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Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) following allogeneic hematopoietic stem cell transplantation (alloHSCT) have a poor prognosis, and alternative therapies are needed for this patient population. Blinatumomab, a bispecific T cell engager immunotherapy, was evaluated in an open-label, single-arm, phase II study of adults with R/R Philadelphia chromosome-negative B cell precursor ALL and resulted in a rate of complete remission (CR) or CR with partial hematologic recovery of peripheral blood counts (CRh) of 43% within 2 treatment cycles. We conducted an exploratory analysis to determine the efficacy and safety of blinatumomab in 64 patients who had relapsed following alloHSCT before enrollment in the phase II study. Forty-five percent of the patients (29 of 64) achieved a CR/CRh within the first 2 cycles of treatment, 22 of whom had a minimal residual disease (MRD) response (including 19 with a complete MRD response). After 1 year and 3 years of follow-up, the median relapse-free survival was 7.4 months for patients who achieved CR/CRh in the first 2 cycles, and the median overall survival was 8.5 months; overall survival rate (Kaplan-Meier estimate) was 36% at 1 year and 18% at 3 years. Grade 3 and 4 adverse events were reported in 20 patients (31%) and 28 patients (44%), respectively, with grade 3 and 4 neurologic events in 8 and 2 patients, respectively, and grade 3 cytokine release syndrome in 2 patients. Eight patients had fatal adverse events, including 5 due to infections. Seven patients had grade $\leq$ 3 graft-versus-host disease during the study, none of which resulted in the discontinuation of blinatumomab or hospitalization. Our data suggest that blinatumomab is an effective salvage therapy in this patient population.

INTRODUCTION

The outcomes of patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) following allogeneic hematopoietic stem cell transplantation (alloHSCT) are poor. A retrospective analysis of adults with ALL who relapsed after first alloHSCT and received salvage therapies, including a second HSCT, donor lymphocyte infusion with or without previous chemotherapy, radiation therapy, cytoreductive chemotherapy, mild chemotherapy, or palliative care, showed 1- and 2-year overall survival rates of 17% and 10%, respectively [1]. Overall survival rates from a similar analysis were 16% at 2 years and 8% at 5 years [2]. Two studies that focused on outcomes of second alloHSCT found overall survival rates of 23% at 1 year [3] and 11% and 35% at 3 years [3,4]. Thus, there is a need for more effective salvage therapies for patients with ALL who relapse after alloHSCT.

CD19 is expressed in almost all (> 90%) tested B lineage ALL cells [5,6] and is a target for immunotherapy in ALL. Blinatumomab is a bispecific T cell engager (BiTE) immunotherapy

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Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.
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with dual specificity for CD19 and CD3 [7,8]. Blinatumomab simultaneously binds $CD3^+$ cytotoxic T cells and $CD19^+$ B cells and redirects T cells to lyse malignant and normal B cells [7].

In a phase II study of 189 adults with R/R Philadelphia chromosome (Ph)-negative B cell precursor ALL, treatment with single-agent blinatumomab resulted in a rate of complete remission (CR) or CR with partial hematologic recovery of peripheral blood counts (CRh) of 43% within the first 2 cycles of treatment [9]. The median relapse-free survival was 5.9 months, and median overall survival was 6.1 months [9].

In the present exploratory analysis, we evaluated the efficacy and safety of blinatumomab in the 64 patients who had relapsed following alloHSCT before enrollment in the phase II blinatumomab study.

METHODS

Study Design and Patients

Details of the design of the phase II study and study participants have been published previously [9]. In brief, this open-label, single-arm, phase II study was conducted in Europe and the United States. For the current analysis, eligible patients were age ≥18 years with R/R Ph-negative B cell precursor ALL who had relapsed following alloHSCT before enrollment in the study; alloHSCT must have been performed at least 3 months before the start of treatment. Additional eligibility criteria included ≥10% bone marrow blasts with or without measurable extramedullary disease, Eastern Cooperative Oncology Group performance status of ≤2, no active acute (grade II-IV) or active chronic graft-versus-host disease (GVHD) or systemic treatment for GVHD within 2 weeks before treatment start, and no history or presence of clinically relevant central nervous system (CNS) pathology. This study is registered at ClinicalTrials.gov (NCT 01466179).

Patients received up to 5 cycles of blinatumomab with an end-of-study visit 30 days after the last treatment cycle and efficacy follow-up visits at 3, 6, 9, 12, 18, and 24 months after the start of treatment. Blinatumomab was administered by continuous i.v. infusion at 9 μg/day for the first 7 days of the cycle 1, 28 μg/day from day 8 through the end of cycle 1, and 28 μg/day in the subsequent cycles. A cycle consisted of continuous i.v. infusion of blinatumomab over 4 weeks, followed by a 2-week treatment-free interval. Blinatumomab treatment was interrupted if a patient experienced a grade 3 CNS-related adverse events or other clinically relevant grade 3 or 4 adverse events and was restarted when the adverse event had resolved to grade 1 or baseline. Blinatumomab was discontinued if treatment was interrupted for more than 2 weeks due to an adverse event, a grade 4 CNS event, or at least 2 seizures.

Patients who achieved CR or CRh within the first 2 cycles of treatment could receive up to 3 additional cycles of consolidation treatment and could also undergo alloHSCT. Patients with hematologic relapse during the follow-up period (at least 3 months after the completion of treatment) could receive up to 3 additional cycles of treatment (9 μg/day for the first 7 days) for a maximum of 8 cycles.

Outcomes of Patients with Previous AlloHSCT

Study endpoints included CR/CRh rate within the first 2 cycles of treatment with blinatumomab, alloHSCT after CR/CRh, minimal residual disease (MRD) response (prespecified exploratory endpoint), incidence of adverse events, relapse-free survival, and overall survival.

CR was defined as bone marrow blasts ≤5% with no evidence of disease and full recovery of peripheral blood counts (platelet count >100,000/μL and absolute neutrophil count >1,000/μL). CRh was defined as bone marrow blasts ≤5% with no evidence of disease and partial recovery of peripheral blood counts (platelet count >50,000/μL and absolute neutrophil count >500/μL).

MRD response was defined as MRD $<10^{-4}$ leukemic cells as measured by polymerase chain reaction (PCR) at a central laboratory. Complete MRD response, a subset of MRD response, was achieved if no PCR amplification of individual rearrangements of immunoglobulin genes or T cell receptor genes was detected. Assay requirements were sensitivity of at least 10^{-4} and quantitative measurement range of at least 10^{-4}.

Determination of T Cell Subsets at Study Baseline

Samples of lymphocyte subsets were obtained at screening from all patients to investigate any effect of previous transplantation on the number of T cells at study baseline. Flow cytometry was used to determine the numbers of $CD4^+$ and $CD8^+$ T cells, including $CD4^+$ naïve T cells, central memory T cells (T_{CM} cells), and effector memory T cells (T_{EM} cells). and $CD8^+$ naïve T cells, T_{CM} cells, T_{EM} cells, and effector memory RA T cells (T_{EMRA} cells).

Statistical Analysis

Patients who had undergone alloHSCT before enrollment into the phase II study were included in the exploratory analysis. The proportion of patients who achieved responses (with 95% confidence intervals [CIs]) are presented; relapse-free survival and overall survival are described with Kaplan-Meier estimates. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC).

The analysis of relapse-free survival was restricted to patients who had CR or CRh and was calculated relative to the date of bone marrow aspiration when CR or CRh was first achieved. The date of detection of hematologic relapse, extramedullary disease, or death due to any cause, whichever was earlier, served as the event date for relapse-free survival. A patient with CR or CRh who did not have hematologic relapse and did not die was censored on the date of the last available bone marrow aspiration or the last survival follow-up visit, whichever was later. Overall survival was calculated relative to the start of blinatumomab treatment. Patients alive were censored on the last documented visit date or last contact date.

RESULTS

Patients and Treatment

Sixty-four of the 189 patients enrolled and treated with blinatumomab in the phase II study had relapsed after previous alloHSCT, of whom 67% were male and 63% were age <35 years (Table 1). Similar proportions of patients had either a matched sibling (47%) or an unrelated (50%) donor (20.3% matched, 12.5% unmatched, 3.1% cord blood, and 31% with unavailable data). Fifty-five patients (86%) had received salvage therapy after alloHSCT and before treatment with blinatumomab. Thirty-four patients (53%) had received a myeloablative conditioning regimen, 10 (16%) had received a reduced-intensity conditioning regimen, 6 (9%) had undergone 2 previous transplantations before receiving blinatumomab and had received myeloablative and reduced-intensity conditioning regimens, and 14 (22%) had received regimens that were not specified or not available. Twelve patients (19%) were reported to have received antithymocyte globulin (ATG) therapy as part of their conditioning regimen, between 103 and 574 days before enrollment.

As of the data cutoff date (June 20, 2014), 50 patients (78%) had discontinued the study, including 47 (73%) who had died, 1 (1.6%) who was lost to follow-up, and 2 (3.1%) who withdrew from the study. Causes of death were disease progression in 33 patients (53%); sepsis in 5 patients (8%), including 2 with fatal adverse events of sepsis; respiratory insufficiency/failure in 4 patients (6%); brain hemorrhage, gastrointestinal hemorrhage, and grade IV GVHD in 1 patient each (1.6%): and unknown cause in 2 patients (3.1%).

Efficacy of Blinatumomab in Patients with Previous AlloHSCT

Forty-five percent of patients (29 of 64) with previous alloHSCT achieved a CR/CRh within the first 2 cycles of treatment (Table 2). The rate of CR/CRh was 43% (54 of 125) among patients who did not have previous alloHSCT.

Among the patients with previous alloHSCT, CR/CRh within the first 2 cycles was achieved by 6 of 12 patients (50%) who received previous ATG, compared with 23 of 52 patients (44%) who did not receive previous ATG. Among the 29 patients with previous HSCT who achieved a CR/CRh within the first 2 cycles, 7 underwent subsequent alloHSCT after treatment with blinatumomab while in remission, and 3 underwent subsequent alloHSCT after relapse. In addition, 22 of the 29 patients who achieved CR/CRh within the first 2 cycles had an MRD response, including 19 with a complete MRD response (Table 2). MRD response rates were similar in patients who did not undergo alloHSCT before receiving blinatumomab (Supplementary Table S1).

Among the 5 patients who died of sepsis during the study, 3 did not respond to blinatumomab, 1 had an unknown response

Table 1
Demographic Data and Baseline Disease Characteristics of the Patients with Previous AlloHSCT (N = 64)

Characteristic	Value
Male sex, n (%)	43 (67)
Age, yr, median (range)	32 (19–74)
Age group, n (%)	
18 to <35 yr	40 (63)
35 to <65 yr	22 (34)
≥65 yr	2 (3)
Donor type, n (%)	
Haploidentical	2 (3)
Sibling	30 (47)
Unrelated	32 (50)
Degree of matching	
Matched*	13 (20)
Mismatched†	8 (12)
Cord blood (both donors 4/6 match)	1 (2)
Unavailable	10 (16)
Previous salvage after alloHSCT, before blinatumomab, n (%)	55 (86)
Number of previous salvage therapies before blinatumomab, n (%)	
None	9 (14)
1	23 (36)
2	12 (19)
≥3	20 (31)
Conditioning regimens for previous alloHSCT, n (%)	
Myeloablative	34 (53)
Reduced intensity	10 (16)
Myeloablative and reduced intensity‡	6 (9)
Not specified/not available	14 (22)
ATG therapy as part of conditioning regimen, n (%)	12 (19)
History of GVHD, n (%)	19 (30)
Chronic	4 (6)
Acute	1 (2)
Not specified	14 (22)
Time from previous alloHSCT to first blinatumomab dose, mo, median (range)	9.7 (3.3-40.2)
Number of previous relapses§, n (%)	
1	23 (36)
2	24 (38)
>2	17 (27)
Baseline bone marrow blast category (central laboratory), n (%)	
10% to <50%	19 (30)
≥50%	42 (66)
Lymphocyte count, × 10^9/L, mean (SD)	7.6 (15.8)
Neutrophil count, × 10^9/L, mean (SD)	2.1 (2.7)

* Matched patients: 10/10, 8 patients; 11/11, 1 patient; fully matched, 4 patients.
† Mismatched patients: 9/10, 4 patients; 8/10, 2 patients; 4/6, 1 patient; and mismatched (not specified), 1 patient.
‡ Underwent 2 transplantations before receiving blinatumomab.
§ Before receiving blinatumomab.

to blinatumomab, and 1 developed sepsis after alloHSCT. Among the 4 patients who died of respiratory insufficiency/failure, 1 relapsed and 3 did not respond to blinatumomab. The patient who died of brain hemorrhage had relapsed, the patient who died of gastrointestinal hemorrhage had not responded to blinatumomab, and the patient who had grade IV acute GVHD underwent an on-study alloHSCT and died 6 months after completing blinatumomab treatment.

Table 2
Clinical Outcomes in the Patients with Previous AlloHSCT

Outcome	Value
Hematologic response (N = 64), n (%) (95% CI)	
CR/CRh in first 2 cycles	29 (45) (33-58)
CR in first 2 cycles	18 (28) (18-41)
CRh in first 2 cycles	11 (17) (9-29)
Blast-free hypoplastic/aplastic bone marrow	4 (6) (2-15)
Progressive disease	12 (19) (10-31)
Failure to respond to therapy	12 (19) (10-31)
No response assessment	7 (11)
Molecular response*, n (%) (N = 29)	
MRD response	22 (76)
Complete MRD response	19 (66)
MRD nonresponse	4 (14)
No MRD response assessment	3 (10)

* Based on 29 patients who had achieved CR/CRh within the first 2 cycles.

The median relapse-free survival was 7.4 months (95% CI, 5.0 to 10.1 months) in patients who achieved CR/CRh in the first 2 cycles, with a median duration of follow-up of 12.4 months (95% CI, 11.5 to 18.0 months) (Table S2; Figure 1A). The median relapse-free survival was 11.4 months (95% CI, 2.3 to 24.9 months) in patients who achieved CR/CRh and had 1 previous relapse and 6.2 months (95% CI, 3.8 months to not estimable [NE]) for patients who had at least 2 previous relapses (Supplementary Table S2). The median overall survival was 8.5 months (95% CI, 4.2 to 11.2 months), with a median follow-up of 16.6 months (95% CI, 12.4 to 23.3 months) (Supplementary Table S2; Figure 1B). Similar to relapse-free survival, overall survival was approximately twice as long for patients with 1 previous relapse compared with patients with at least 2 previous relapses (14.3 months [95% CI, 4.0 to 23.1 months] versus 6.5 months [95% CI, 3.5 to 9.3 months]) (Supplementary Table S2). The median relapse-free survival and overall survival at 3 years was 7.4 months (95% CI, 5.0 to 10.1 months) and 8.5 months (95% CI, 4.2 to 1.2 months), respectively (median follow-up: relapse-free survival, 34.9 months [95% CI, 34.4 to 35.6 months]; overall survival, 36.0 months [95% CI, 35.6 to 36.4 months]) (Supplementary Figure 1). The overall survival rate (Kaplan-Meier estimate) was 36% (95% CI, 24% to 48%) at 1 year and 18% (95% CI, 9% to 29%) at 3 years.

Of the 19 patients with previous HSCT who achieved a CR/CRh during the first 2 cycles of treatment and had a complete MRD response, the median relapse-free survival was 7.6 months (95% CI, 3.8 to 11.2 months) (n = 16) and the median overall survival was 23.1 months (95% CI, 9.4 to 25.3 months) (n = 10), with a median follow-up of 16.6 months (95% CI, 12.4 to 19.0 months). Of the 10 patients who achieved a CR/CRh during the first 2 cycles of treatment and did not have a complete MRD response, the median relapse-free survival was 6.1 months (95% CI, .1 month to NE) (n = 7) and the median overall survival was 12.7 months (95% CI, 4.0 months to NE) (n = 6), with a median follow-up of 12.8 months (95% CI, 11.2 to 23.3 months).

Safety

All 64 patients with previous alloHSCT (100%) experienced at least 1 adverse event during the study, with grade 3, grade 4, and serious adverse events reported in 20 (31%), 28 (44%),

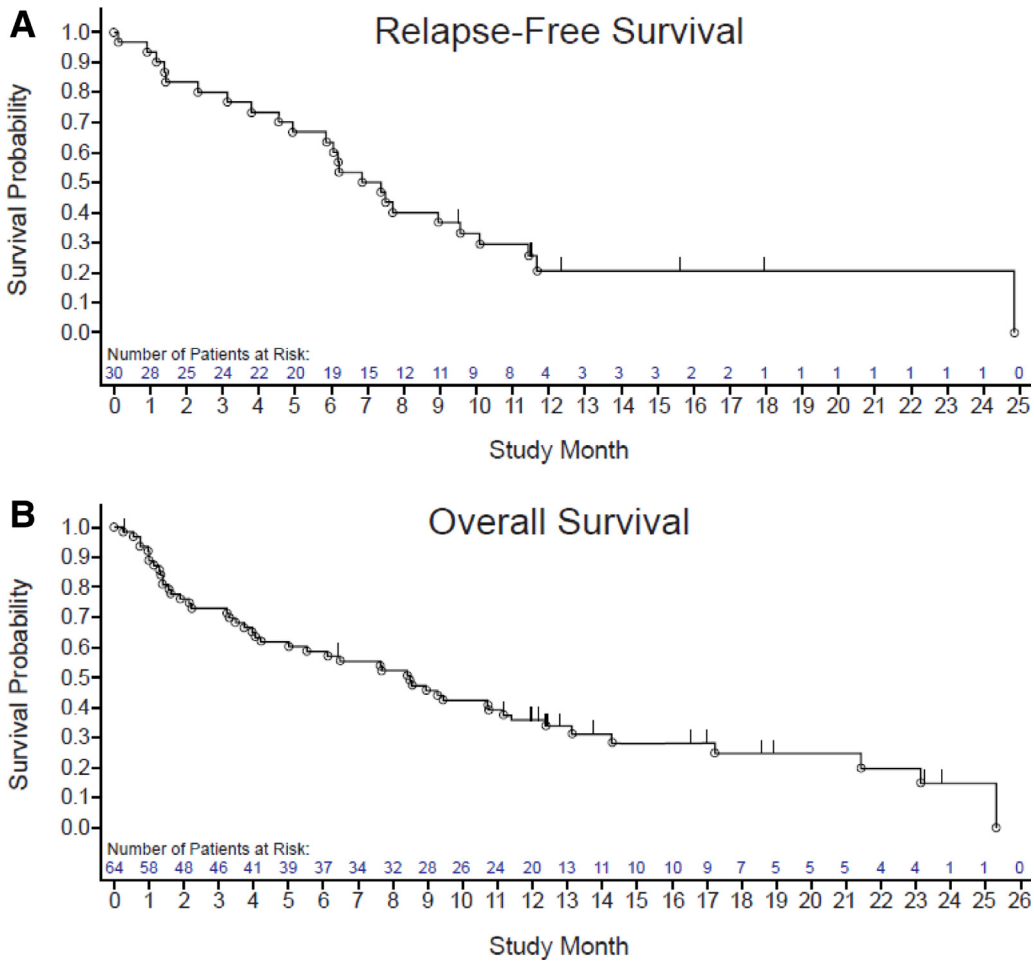

Figure 1. Relapse-free survival and overall survival for patients with previous alloHSCT. (A) Relapse-free survival for patients who achieved CR/CRh. (B) Overall survival. Vertical lines represent patients who were censored.

and 45 (70.3%) patients, respectively (Table 3). Eight patients (12.5%) had a grade 3 neurologic events, and 2 patients (3%) had grade 3 cytokine release syndrome. Two patients had a grade 4 neurologic event, and there were no grade 4 events of cytokine release syndrome. The 3 most common grade ≥3 adverse events were neutropenia, febrile neutropenia, and anemia. Eight patients had fatal adverse events, including 5 due to infections (2 from sepsis, 1 with *Fusarium* infection, 1 with bacteremia, and 1 with *Candida* infection considered related to blinatumomab treatment); none of these patients had achieved CR/CRh while receiving blinatumomab. There were no fatal neurologic or cytokine release events.

In general, the incidences of adverse events were similar among patients with and without previous alloHSCT. A notable exception was the incidence of grade 4 adverse events, which was 2-fold higher in patients who had undergone previous-alloHSCT (Table 3).

Seven patients (11%) experienced GVHD during the study (Table 4), including 6 after receiving blinatumomab and 1 after undergoing subsequent on-study alloHSCT. One patient had GVHD of the mouth (grade 1, chronic), 1 had GVHD of the skin (grade 2 chronic); 2 had cutaneous GVHD (one grade I and one grade III, both acute), 1 had GVHD events involving joints (grade 2 acute arthralgia) and liver (grade 3), 1 had grade II acute unspecified GVHD, and 1 had grade II acute GVHD of the oral mucosa. There were no grade 4 or 5 GVHD events. None of the GVHD events was considered serious, none resulted in the discontinuation of blinatumomab, and none resulted in hospitalization. All patients were treated with steroids, and 1 patient also received tacrolimus (Table 4).

Seventeen of 19 patients with a history of GVHD before treatment with blinatumomab did not develop reactivation of GVHD following treatment with blinatumomab; only 2 patients with a history of GVHD developed GVHD during the study.

T Cell Populations at Screening

Blood samples for the determination of T cell numbers were available for 61 patients (95%) in the previous alloHSCT group and for 114 patients (91%) in the no previous alloHSCT group. The distribution of $CD4^+$ and $CD8^+$ cell subsets measured at screening was similar in the 2 groups of patients, although there was an apparent trend toward higher numbers of T_{EM} and T_{EMRA} cells in the previous alloHSCT group (Figure 2).

DISCUSSION

The results from this exploratory analysis demonstrate that blinatumomab is effective in patients with R/R Ph-negative B cell precursor ALL who had relapsed following alloHSCT, a patient population with historically poor outcomes. Of note, 65% of the patients in our study had 2 or more previous

Table 3
Adverse Events

Adverse Events*	Patients with Previous AlloHSCT (N = 64), n (%)	Patients without Previous AlloHSCT (N = 125), n (%)
All events, any grade	64 (100.0)	124 (99.2)
Grade 3	20 (31.3)	52 (41.6)
Neurologic events	8 (12.5)	14 (11.2)
Cytokine release syndrome	2 (3.1)	1 (.8)
Infections	14 (21.9)	26 (20.8)
Grade 4	28 (43.8)	27 (21.6)
Neurologic events	2 (3.1)	1 (.8)
Cytokine release syndrome	0 (.0)	0 (.0)
Infections	6 (9.4)	6 (4.8)
Serious	45 (70.3)	78 (62.4)
Fatal	8 (12.5)	20 (16.0)
Sepsis	1 (1.6)	3 (2.4)
Disease progression	1 (1.6)	1 (.8)
Fusarium infection	1 (1.6)	1 (.8)
Septic shock	1 (1.6)	1 (.8)
Candida infection†	1 (1.6)	0 (.0)
Enterococcal bacteremia	1 (1.6)	0 (.0)
Gastrointestinal hemorrhage	1 (1.6)	0 (.0)
Respiratory failure	1 (1.6)	0 (.0)
Grade ≥3 adverse events occurring in ≥5 patients		
Febrile neutropenia	13 (20.3)	36 (28.8)
Neutropenia	14 (21.9)	16 (12.8)
Anemia	11 (17.2)	16 (12.8)
Pneumonia	6 (9.4)	11 (8.8)
Thrombocytopenia	9 (14.1)	7 (5.6)
Leukopenia	6 (9.4)	9 (7.2)
Elevated alanine aminotransferase	8 (12.5)	6 (4.8)
Pyrexia	7 (10.9)	7 (5.6)
Hypokalemia	6 (9.4)	7 (5.6)
Decreased white blood cell count	5 (7.8)	4 (3.2)
Elevated aspartate aminotransferase	5 (7.8)	3 (2.4)
Elevated serum bilirubin	5 (7.8)	3 (2.4)
Encephalopathy	5 (7.8)	1 (.8)
Hypotension	5 (7.8)	1 (.8)

Adverse events were graded using Common Terminology Criteria for Adverse Events, version 4.0.
* During treatment until 30 days after treatment or before alloHSCT if applicable.
† Considered by the investigator to be related to blinatumomab treatment.

relapses, implying an especially dismal outcome with standard of care therapy [2,3].

Among the total patient population of the phase II study, 43% of patients achieved a CR/CRh within the first 2 cycles of treatment, the median relapse-free survival was 5.9 months, and the median overall survival was 6.1 months [9]. The outcomes of patients who underwent previous alloHSCT were similar; 45% achieved a CR/CRh within the first 2 cycles, the median relapse-free survival was 7.4 months, and the median overall survival was 8.5 months. The survival rates of 36% at 1

Table 4
Patients with GVHD Events*

Patient	History of GVHD	GVHD Event	Worst Grade	Chronic/Acute	Medication for GVHD	Continuation of Blinatumomab
1	No	Mouth	1	Chronic	Budesonide	Yes
2	No	Skin	2	Chronic	Not reported	Yes
3	Yes	Cutaneous	3	Acute	Dexamethasone	Yes
4	No	Cutaneous	1	Acute	Dexamethasone	Yes
5†	Yes	Arthralgia	2	Acute	Dexamethasone Methylprednisolone, tacrolimus	Not applicable‡
		Liver	3	Acute		
6	No	Not specified	2	Acute	Dexamethasone	Yes
7	No	Oral mucosa	2	Chronic	Methotrexate	Yes

* During treatment until 30 days after treatment; graded using Common Terminology Criteria for Adverse Events, version 4.0.
† This patient had 2 different GVHD events.
‡ GVHD occurred after treatment with blinatumomab ended, within 30 days of the last dose.

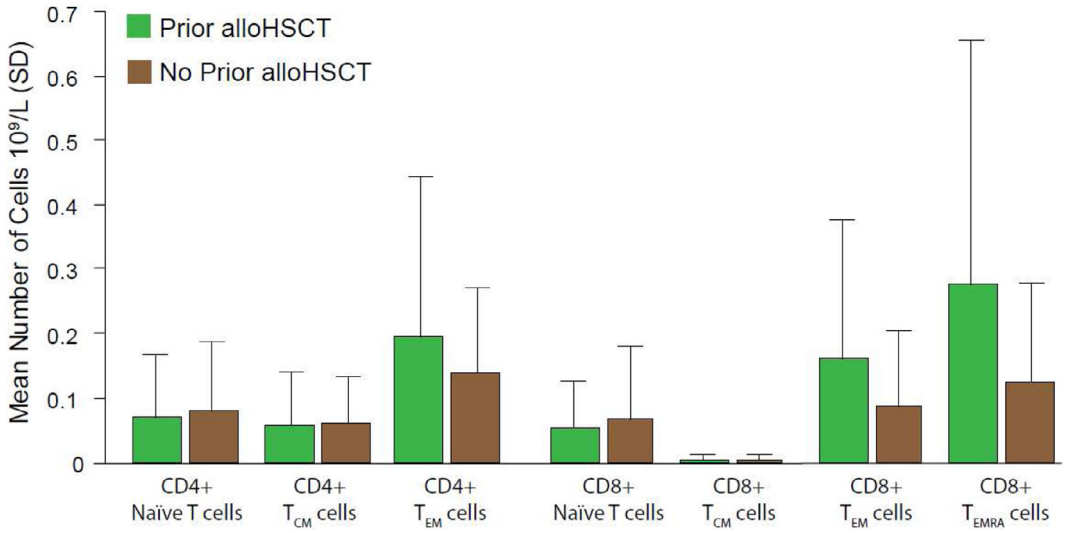

Figure 2. T cell subsets at baseline in patients with and without previous alloHSCT. The numbers of $CD4^+$ and $CD8^+$ T cells were determined by flow cytometry.

year and 18% at 3 years are comparable to those obtained after a second alloHSCT [3]. Patients who experienced more than 1 relapse after their previous alloHSCT and before treatment with blinatumomab had shorter relapse-free survival and overall survival compared with those with only 1 relapse. A decreasing survival rate after subsequent lines of salvage therapy has previously been reported in patients with relapsed ALL [10].

Similar proportions of patients in the previous alloHSCT and no previous alloHSCT groups had a complete MRD response (66% versus 62%), providing additional evidence that blinatumomab is effective in patients with more aggressive ALL. As expected, patients who had an MRD response had longer relapse-free survival and overall survival compared with patients who did not have an MRD response.

Our results are comparable to the findings in a blinatumomab arm of a phase III study that compared the efficacy and safety of blinatumomab with chemotherapy. In that study, 34% of patients had received previous alloHSCT, and the treatment benefit with blinatumomab was consistent among patients with and patients without previous alloHSCT. Remission rates also favored blinatumomab in both groups of patients [11].

Other novel therapeutic agents that have demonstrated efficacy in patients with R/R ALL include anti-CD19 chimeric antigen receptor T cell (CAR T-cell) therapy [12–14] and the anti-CD22 antibody-calicheamicin conjugate inotuzomab ozogamicin [15–17]. A subgroup analysis of patients with previous transplantation (n = 46) and without previous transplantation (n = 29) treated with the CAR T cell agent tisagenlecleucel showed a slightly higher rate of CR/CRh in the former group; the CR/CRh rate was 81% for the overall patient population [12]. Other efficacy outcomes were not reported for this subgroup of patients. Two additional studies reported CR rates of 100% (n = 8) [13] and 84% (n = 19) [14] among patients with previous HSCT treated with CAR T cell therapy. Those studies did not report the survival of patients with previous HSCT, however. For the overall patient populations, 1-year survival rates were 61% [13] and 76% [14], and after long-term follow-up, the median overall survival among patients with low versus high disease burden was 20.1 months versus 12.4 months [13]. In the phase III study of inotuzomab ozogamicin versus standard of care, patients with and without previous HSCT treated with inotuzomab ozogamicin had similar CR/CRh rates (76.5% and 81.5%, respectively); relapse-free and overall survival of patients with previous HSCT was not reported [17].

The adverse events reported in the present study were consistent with those reported in previous blinatumomab clinical studies and were generally balanced between the previous alloHSCT and no previous alloHSCT groups. An exception was the incidence of grade 4 adverse events, which was 2-fold higher in the previous-alloHSCT group, a heavily pretreated population of patients. Fatal adverse events were due mainly to infections and occurred in patients with uncontrolled leukemia. Apart from relapse, there were no other neoplastic causes of death, and no cases of post-transplantation lymphoproliferative disease occurred after blinatumomab therapy and during follow-up. The incidence of grade ≥3 neurologic events was similar in the 2 groups. Neurologic events of grade ≥3 were managed by treatment interruption or discontinuation, which did not appear to substantially impact the response to blinatumomab [9]. The low incidence of grade ≥3 cytokine release syndrome was likely due to premedication with dexamethasone and the use of a stepped-dosage regimen [9]. A low incidence of cytokine release syndrome was also observed in the phase III study using these mitigation strategies [11].

Blinatumomab treatment did not appear to be associated with an increase in GVHD among patients with previous alloHSCT. All but 2 cases of GVHD (which was observed in 11% of the patients) were mild or moderate in severity; none resulted in hospitalization, and none affected blinatumomab treatment (ie, blinatumomab administration was not interrupted). Of note, only 2 of the 7 patients who experienced GVHD after treatment with blinatumomab had a history of GVHD; one-third of patients who had undergone previous alloHSCT had a history of GVHD. The incidence of GVHD in our study cohort is lower than that observed in patients who receive donor lymphocyte infusion for relapse after alloHSCT. Up to 60% of patients who receive donor lymphocyte infusions develop acute GVHD, approximately one-third develop clinically significant GVHD, and GVHD is the leading cause of mortality in these patients [18,19]. Blinatumomab treatment was not associated with any fatal cases of veno-occlusive disease, which is considered a major toxicity in patients treated with inotuzumab ozogamicin [15–17,20]. In addition, we did not observe any cases of Epstein-Barr virus-associated post-transplantation lymphoproliferative disorder.

The proportions of specific T cell populations at baseline were similar in the previous allo HSCT and no previous alloHSCT groups, even though approximately one-third of patients had received ATG before alloHSCT. These data reflect the similar outcomes observed in both groups of patients. Although this was not investigated in the present study, it has been reported that a cutoff of 8.52% regulatory T cells at baseline identified 100% of patients who will respond to blinatumomab and excluded 70% of those who will not respond to blinatumomab [21].

Our present study has some limitations. This phase II study was not specifically designed to prospectively evaluate the outcomes of patients who underwent previous alloHSCT, potentially limiting the capture of transplantation data. In addition, this retrospective analysis was performed on a small subset of patients enrolled in a single-arm, open-label study.

In summary, blinatumomab appears to be a feasible and effective salvage therapy for patients with R/R ALL after alloHSCT and is not associated with a higher rate of severe side effects compared with patients who do not undergo alloHSCT. Several ongoing studies in patients with R/R ALL are evaluating blinatumomab in combination with other agents, including inotuzumab ozogamicin, the anti-PD-1 immunotherapy agents pembrolizumab and nivolumab, and the anti-CTLA-4 immunotherapy agent ipilimumab. Further improvements in the outcomes of patients with R/R ALL await the results of these studies.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.04.010.

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