9;22) translocation that generates a chimeric fusion protein, BCR-ABL1, with dysregulated tyrosine kinase activity.

The presence of the Philadelphia chromosome has historically been associated with a very poor prognosis, but response and survival outcomes have significantly improved over the last decade. The addition of targeted tyrosine kinase inhibitors (TKIs) to induction and consolidation chemotherapy followed by allogeneic hematopoietic stem-cell transplantation (alloHSCT) has yielded > 90% complete remission (CR)¹ and up to

ASSOCIATED CONTENT



Appendix
DOI: <https://doi.org/10.1200/JCO.2016.69.3531>

DOI: <https://doi.org/10.1200/JCO.2016.69.3531>

60% 5-year overall survival (OS) rates.²⁻⁴ TKIs have also permitted de-escalation of chemotherapy without loss of response or event-free survival in older patients, and deep molecular responses may be achieved in some patients.⁴ A retrospective analysis in the post-transplantation setting has shown that use of prophylactic TKIs is associated with a significantly lower incidence of relapse among patients with Ph⁺ ALL.⁵ However, relapse remains clinically challenging and is frequently associated with resistance substitutions in the ABL kinase domain, particularly within the threonine 315 residue (T315I).^{6,7} Although alternative TKIs for salvage therapy may be effective in some patients,^{8,9} remission is short.^{10,11} In the first-line setting and in the context of alloHSCT, minimal residual disease (MRD), as assessed by reverse transcription quantitative polymerase chain reaction (RT-qPCR), may provide additional prognostic information for relapse.¹²⁻¹⁴ There is no current evidence of long-term survival mediated by TKIs after relapse.¹¹ Sequential TKI exposure can permit emergence of compound mutations that eventually confer resistance to all TKIs.¹⁵⁻¹⁷ Relapse can also occur without detection of *BCR-ABL1* mutations, suggesting that there are kinase-independent pathways to leukemic cell survival and proliferation. Therefore, alternative approaches beyond kinase inhibition that increase the potential for achieving CR and longer OS are needed in relapsed/refractory (R/R) Ph⁺ ALL.

Blinatumomab is a bispecific T-cell engager antibody construct that is designed to direct cytotoxic T cells to CD19-expressing B cells.¹⁸ A large phase II study confirmed anti-leukemia activity and tolerability of blinatumomab in adults with R/R Ph⁻ ALL and reported 43% CR or CR with partial hematologic recovery (CRh), 82% MRD response, and relapse-free survival (RFS) of 5.9 months.¹⁹ Patients with Ph⁺ ALL are distinct from those with Ph⁻ ALL and often have different baseline demographics that may have a significant impact on clinical outcomes. Here, we evaluated the efficacy and tolerability of single-agent blinatumomab in patients with R/R Ph⁺ ALL who progressed after or were intolerant to a second-generation or later TKI.

PATIENTS AND METHODS

Patients

This was an open-label, single-arm, multicenter, phase II study of blinatumomab in adults with R/R Ph⁺ ALL at 19 European and US centers. Eligible adults (age \geq 18 years) had Ph⁺ B-precursor ALL, had relapsed after or were refractory to at least one second-generation or later TKI (dasatinib, nilotinib, bosutinib, ponatinib), or were intolerant to second-generation or later TKIs and intolerant or refractory to imatinib. The Philadelphia chromosome was detected by cytogenetics, fluorescence in situ hybridization, and/or *BCR-ABL1* PCR at individual study sites. Additional eligibility requirements included $>$ 5% bone marrow blasts as determined by a central laboratory and an Eastern Cooperative Oncology Group status \leq 2. Key exclusion criteria were alloHSCT within 12 weeks before the start of blinatumomab treatment, active acute or chronic (grade 2 to 4) graft-versus-host disease, systemic treatment of graft-versus-host disease within 2 weeks before treatment start, history or presence of clinically relevant CNS pathology, active CNS ALL, and isolated extramedullary disease. Any TKI therapy, antitumor therapy other than blinatumomab, chronic systemic high-dose corticosteroid therapy, or other immunosuppressive therapies were prohibited during treatment. Each center's institutional review board or ethics committee approved the study; all patients provided written informed consent.

Study Procedures

Patients received blinatumomab as a continuous intravenous infusion at fixed stepwise doses (9 μ g/day in week 1 of cycle 1 followed by 28 μ g/day thereafter).^{19,20} Each treatment cycle included 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval. Patients received two initial cycles of blinatumomab to induce remission. CR was defined as \leq 5% bone marrow blasts, platelets $>$ 100,000/ μ L, and absolute neutrophil count $>$ 1,000/ μ L; CRh was defined as \leq 5% bone marrow blasts, platelets $>$ 50,000/ μ L, and absolute neutrophil count $>$ 500/ μ L. If CR/CRh was achieved, the patient could receive up to three additional cycles of blinatumomab as consolidation therapy, unless alloHSCT was scheduled earlier.

To reduce tumor burden and cytokine release syndrome (CRS), patients with a high baseline blast count as determined by a local laboratory ($>$ 50% bone marrow blasts or \geq 15,000/ μ L peripheral blast count) received prephase treatment with dexamethasone 10 mg/m² per day (for up to 5 days) up to a maximum of 24 mg/day (absolute). All patients were given dexamethasone 20 mg intravenously 1 hour before each cycle and dose step and within 1 hour before restarting treatment for dose interruptions. For dose interruptions that resulted from a neurologic event, patients received dexamethasone at least 24 mg/day, with stepwise reductions over 4 days. Intrathecal chemoprophylaxis (eg, methotrexate 12 to 15 mg, cytarabine 40 mg, and dexamethasone 4 mg or equivalent) was required before initiation of treatment and at the end of treatment cycles. Detailed descriptions regarding blinatumomab dose modifications, interruptions, and discontinuation are provided in the Appendix (online only).

Hematologic and molecular responses were assessed by bone marrow aspirate or biopsy on day 29 of each cycle by using a central reference laboratory. MRD response was determined by *BCR-ABL1* quantification only for patients achieving CR/CRh. Complete MRD response was defined as no detectable *BCR-ABL1* transcripts by allele-specific real-time qPCR with an internal *ABL* amplification control, as established by a central laboratory (LabCorp, Burlington, NC; assay sensitivity \geq 10⁻⁵; 0.00% *BCR-ABL1/ABL1*). *p190* and *p210* designation was based on determination of *e1a2* (*p190*) or *b2a2/b3a2* (*p210*) transcript levels from RT-qPCR performed on pretreatment bone marrow aspirates.²¹ Adverse events (AEs) and serious AEs, which were recorded from treatment start until at least 30 days after treatment end, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.²²

Statistical Methods

The primary end point was the proportion of patients who achieved CR/CRh during the first two cycles of blinatumomab treatment. Sample size was calculated for a Simon's two-stage design²³ based on a one-sided type I error of 0.025 and a power of 90% to detect the effective response rate assumption of \geq 30% over an ineffective treatment rate of \leq 10%.

Major secondary end points included MRD response rate during the first two cycles of treatment, RFS, OS, and alloHSCT after blinatumomab-induced remission. RFS was measured from the time of first CR/CRh to hematologic or extramedullary relapse or death resulting from any cause. OS was measured from the time of first blinatumomab dose to death resulting from any cause. Kaplan-Meier methods were used to estimate probability of RFS and OS over time; OS among MRD responders was evaluated using the landmark analysis approach to minimize bias that patients must survive to their first MRD assessment to be included.

RESULTS

Patient Characteristics

Between January 3, 2014, and May 20, 2015, 45 patients were enrolled and treated with blinatumomab. Median age was 55 years (range, 23 to 78 years). Forty-four percent of patients had relapsed after prior alloHSCT. Median baseline bone marrow blast percentage was 80% (range, 6% to 98%). At data cutoff (May 20,

2015), 23 patients (51%) remained in the study (21 were in follow-up, and two were still receiving treatment).

Eighty-four percent of patients had received ≥ 2 prior TKIs; 51% had received prior ponatinib (third-generation TKI; Table 1). All patients were either refractory to (56%), had relapsed on (33%), or exhibited disease progression after (11%) their prior TKI therapy; no patient had TKI intolerance listed as the reason for discontinuation of their prior TKI therapy. One patient had ALL resistant to imatinib and was never exposed to a second-generation or later TKI (protocol deviation).

Fifty-nine percent of patients had additional cytogenetic abnormalities. A subset of patients ($n = 10$) had both *p190* and *p210* transcripts, although in all patients, *p210* was 2.1- to 3.5-fold higher and thus designated as *p210*. Of 37 patients evaluable for TKI mutational analysis, 46% had *ABL1* kinase domain mutations, including the T315I mutation (27%; Table 1).

Response

The median number of blinatumomab cycles received was two (range, one to five). Thirty-six percent (95% CI, 22% to 51%) of

patients ($n = 16$) achieved CR/CRh within the first two cycles, with most patients ($n = 14$) achieving CR (Table 2). Among evaluable responders in cycle 1, 10 achieved CR before initiation of a second cycle, two achieved CRh, and two were without hematologic recovery. Two patients had inevaluable responses at the end of cycle 1; however, both achieved blast clearance by the end of cycle 2 (one with CR and one with CRh). Among nonresponders or those with progressive disease at the end of cycle 1, two achieved CR with incomplete hematologic recovery (CRi) at the end of cycle 2. The one patient who never received a second-generation or later TKI (protocol deviation) did not respond to treatment. Twelve (86%) of the 14 CR responders and both patients with CRh also achieved a complete MRD response; the remaining two responders had persistent measurable MRD and relapsed during subsequent cycles of therapy.

Patients achieved responses to blinatumomab regardless of prior TKI therapy: 47% had three or more prior TKIs and 35% had received prior ponatinib. Similarly, responses were also observed regardless of *ABL1* kinase domain mutational status (Fig 1). Specifically, among the 10 patients with the T315I mutation (nine of whom had received prior ponatinib), four (40%) responded, with all four CR/CRh responders also achieving a complete MRD response.

Subgroup analyses of response showed no statistically significant differences based on collected baseline features, including age and prior therapies, but the largest difference in median CR/CRh response was observed between the subgroups of $< 50\%$ and $\geq 50\%$ bone marrow blasts at baseline (64% [95% CI, 31% to 89%] and 27% [95% CI, 13% to 44%], respectively; Fig 1).

Survival

Median RFS was 6.7 months (95% CI, 4.4 to NE [not estimable] months), with a median follow-up of 9.0 months. Median RFS among the 14 patients who achieved a complete MRD response was 6.8 months (95% CI, 4.4 to NE months) with a median follow-up of 9.0 months, which was similar to that of the entire CR/CRh responder patient population; RFS was not significantly impacted when censoring for alloHSCT (Fig 2A). No difference in median RFS was observed between responders younger than age 55 years (5.5 months; 95% CI, 3.6 to NE months) and adults age 55 years or older (6.7 months; 95% CI, 3.8 to NE months). Of the 16 responders, seven (44%) were alive without relapse, eight (50%) had relapsed with a median time to relapse of 6.7 months (95% CI, 4.4 to NE months), and one patient died in CR after alloHSCT (133 days after achieving CR). Of the patients who had relapsed, three had relapsed during treatment (including two CR responders who did not achieve a complete MRD response), two relapsed without receiving alloHSCT, and three relapsed after receiving alloHSCT.

Median OS was 7.1 months (95% CI, 5.6 to NE months) with or without censoring for alloHSCT (Fig 2B), with a median follow-up of 8.8 months. Using a landmark OS analysis (landmark time point at the end of cycle 2 of blinatumomab treatment), median OS was not reached for the 18 patients who achieved a complete MRD response, with a median follow-up of 5.3 months. Among MRD nonresponders, the median OS was 3.9 months (95% CI, 3.0 to NE months).

alloHSCT

Of the 16 CR/CRh responders, seven (44%) proceeded to alloHSCT, including four who remained in continuous

Table 1. Patient Demographic and Clinical Characteristics at Baseline

Characteristic	Patients (N = 45)	
	No.	%
Sex		
Male	24	53
Female	21	47
Median age, years (range)	55 (23-78)	
Age group, years		
18 to < 55	22	49
≥ 55	23	51
Cytogenetics and molecular analyses*		
Philadelphia chromosome and other cytogenetic abnormalities	22/38	58
<i>ABL1</i> kinase domain mutations	17/37	46
T315I mutation	10/37	27
No. of prior TKI treatments†		
1	7	16
2	21	47
3	13	29
4	4	9
Prior TKI‡	45	100
Imatinib	25	56
Dasatinib	39	87
Nilotinib	16	36
Ponatinib	23	51
Prior alloHSCT		
Yes	20	44
No	25	56
Bone marrow blasts (central review)		
< 10%	2	4
10% to < 50%	9	20
50% to < 75%	6	13
$\geq 75\%$	28	62

Abbreviations: *ABL1*, Abelson murine leukemia viral oncogene homolog 1; alloHSCT, allogeneic hematopoietic stem-cell transplantation; TKI, tyrosine kinase inhibitor.

*Philadelphia chromosome was detected by cytogenetics/metaphase spread, fluorescence in situ hybridization, or *BCR-ABL1* polymerase chain reaction. Numerators indicate the number of patients in each subgroup, and denominators indicate the number of evaluable patients tested by a specific methodology.

†One patient had acute lymphoblastic leukemia that was resistant to imatinib and was never exposed to a second-generation or later TKI (protocol deviation).

‡Prior TKI use was not mutually exclusive.

Table 2. Response Outcomes During the First Two Cycles and Transplantation Realization

Outcome	Patients (n/N1)*	Proportion (%)	95% CI
Primary end point			
CR/CRh during the first two cycles	16/45	36	22 to 51
Philadelphia chromosome and other cytogenetic abnormalities	10/22	45	24 to 68
ABL1 kinase domain mutations	6/17	35	14 to 62
T315I mutation	4/10	40	12 to 74
<i>p190 BCR/ABL1</i> isoform†	10/26	39	20 to 59
<i>p210 BCR/ABL1</i> isoform†	5/16	31	11 to 59
No. of prior TKI therapies			
1	1/7	14	< 1 to 58
2	7/21	33	15 to 57
≥ 3	8/17	47	23 to 72
Prior ponatinib	8/23	35	16 to 57
Prior alloHSCT	5/20	25	9 to 49
Age 18 to < 55 years	8/22	36	17 to 59
Age ≥ 55 years	8/23	35	16 to 57
Bone marrow blasts < 50%	7/11	64	31 to 89
Bone marrow blasts ≥ 50%	9/34	27	13 to 44
Secondary end points			
Best response during the first two cycles			
CR	14/45	31	18 to 47
CRh	2/45	4	1 to 15
Complete MRD response‡	14/16	88	62 to 98
alloHSCT after blinatumomab-induced remission§	4/16	25	7 to 52
Age 18 to < 55 years	2/8	25	3 to 65
Age ≥ 55 years	2/8	25	3 to 65
100-day post-transplant mortality rate§	1/4	25	4 to 87

Abbreviations: alloHSCT, allogeneic hematopoietic stem-cell transplantation; *ABL1*, Abelson murine leukemia viral oncogene homolog 1; *BCR*, breakpoint cluster region; CR, complete remission; CRh, CR with partial hematologic recovery; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor.

*n/N1, number of responders/total number of patients with evaluable data under each category.

†Isoform designation was determined by MRD status at baseline by using reverse transcription quantitative polymerase chain reaction (PCR) on pretreatment bone marrow aspirates. A subset of patients (n = 10) had both *p190* and *p210* transcripts, although in all of these patients, *p210* was 2.1- to 3.5-log higher; the transcripts were thus assigned a designation of *p210*. Further details are provided in Patients and Methods.

‡Among CR/CRh responders only; includes all four CR/CRh patients with the T315I mutation.

§For patients who received alloHSCT during blinatumomab-induced remission without other antileukemia therapy. Complete MRD response was defined as no detectable PCR amplification of *BCR-ABL1* genes (sensitivity ≥ 10⁻⁵) as assessed by a central laboratory.

blinatumomab-induced remission without other antileukemia therapy and three who received blinatumomab with other antileukemia therapy. Of the latter three patients, one received other anticancer therapy prior to alloHSCT and remained in remission, and two had relapsed before proceeding to alloHSCT. The 100-day mortality was 25% (one death) among the four patients who received alloHSCT while in blinatumomab-induced remission (Table 2). One responder received a second alloHSCT after blinatumomab-induced remission.

AEs

Among the 45 patients who received blinatumomab, the most common treatment-emergent AEs included pyrexia (58%), febrile neutropenia (40%), and headache (31%) (Table 3). Thirty-seven patients (82%) had grade ≥ 3 treatment-emergent AEs, the most frequent of which were febrile neutropenia (27%), thrombocytopenia (22%), and anemia (16%). Twenty patients (44%) had grade ≥ 3 treatment-emergent AEs that were considered possibly related to blinatumomab (per investigator's assessment), most commonly febrile neutropenia and increased levels of alanine aminotransferase (11% each). Thirty-three patients (73%) had grade 3 AEs, and 16 patients (36%) had grade 4 AEs. Five patients (none of whom achieved CR/CRh) had fatal AEs: multiorgan

failure (age 55 years), infection (sepsis, age 40 years; septic shock, age 33 years), cerebral hemorrhage (age 25 years), and respiratory failure (age 42 years). One fatal AE (septic shock) was considered treatment-related by the investigator. This patient had disease persistence and died 13 days after protocol-directed discontinuation of blinatumomab.

CRS occurred in three patients (all grade 1 or 2), but none of the CRS events resulted in treatment discontinuation or interruption. Twenty-one patients (47%) experienced neurologic events, most commonly paresthesia (13%), confusional state (11%), dizziness (9%), and tremor (9%; Table 3). Three patients had grade 3 neurologic events (aphasia, hemiplegia, and nervous system disorder or depressed level of consciousness). However, only one patient required treatment interruption (aphasia). No patients had grade 4 or 5 neurologic events. All but one of the grade 3 neurologic events resolved, with a maximum duration of 15 days.

DISCUSSION

In this primary analysis of a phase II study in adults with heavily pretreated R/R Ph⁺ ALL, treatment with single-agent blinatumomab resulted in a 36% CR/CRh rate within the first two cycles,

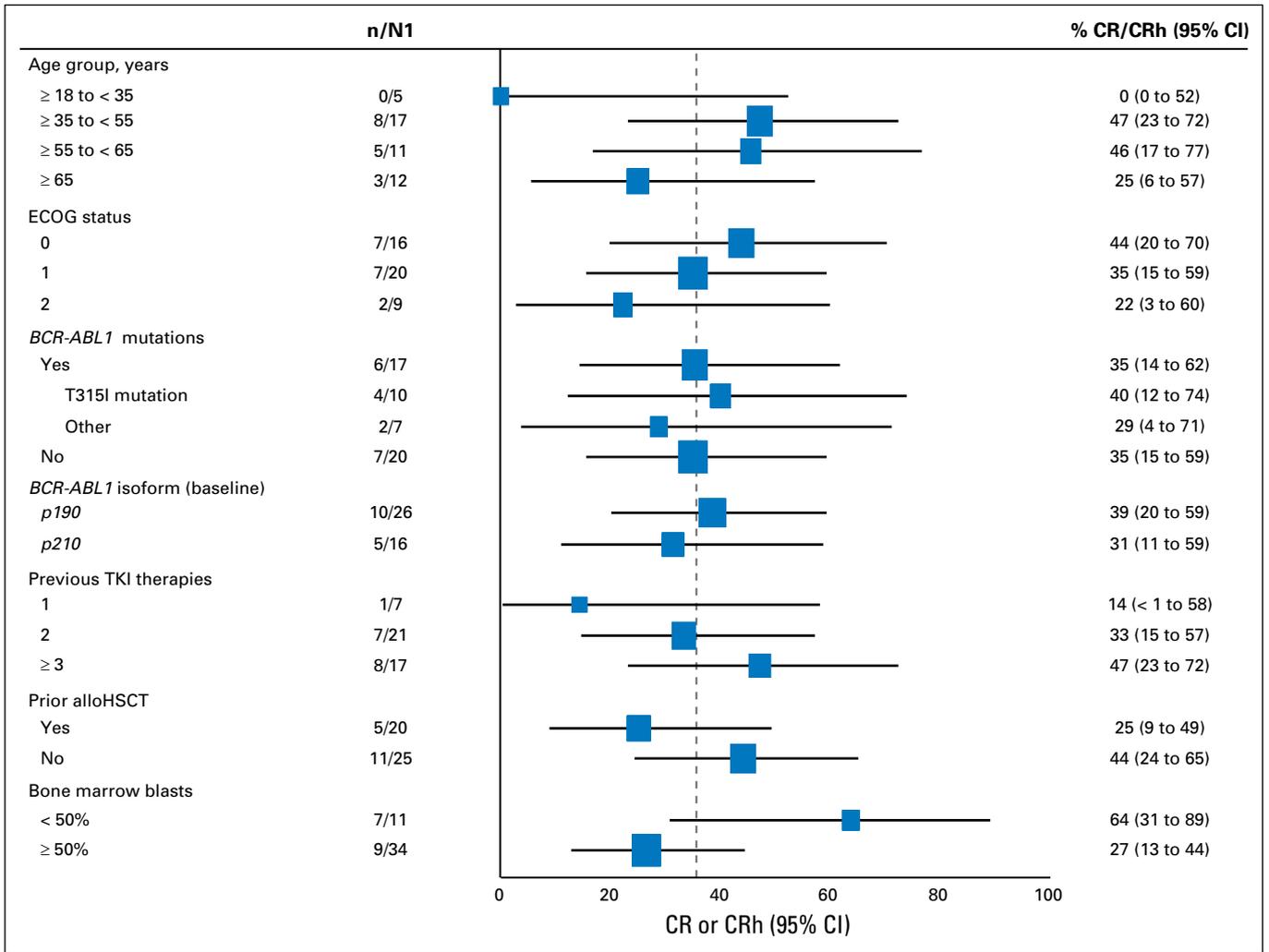


Fig 1. Overall responses (complete remission/complete remission with partial hematologic recovery [CR/CRh]) during the first two treatment cycles among prespecified patient subgroups. The dashed line represents the point estimate for CR/CRh for the entire patient population, and the box size indicates the relative population weight. n/N1, number of responders/total number of patients with evaluable responses within each category. alloHSCT, allogeneic hematopoietic stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

with 88% of responders also achieving a complete MRD response. Median RFS and OS were 6.7 and 7.1 months, respectively. AEs were consistent with those previously observed for blinatumomab in the setting of R/R Ph⁻ ALL. As predicted by the mechanism of action of blinatumomab, these data demonstrate that hematologic and molecular responses were independent of *BCR-ABL1* status, including the presence of the T315I mutation. More than one third of patients (38%) had at least one *BCR-ABL1* mutation, including 10 with the T315I mutation, a recognized negative prognostic factor, even for treatment with ponatinib and/or alloHSCT.^{24,25} In fact, the T315I mutation along with additional kinase domain mutations have been associated with poor treatment responses and outcomes, possibly as a result of increased genetic heterogeneity among leukemic subclones that may lead to TKI-based drug resistance.²⁶

All patients had heavily pretreated R/R Ph⁺ ALL, with nearly half (47%) having failed two prior TKI treatments and one third (38%) having failed three or more prior TKI treatments; 62% had ≥ 75% blasts at baseline; or 44% had relapsed

after alloHSCT. Notably, these data show that the proportion of patients who achieved CR/CRh was in line with that reported for less heavily pretreated populations or those in the Ph⁻ setting (36% v 43% in Ph⁻ ALL), with similar or better response duration than that observed with TKI therapies.²⁷⁻²⁹ Although not statistically significant, a higher CR/CRh rate was observed in patients with a low (< 50%) blast percentage at baseline compared with patients who had a high (≥ 50%) blast percentage (Fig 1), a trend consistent with blinatumomab treatment in the Ph⁻ setting.¹⁹ Interestingly, the five patients younger than age 35 years did not respond, which may be the result of higher disease burden (eg, ≥ 50% bone marrow blasts) and disease aggressiveness (eg, shorter median time from initial diagnosis to treatment and from first prior alloHSCT to relapse) among these patients. Given the very small number of patients, however, this is highly exploratory and speculative. Tumor load may be a marker of disease aggressiveness of leukemia, which may or may not be modified by cytoreduction. Alternatively, any potential association between tumor load and response may

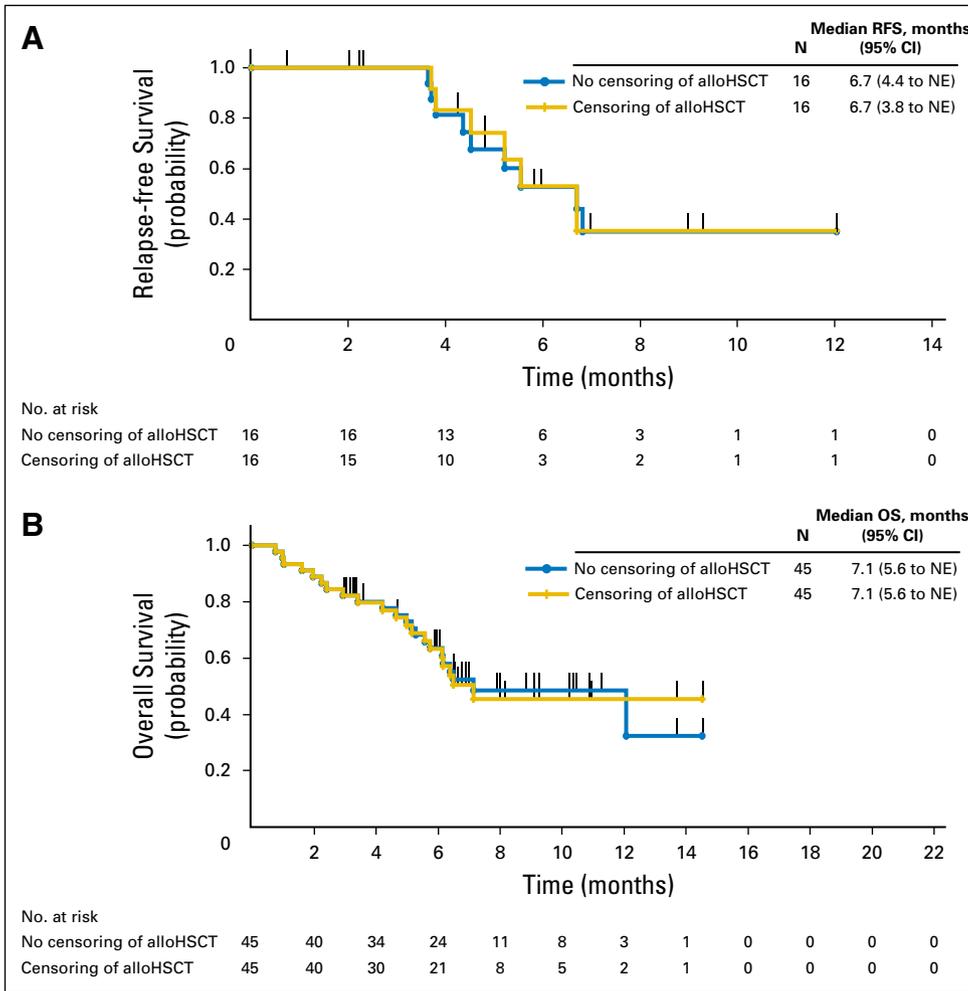


Fig 2. (A) Relapse-free survival (RFS) and (B) overall survival (OS) with and without censoring at time of allogeneic hematopoietic stem-cell transplantation (alloHSCT). NE, not estimable.

reflect an unfavorable effector-to-target ratio, which could be amenable to intervention. In a randomized trial of blinatumomab versus standard chemotherapy for R/R Ph⁻ ALL, the survival benefit of blinatumomab was observed even among patients with high bone marrow blasts.³⁰

Therapeutic options for patients with R/R Ph⁺ ALL are scarce and restricted to untargeted therapies such as combination chemotherapy, interferon-alpha, or omacetaxine mepesuccinate, which provide only short-term and primarily hematologic responses with poor cytogenetic efficacy.³¹⁻³³ For eligible patients with Ph⁺ ALL and the T315I mutation, alloHSCT remains the best treatment option, providing acceptable OS rates and, in some cases, long-term control of the malignancy. Because of its TKI-independent mechanism of action, blinatumomab can overcome the T315I resistance mechanism to induce directed immune-mediated cell death of Ph⁺ blasts. However, it is unknown whether *BCR-ABL1*-independent signaling in patients with ALL that is refractory to TKIs may also predispose patients to be resistant to blinatumomab treatment. Here, response rates to blinatumomab and RFS were found to be similar between younger (age younger than 55 years) and older (age 55 years or older) adults, which was also reported for Ph⁻ ALL,³⁴ suggesting a benefit for older adults who are typically ineligible for alloHSCT or have

increased comorbidities. Moreover, blinatumomab induced complete MRD responses in 88% of Ph⁺ patients who achieved CR/CRh, suggesting that blinatumomab is an effective bridge to transplantation.

Because duration of response to TKIs is short in Ph⁺ ALL,³⁵ consolidative alloHSCT remains the standard of care for eligible patients, and achievement of CR and MRD response is desirable for stem-cell transplantation. Ph⁺ patients, such as those treated in this trial, tend to be older and likely ineligible for myeloablative conditioning regimens.³⁶ However, these patients may be eligible to receive reduced-intensity conditioning regimens, and recent reports suggest that MRD status has prognostic relevance in this setting, presumably because of greater reliance on graft-versus-leukemia effects and less reliance on cytoreduction after the conditioning regimen.^{8,13,37} Recurrence of leukemia after transplantation in patients with incomplete MRD response also raises the necessity for rigorous and standard MRD monitoring of these patients, as is currently done in pediatric and cooperative studies in the adult ALL setting.^{38,39}

In summary, these data demonstrate efficacy of single-agent blinatumomab in R/R Ph⁺ ALL, suggesting a possible future role in Ph-like ALL and combination therapies with TKIs for this disease setting.

Table 3. AEs and Neurologic Events (regardless of causality)

Event	Grade							
	Any		1 to 2		3		4	
	No.	%	No.	%	No.	%	No.	%
Patients with AEs	45	100	45	100	33	73	16	36
AEs of grade ≥ 3 occurring in $\geq 5\%$ of patients*								
Pyrexia	26	58	24	53	5	11	0	0
Febrile neutropenia	18	40	9	20	12	27	0	0
Headache	14	31	13	29	3	7	0	0
Anemia	13	29	9	20	7	16	1	2
Thrombocytopenia	10	22	4	9	5	11	7	16
Pain	7	16	4	9	4	9	0	0
Increased aspartate aminotransferase	6	13	3	7	3	7	2	4
Increased alanine aminotransferase	5	11	1	2	5	11	0	0
Device-related infection	5	11	3	7	3	7	0	0
Neutropenia	3	7	0	0	0	0	3	7
Patients with neurologic events	21	47	20	44	3	7	0	0
Neurologic events occurring in two or more patients								
Paresthesia	6	13	6	13	0	0	0	0
Confusional state	5	11	5	11	0	0	0	0
Dizziness	4	9	4	9	0	0	0	0
Tremor	4	9	4	9	0	0	0	0
Aphasia	2	4	1	2	1	2	0	0
Cerebellar syndrome	2	4	2	4	0	0	0	0
Memory impairment	2	4	2	4	0	0	0	0
Nervous system disorder	2	4	1	2	1	2	0	0

Abbreviation: AE, adverse event.

*Cutoff based on grade ≥ 3 AEs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

- Fielding AK: Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Hematology (Am Soc Hematol Educ Program)* 2011: 231-237, 2011
- Fielding AK: Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: A broader range of options, improved outcomes, and more therapeutic dilemmas. *Am Soc Clin Oncol Educ Book* 2015:e352-e359, 2015
- Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al: Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: A GRAALL study. *Biol Blood Marrow Transplant* 19:150-155, 2013
- 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* 125:3711-3719, 2015

- Brissot E, Labopin M, Beckers MM, et al: Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica* 100:392-399, 2015
- Soverini S, Colarossi S, Gnani A, et al: Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. *Haematologica* 92:401-404, 2007
- Maino E, Sancetta R, Viero P, et al: Current and future management of Ph/BCR-ABL positive ALL. *Expert Rev Anticancer Ther* 14:723-740, 2014
- Ottmann OG, Pfeifer H: Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *Hematology (Am Soc Hematol Educ Program)* 2009:371-381, 2009
- Leoni V, Biondi A: Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia. *Haematologica* 100:295-299, 2015
- Lilly MB, Ottmann OG, Shah NP, et al: Dasatinib 140 mg once daily versus 70 mg twice daily

in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. *Am J Hematol* 85:164-170, 2010

- Cortes JE, Kim DW, Pinilla-Ibarz J, et al: A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med* 369:1783-1796, 2013
- Radich JP: Molecular measurement of minimal residual disease in Philadelphia-positive acute lymphoblastic leukaemia. *Best Pract Res Clin Haematol* 15:91-103, 2002
- Ravandi F, Jorgensen JL, Thomas DA, et al: Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. *Blood* 122:1214-1221, 2013
- Scheuring UJ, Pfeifer H, Wassmann B, et al: Serial minimal residual disease (MRD) analysis as a predictor of response duration in Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL) during imatinib treatment. *Leukemia* 17:1700-1706, 2003
- Miller GD, Bruno BJ, Lim CS: Resistant mutations in CML and Ph(+)/ALL: Role of ponatinib. *Bio-logsics* 8:243-254, 2014

16. Zabriskie MS, Eide CA, Tantravahi SK, et al: BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. *Cancer Cell* 26:428-442, 2016
17. Deininger MW, Hodgson JG, Shah NP, et al: Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. *Blood* 127:703-712, 2016
18. Bargou R, Leo E, Zugmaier G, et al: Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. *Science* 321:974-977, 2008
19. 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* 16:57-66, 2015
20. Topp MS, Gökbuget N, Zugmaier G, et al: Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol* 32:4134-4140, 2014
21. van Rhee F, Hochhaus A, Lin F, et al: p190 BCR-ABL mRNA is expressed at low levels in p210-positive chronic myeloid and acute lymphoblastic leukemias. *Blood* 87:5213-5217, 1996
22. National Cancer Institute: NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Bethesda, MD, National Cancer Institute, 2014
23. Simon R: Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 10:1-10, 1989
24. Nicolini FE, Basak GW, Soverini S, et al: Allogeneic stem cell transplantation for patients harboring T315I BCR-ABL mutated leukemias. *Blood* 118:5697-5700, 2011
25. Soverini S, Gnani A, Colarossi S, et al: Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. *Blood* 114:2168-2171, 2009
26. Parker WT, Yeung DT, Yeoman AL, et al: The impact of multiple low-level BCR-ABL1 mutations on response to ponatinib. *Blood* 127:1870-1880, 2016
27. Ottmann OG, Larson RA, Kantarjian HM, et al: Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia* 27:1411-1413, 2013
28. Ottmann O, Dombret H, Martinelli G, et al: Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: Interim results of a phase 2 study. *Blood* 110:2309-2315, 2007
29. Cortes JE, Kantarjian H, Shah NP, et al: Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med* 367:2075-2088, 2012
30. Kantarjian H, Stein A, Gökbuget N, et al: Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 376:836-847, 2017
31. Cortes-Franco J, Khoury HJ, Nicolini FE, et al: Safety and efficacy of subcutaneous-administered omacetaxine mepesuccinate in imatinib-resistant chronic myeloid leukemia (CML) patients who harbor the BCR-ABL T315I mutation: Results of an ongoing multicenter phase 2/3 study. *Blood* 114:644, 2009 (abstr)
32. Cortes J, Talpaz M, Bixby D, et al: A phase I trial (AP 24534) in patients with refractory chronic myelogenous leukemia (CML) and other hematologic malignancies: Emerging safety and clinical response findings. *Blood* 116:210, 2010 (abstr)
33. Kantarjian HM, DeAngelo DJ, Stelljes M, et al: Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 375:740-753, 2016
34. Kantarjian HM, Stein AS, Bargou RC, et al: Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: Results from two phase 2 studies. *Cancer* 122:2178-2185, 2016
35. Eide CA, O'Hare T: Chronic myeloid leukemia: Advances in understanding disease biology and mechanisms of resistance to tyrosine kinase inhibitors. *Curr Hematol Malig Rep* 10:158-166, 2015
36. Goldstone AH, Richards SM, Lazarus HM, et al: In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: Final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 111:1827-1833, 2008
37. Bassan R, Spinelli O, Oldani E, et al: Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood* 113:4153-4162, 2009
38. Spinelli O, Peruta B, Tosi M, et al: Clearance of minimal residual disease after allogeneic stem cell transplantation and the prediction of the clinical outcome of adult patients with high-risk acute lymphoblastic leukemia. *Haematologica* 92:612-618, 2007
39. Bassan R, Spinelli O, Oldani E, et al: Different molecular levels of post-induction minimal residual disease may predict hematopoietic stem cell transplantation outcome in adult Philadelphia-negative acute lymphoblastic leukemia. *Blood Cancer J* 4:e225, 2014

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Support

Supported by Amgen.

Prior Presentation

Presented in part as an oral presentation at the 57th American Society of Hematology Annual Meeting and Exposition, Orlando, FL, December 5-8, 2015.



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Acknowledgment

We thank Heinz Horst, MD, PhD (Department of Internal Medicine II), and Wolfram Klapper, MD (Department of Pathology), University Hospital Schleswig-Holstein, Campus Kiel, Germany, for providing expert analysis of cytomorphology and histopathology, respectively, and Janice Y. Ahn, PhD, (Amgen) for medical writing assistance in the preparation of this manuscript.

Appendix

METHODS

Dose modifications, interruptions, and discontinuation. Blinatumomab was temporarily or permanently reduced to 9 $\mu\text{g}/\text{day}$, if necessary, on the basis of the investigator's judgment for reasons of safety. Patients with dose reductions had the option to receive the higher dose level of 28 $\mu\text{g}/\text{day}$ once the adverse event (AE; except for neurologic events) resolved to at least grade 1 for ≥ 7 days. Dexamethasone pretreatment was required for all patients who restarted blinatumomab treatment. For patients with signs of cytokine release syndrome, oral or intravenous dexamethasone 8 mg was given three times per day for up to 3 days and reduced stepwise over 4 days. For grade ≥ 3 cytokine release syndrome, tumor lysis syndrome, and disseminated intravascular coagulation/coagulopathy, treatment was interrupted until the event resolved to at least grade 1. For grade ≥ 3 infections, blinatumomab was interrupted until the infection was adequately controlled or resolved per investigator opinion, and then allowed to restart at the lowest starting dose (9 $\mu\text{g}/\text{day}$). Blinatumomab was permanently discontinued for grade 4 AEs that were possibly related to blinatumomab or for AEs that lasted 2 weeks or longer. For grade ≥ 3 neurologic events, blinatumomab was stopped immediately, and the patient was assessed by physical examination, vital signs, and safety laboratories. To exclude potential infectious causes, cerebrospinal fluid was collected and assessed by cytology, cell count, B- and T-cell measurements, and viral studies. For grade 3 neurologic events or serious AEs leading to treatment interruption, treatment was restarted no earlier than 72 hours after stopping infusion but within 2 weeks.