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ORIGINAL REPORT

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

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ABSTRACT

Purpose
Patients with relapsed or refractory acute lymphoblastic leukemia (ALL) have a dismal prognosis. CD19 is homogenously expressed in B-precursor ALL and can be targeted by the investigational bispecific T cell–engager antibody blinatumomab. A phase II trial was performed to determine clinical activity in this patient cohort.

Patients and Methods
Thirty-six patients with relapsed or refractory B-precursor ALL were treated with blinatumomab in cycles of 4-week continuous infusion followed by a 2-week treatment-free interval in a single-arm study with a dose-finding stage and an extension stage. The primary end point was complete remission (CR) or CR with partial hematologic recovery (CRh). Major secondary end points included minimal residual disease (MRD) response, rate of allogeneic hematopoietic stem-cell transplantation (HSCT) realization, relapse-free survival (RFS), overall survival (OS), and incidence of adverse events (AEs).

Results
Median age was 32 years (range, 18 to 77 years). Twenty-five patients (69%) achieved a CR or CRh, with 88% of the responders achieving an MRD response. Median OS was 9.8 months (95% CI, 8.5 to 14.9), and median RFS was 7.6 months (95% CI, 4.5 to 9.5). Thirteen responders (52%) underwent HSCT after achieving a CR or CRh. The most frequent AE during treatment was pyrexia (grade 1 or 2, 75%; grade 3, 6%). In six patients with nervous system or psychiatric disorder AEs and in two patients with cytokine release syndrome, treatment had to be interrupted or discontinued. These medical events were resolved clinically.

Conclusion
The data support further investigation of blinatumomab for the treatment of adult patients with relapsed or refractory ALL in a larger confirmatory study.

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INTRODUCTION

Adult patients with relapsed acute lymphoblastic leukemia (ALL) have a dismal prognosis. A second complete hematologic remission is only achieved by 25% to 45% of patients receiving salvage chemotherapy, with significant treatment-related mortality of up to 15%. Hence, most patients will succumb to their disease, with a median survival of only 2 to 8 months.[1-3] Blinatumomab and other bispecific T cell–engager (BiTE) antibodies transiently induce a cytolytic synapse between a cytotoxic T cell and the cancer target cell. Consequently, granzyme-containing granules and the pore-forming protein perforin fuse with the T-cell membrane and discharge their toxic content. By this mechanism, BiTE molecules can engage all cytotoxic T cells of a patient for redirected lysis of tumor cells.[4] Blinatumomab has dual specificity for CD19 and CD3 and has been shown to induce durable responses in patients with lymphoma or with minimal residual disease (MRD) of ALL.[5-7] In this study, the efficacy of blinatumomab in relapsed or refractory B-precursor ALL—specifically hematologic remission rate,

MRD response, hematopoietic stem-cell transplantation (HSCT) realization, durability of response, overall survival (OS), and tolerability—were assessed. Furthermore, different blinatumomab administration regimens were explored.

PATIENTS AND METHODS

Patients

This was an open-label, multicenter, exploratory, single-arm, phase II study conducted in collaboration with the German Study Group for Adult Acute Lymphoblastic Leukemia. Key inclusion criteria were the presence of $>5\%$ leukemic blasts in bone marrow in patients with primary refractory disease or relapse after induction and consolidation chemotherapy or after HSCT, Eastern Cooperative Oncology Group performance status ≤ 2, and life expectancy ≥ 12 weeks. Key exclusion criteria were Philadelphia chromosome–positive ALL eligible for dasatinib or imatinib treatment, history or presence of clinically relevant CNS pathology, active CNS leukemia, active graft-versus-host disease (GVHD) and/or immunosuppressive therapy for GVHD within 1 week of blinatumomab treatment start, active infections, immunotherapy within 4 weeks or cancer chemotherapy within 2 weeks of treatment start, and neutralizing human antimurine antibodies. The study protocol was approved by the independent ethics committee of each study site, and all patients provided written informed consent. The study was monitored by an independent data monitoring committee (DMC), which reviewed toxicity and efficacy data.

Study Procedures

The treatment regimen was developed based on the treatment experience of the German Study Group for Adult Acute Lymphoblastic Leukemia in this patient population. Accordingly, patients received two initial cycles of blinatumomab to induce remissions. If a hematologic complete remission with complete (CR) or partial hematologic recovery (CRh; platelets $>50{,}000/\mu L$, hemoglobin >7 g/dL, and absolute neutrophil count $>500/\mu L$) was achieved, three additional cycles were administered as consolidation therapy, unless HSCT was scheduled earlier. Cycle duration was based on 4-week T-cell kinetics, as published previously.[6,8,9] In brief, a cycle included 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval, the duration of which was derived from data on T-cell recovery after contraction (decrease of activated T cells after expansion).[10] Blinatumomab was administered in the hospital during the first week of the first cycle, during the first 2 days of each subsequent cycle, and on an outpatient basis thereafter. Bags were changed every 48 hours during the week and every 72 hours on weekends.

The core study was defined as screening plus treatment period (up to five cycles). During the study's dose-finding run-in, dosing schedules were tested in cohorts of five patients who had $\geq$ one evaluable treatment cycle. Patients without an evaluable treatment cycle were replaced but included in the efficacy assessment. On the basis of the experience in MRD-positive ALL, the dose of 15 $\mu g/m^2$ per day was evaluated in the first cohort (cohort 1). Because of grade 4 cytokine release syndrome (CRS) in one patient, a treatment prephase with dexamethasone up to 24 mg for up to 5 days and/or 200 mg/m^2 of cyclophosphamide for up to 4 days was permitted. In addition, in the second cohort (cohort 2a), the initial dose in the first week of treatment was lowered to 5 $\mu g/m^2$ per day and then increased to 15 $\mu g/m^2$ per day. Similarly, in the third cohort (cohort 2b), treatment started at 5 $\mu g/m^2$ per day and then increased to 15 $\mu g/m^2$ per day before another dose escalation to 30 $\mu g/m^2$ per day in week 3. For Simon stages 1 and 2, the treatment schedule of cohort 2a was chosen (Appendix Fig A1, online only).

All patients received CNS relapse prophylaxis (methotrexate 15 mg, cytarabine 40 mg, and dexamethasone 4 mg intrathecally) during screening and on day 28 of each cycle. Intravenous dexamethasone 16 mg (or equivalent) was administered within 1 hour of treatment start. No prophylactic antipyretic medication was administered. Fever symptoms were managed during the course of the study using antipyretics.

Efficacy was assessed by bone marrow aspirate or biopsy on day 29 of each cycle using a central reference laboratory. MRD response was defined as decrease of MRD to $< 10^{-4}$ detectable blasts of nucleated cells using allele-specific real-time quantitative polymerase chain reaction for clonally rearranged immunoglobulin and/or T-cell receptor genes (sensitivity $\geq 10^{-4}$).[6,11] Adverse events (AEs) and serious AEs (SAEs) were recorded from treatment start until at least 30 days after treatment ended or the end-of-core study visit, whichever came later. AEs were graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analysis

The primary end point was the proportion of patients who achieved a CR or CRh within two treatment cycles. The sample size was calculated for a modified Simon two-stage design; different dosing cohorts were evaluated in stage 1, and the cohort with the best tolerability and efficacy outcome (determined by the DMC) was further evaluated in stage 2. With an overall type I and II error rates of 5% and 15%, respectively, an uninteresting response rate (p_0) of 0.10, and a desirable response rate (p_1) of 0.40, the required sample size was five evaluable patients per cohort in stage 1 and 10 at the chosen dosing regimen in stage 2, provided that $\geq$ one patient in the corresponding stage 1 cohort achieved remission (CR or CRh). Accordingly, if $\geq$ four of the 15 evaluable patients at the chosen dose level achieved remission, further development of blinatumomab would be considered warranted.

Secondary end points included MRD response rate, HSCT realization after blinatumomab-induced remission, relapse-free survival (RFS), OS, incidence of AEs, and pharmacokinetics and pharmacodynamics. RFS was measured from the time of first CR or CRh to hematologic or extramedullary relapse or death resulting from any cause. Patients still in remission at data lock were censored at the time of last remission status assessment. OS was measured from the time of first blinatumomab dose to death resulting from any cause. Kaplan-Meier methods were used to estimate the probability of RFS and OS over time. Subgroup analyses were used to evaluate remission rates based on prior HSCT status and prior number of relapses.

RESULTS

Patient Characteristics

Between October 6, 2010, and June 19, 2012, 36 patients were enrolled and treated at nine centers in Germany. Patient characteristics are listed in Table 1 and Appendix Table A1 (online only). All patients had received standard first-line therapy, including at least induction and consolidation. Fifteen patients (42%) had relapsed after prior HSCT.

Dose Evaluation

In the dose-finding stage of the study, three sequential dose cohorts were tested (Appendix Fig A1, online only). Seven patients were included in cohort 1, five in cohort 2a, and six in cohort 2b. Within cohort 1, patients showed the highest rates of AEs overall and of SAEs (Appendix Table A2, online only). One patient developed grade 3 nervous system and psychiatric disorder AEs, and one patient developed grade 4 CRS; both patients were replaced. The lowest rate of AEs and SAEs occurred in cohort 2a; no patient in this cohort stopped treatment prematurely as a result of toxicity. On the basis of the DMC recommendation, and because it had the best tolerability profile, the dose schedule of cohort 2a was chosen for the extension stage of the study, in which an additional 18 patients were treated.

Hematologic Response, RFS, and OS

The proportion of patients achieving a CR or CRh was 69%; 15 patients achieved a CR, and 10 patients achieved a CRh within the first

Table 1. Patient Demographic and Clinical Characteristics (N = 36)

Characteristic	No.	%
Age, years		
Median	32	
Range	18-77	
Sex		
Male	22	61
Female	14	39
Prior therapy/disease status		
No prior HSCT	21	58
Primary refractory	3	8
First salvage after first CR		
≤ 12 months after initial diagnosis	5	14
> 12 months after initial diagnosis	6	17
≥ Second salvage	7	19
Prior HSCT	15	42
Cytogenetic factors		
Ph positive	2	6
t(4;11)	4	11
Bone marrow blasts at screening, %*		
Median	77	
Range	6-97	

Abbreviations: CR, complete remission; HSCT, hematopoietic stem-cell transplantation; Ph, Philadelphia chromosome.
*Based on central laboratory screening results unless unavailable (data from two patients based on local laboratory screening).

two treatment cycles (Table 2). The highest proportions of patients with a CR or CRh were observed among those in first salvage who were treated in early or late relapse (five of five and six of six patients responded, respectively), followed by patients in second salvage with relapsed disease (six of 10 patients responded). The proportion of patients with a CR or CRh was lowest among those who had relapsed after HSCT, with eight of 15 patients responding (Table 3). One of the two patients with Philadelphia chromosome–positive ALL and three of the four patients with t(4;11) also achieved a CR or CRh. Among the 25 responders, 22 patients (88%) achieved an MRD response, 18 of whom achieved the response at the end of cycle one (Table 2).

Table 2. Response to Treatment

Response	All Patients (N = 36) No.	%	95% CI
CR or CRh	25	69	52 to 84
CR	15	42	26 to 59
CRh	10	28	14 to 45
Partial remission*	2	6	—
Hypocellular bone marrow	3	8	—
Refractory	4	11	—
Not evaluable†	2	6	—

MRD Response‡	Responders (n = 25) No.	%
Across cycles	22	88
End of cycle one	18	72
End of cycle two	3	12
End of cycle three	1	4
No MRD response	3	12

Abbreviations: CR, complete remission; CRh, CR with partial hematologic recovery (≤ 5% blasts in bone marrow, no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts [at least platelets > 50,000/μL, hemoglobin ≥ 7 g/dL, and absolute neutrophil count > 500/μL); MRD, minimal residual disease.
*Bone marrow blasts ≤ 25%, and platelets < 50,000/μL and/or neutrophils < 500/μL.
†Resulting from lack of bone marrow assessment.
‡MRD level $< 10^{-4}$.

Table 3. Response by Salvage Category

Response	No Prior HSCT (n = 21) First Salvage After First CR (≤ 12 months after initial diagnosis) (n = 5)	First Salvage After First CR (> 12 months after initial diagnosis) (n = 6)	≥ Second Salvage or Primary Refractory (n = 10)	Prior HSCT (n = 15)
CR or CRh	5	6	6	8
CR	3	5	3	4
CRh	2	1	3	4
Partial remission*	0	0	1	1
Hypocellular bone marrow	0	0	0	3
Refractory	0	0	1	3
Not evaluable†	0	0	2	0

Abbreviations: CR, complete remission; CRh, CR with partial hematologic recovery (≤ 5% blasts in bone marrow, no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts [at least platelets > 50,000/μL, hemoglobin ≥ 7 g/dL, and absolute neutrophil count > 500/μL); HSCT, hematopoietic stem-cell transplantation.
*Bone marrow blasts ≤ 25% and platelets < 50,000/μL and/or neutrophils < 500/μL.
†Resulting from lack of bone marrow assessment.

Median RFS was 7.6 months (median follow-up time, 9.7 months). If censored for subsequent HSCT, median RFS was 7.9 months (Fig 1A). No marked difference in RFS was observed for patients who achieved a CR versus CRh. Median OS was 9.8 months, with a follow-up of 12.1 months (Fig 1B). When measured from the start of remission, patients with a CR (n = 15) and patients with a CRh (n = 10) had a median OS of 13.2 and 8.3 months, respectively. A statistically nonsignificantly shorter OS was observed in patients who relapsed after prior HSCT (median, 8.8 months) compared with those who relapsed without having had prior HSCT (median, 14.1 months; Fig 1C). Median number of treatment days across the entire study was 55 days (range, 1 to 150 days), with four patients having completed five cycles of blinatumomab.

Of the 25 patients who achieved a CR or CRh, 13 proceeded to HSCT while still in remission. Of those, six patients died as a result of treatment-related mortality, and two relapsed. Three of the 13 patients had undergone prior transplantation before receiving blinatumomab, with two of those patients being in ongoing OS follow-up (281 and 269 days, respectively). Twelve of the 25 responders did not undergo HSCT while in remission. Eight of the 12 patients relapsed: four during and four after blinatumomab treatment (four are still in remission). In total, no patients who underwent HSCT and five patients who did not undergo HSCT after blinatumomab completed five cycles of treatment (of the latter, one relapsed). Overall, of the 10 relapses, three were CD19 negative (one extramedullary), four were CD19 positive (two extramedullary), and one was of unknown CD19 status. No CNS relapses occurred. Seven responders died without documented relapse.

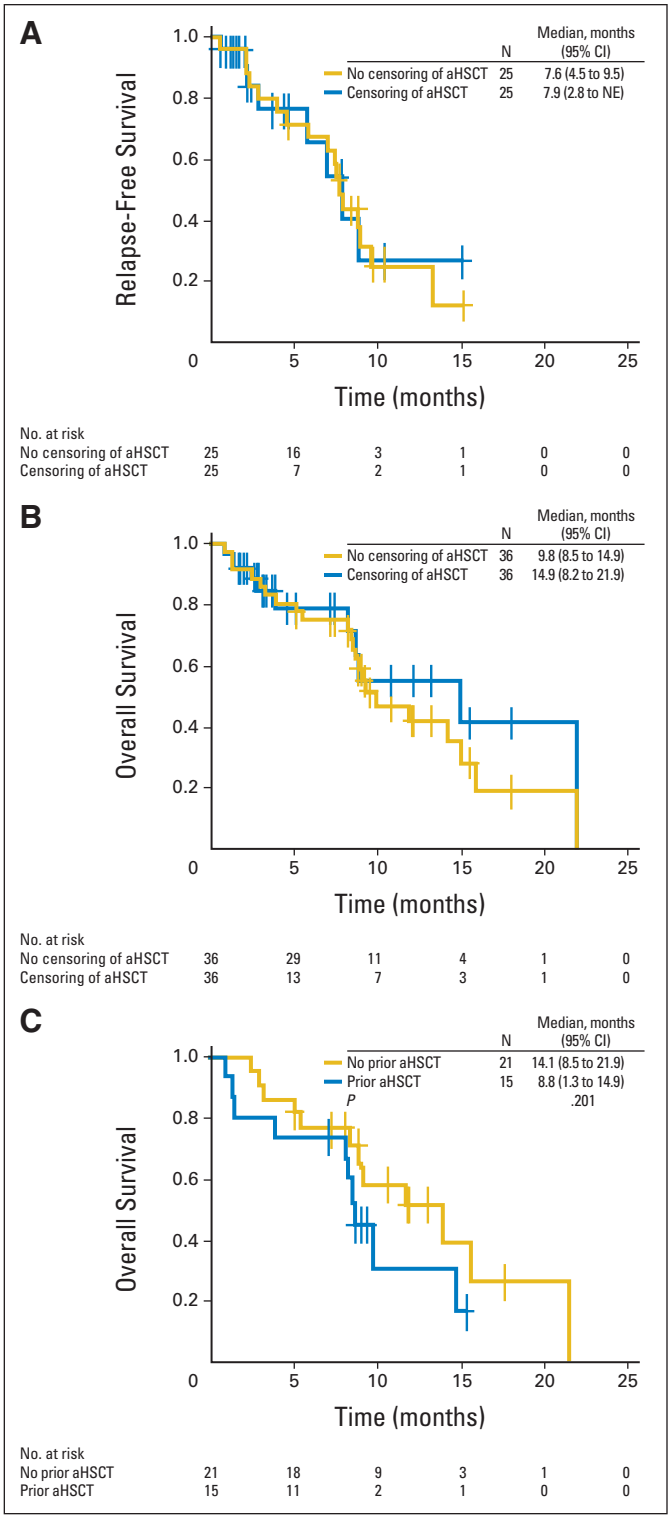

Fig 1. (A) Relapse-free survival (RFS) and (B) overall survival (OS) with and without censoring at time of allogeneic hematopoietic stem-cell transplantation (aHSCT) and (C) OS comparing no prior aHSCT versus prior aHSCT.

AEs

Among the 36 patients treated, the most common AEs, regardless of grade or causality, were pyrexia (81%), fatigue (50%), headache (47%), tremor (36%), and leukopenia (19%). Most AEs were transient and developed in the first days of the first cycle. The most common grade ≥ 3 AEs were transient leukopenia and thrombocytopenia (Table 4). Sixty-seven percent of patients had SAEs, primarily infections (33%) and nervous system and psychiatric disorders (22%). Overall, 22 of 36 patients died. Six patients died as a result of infections during the core study period (Table 4). Of those, five deaths were reported during or after blinatumomab therapy but before HSCT. None of the five patients had reached a CR or CRh. Four of the five deaths were reported as not related and one as possibly related to blinatumomab. This death occurred in a patient who had undergone HSCT before blinatumomab treatment; the patient died as a result of disseminated fungal infection of the brain. Fungal prophylaxis was then made mandatory for all relapsed HSCT recipients who had a medical history of GVHD. The sixth patient died as a result of infectious complications after HSCT, deemed unrelated to blinatumomab.

Six (17%) of the 36 patients treated had nervous system or psychiatric disorders requiring treatment interruption or permanent discontinuation (Table 5). Five of the six patients had grade 3 events; one had a grade 2 event. Three of the six patients showed signs of encephalopathy with tremor, aphasia, and confusion; the other three patients had epilepsy or convulsions. In five of the six patients, nervous system or psychiatric disorders were recorded within the first week of a cycle (in one patient, within 4 hours of dose escalation from 5 to 15 $\mu g/m^2$ per day). After clinical resolution of the events, all six patients were re-exposed to blinatumomab. The three patients with epilepsy or convulsions successfully resumed treatment with antiseizure prophylaxis. Two of the three patients with encephalopathy discontinued treatment permanently after resumption because of reappearance of nervous system or psychiatric disorder AEs in more pronounced form. A statistical analysis of association of such AEs with patient characteristics or with the intrathecal therapy time points was not performed, because of small sample sizes.

Two patients had grade 4 CRS. One of them, who also presented with tumor lysis syndrome, permanently discontinued treatment, whereas the other patient was successfully re-exposed to blinatumomab after treatment interruption. Both patients had high leukemic burden with bone marrow blast proportions of 88% and 90%, respectively; one patient also had signs of extramedullary involvement. Both patients achieved a CR. None of the nonresponders had CRS. A treatment prephase consisting of dexamethasone 10 mg/m^2 (up to 5 days) and cyclophosphamide 200 mg/m^2 (up to 3 days) was recommended thereafter for patients with high tumor load in this study. No incidence of grade ≥ 3 CRS was reported during the remainder of the study.

DISCUSSION

Single-agent blinatumomab in relapsed or refractory ALL has shown a CR or CRh rate of 69% and median OS of 9.8 months. However, the sample size in this trial was small, with ≤ 10 patients in the subgroups without prior HSCT. Of the 15 patients who had undergone prior HSCT, four (26%) achieved a CR, and four achieved a CRh. Thus, although antileukemic activity of blinatumomab has been demonstrated, the degree of antileukemic activity needs to be determined by a confirmatory trial with a larger sample size. Combination chemotherapies have been reported to achieve response rates of 31% to 44% and median OS of 2 to 8 months.[1-3] Data on single-agent treatments

Table 4. AEs Regardless of Causality*

	Dose-Finding Stage						Extension Stage		Optimal Dose	
	Cohort 1 (15 $\mu g/m^2$ per day; n = 7)		Cohort 2a (5 to 15 $\mu g/m^2$ per day; n = 5)		Cohort 2b (5 to 15 to 30 $\mu g/m^2$ per day; n = 6)		Cohort 3 (5 to 15 $\mu g/m^2$ per day; n = 18)		Cohorts 2a + 3 (5 to 15 $\mu g/m^2$ per day; n = 23)	
AE	No.	%	No.	%	No.	%	No.	%	No.	%
					Summary					
Worst grade 1 or 2	0	0	2	40	1	17	6	33	8	35
Worst grade ≥ 3	7	100	3	60	5	83	12	67	15	65
Grade 3	1	14	2	40	3	50	4	22	6	26
Grade 4	5	71	0	0	1	17	5	28	5	22
Grade 5†	1	14	1	20	1	17	3	17	4	17
Permanently discontinued treatment because of AEs	4	57	1	20	1	17	3	17	4	17
					Grade ≥ 3 in ≥ 5% of All Patients					
Leukopenia	2	29	0	0	2	33	1	6	1	4
Thrombocytopenia	2	29	0	0	0	0	2	11	2	9
Blood IgA decrease	1	14	0	0	1	17	1	6	1	4
Blood IgG decrease	1	14	0	0	1	17	1	6	1	4
Blood IgM decrease	1	14	0	0	1	17	1	6	1	4
Encephalopathy	1	14	0	0	1	17	1	6	1	4
Fibrin D dimer increase	1	14	0	0	1	17	1	6	1	4
Lymphopenia	3	43	0	0	0	0	0	0	0	0
Tremor	0	0	0	0	1	17	2	11	2	9
Blood potassium decrease	2	29	0	0	0	0	0	0	0	0
C-reactive protein increase	1	14	0	0	0	0	1	6	1	4
Catheter site infection	1	14	1	20	0	0	0	0	1	4
Cytokine release syndrome	1	14	0	0	0	0	1	6	1	4
Febrile neutropenia	1	14	0	0	0	0	1	6	1	4
Gamma-glutamyltransferase increase	1	14	0	0	0	0	1	6	1	4
Hypertension	0	0	1	20	0	0	1	6	2	9
Infection	1	14	0	0	1	17	0	0	0	0
Pyrexia	0	0	0	0	1	17	1	6	1	4
Sinusitis	1	14	0	0	0	0	1	6	1	4
Tumor lysis syndrome	1	14	0	0	0	0	1	6	1	4

Abbreviations: AE, adverse event; Ig, immunoglobulin.
*Includes AEs both unrelated and considered to be possibly related to blinatumomab treatment.
†Fatal (grade 5) AEs reported during core study: cohort 1: infection (n = 1); cohort 2a: fungal pneumonia (n = 1); cohort 2b: *Candida* sepsis (n = 1); cohort 3: pulmonary sepsis and pneumonia (n = 1), sepsis (n = 1), and fungal infection of brain (n = 1).

with newly registered drugs for ALL (eg, clofarabine[12] and liposomal vincristine[13]) show remission rates of 20%. Several other approaches targeting B-cell surface antigens are being explored. Inotuzumab ozogamicin, an anti-CD22 monoclonal antibody conjugated to calicheamicin, has shown an overall response rate of 57% and median OS of 6.2 months.[14] Chimeric antigen receptor (CAR) –modified T cells targeting CD19 have been investigated in several single-center trials. Response rates as high as 83% were reported in a heterogeneous group of adult and pediatric patients with relapsed or refractory or MRD-positive ALL.

The optimal setting for clinical evaluation of new compounds is unclear. In a previous phase II trial, blinatumomab was tested in MRD-positive ALL after induction and consolidation therapy, yielding a molecular response rate of 80% and long-term RFS of 61% after a median follow-up of 33 months.[6] Comparing the results from our trial in ALL with cytologic relapse is difficult, and patient numbers in both trials were small. However, it can be speculated that treatment in earlier stage of relapse (ie, in the presence of MRD after first-line induction chemotherapy) would be more promising in terms of overall outcome. Patients have a lower leukemia burden, are in better condition, and have a lower risk of complications, and more time is available to prepare for HSCT. In addition, in more advanced disease, particularly in relapse after HSCT, the T-cell system might be affected. Finally, it is possible that the lower initial dose of 5 $\mu g/m^2$ per day, as selected for the expansion cohort of the study, compared with an initial dose of 15 $\mu g/m^2$ per day in MRD-positive ALL, may have played a role in the different degrees of sustained leukemia control.

It remains a matter of debate why a significant proportion of patients relapsed despite prior achievement of an MRD response. In first-line treatment, achievement of MRD negativity is strongly associated with outcome[15]; so far, no data are available on the prognostic impact of MRD after relapse in adult ALL. Similar to our findings, in the inotuzumab ozogamicin trial, median survival of the responders was 7.9 months, despite achievement of MRD-negative status in 63% of patients.[14] Genetic instability and selection of multiresistant clones during several lines of relapse treatment may explain rapidly occurring relapses after initial good MRD response in the relapsed or refractory setting.

Retrospective trials in relapsed or refractory ALL have shown long-term remissions only in patients who underwent HSCT after

Table 5. Nervous System and Psychiatric Disorder AEs Leading to Treatment Interruption or Permanent Discontinuation

Patient Identifier	Treatment Cycle	Blinatumomab Dose ($\mu g/m^2$ per day)	AE	CTCAE Grade	Permanent Discontinuation (yes *v* no)
155-002	1	15	Disorientation	3	No
			Encephalopathy		No
	2	15	Encephalopathy	3	Yes
162-001	2	15	Convulsion	3	No
155-006	1	15	Convulsion	2	No
157-004	2	30	Encephalopathy	3	No
157-005	1	5	Epilepsy	3	No
	3	5	Psychotic disorder	2	No
159-002	1	5	Tremor	1	No
			Apraxia	3	No
			Encephalopathy	3	No
			Memory impairment	3	No
	2	5	Tremor	1	Yes
			Aphasia	1	Yes
			Encephalopathy	3	Yes

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.0).

achieving a CR.[2] In our study, HSCT was performed in 52% of patients achieving a CR or CRh. No difference was observed if OS and RFS were censored for HSCT. Similar results were reported from the inotuzumab ozogamicin trial. In particular, the outcome of HSCT was influenced by high post-HSCT mortality.[16] However, both trials were too small, the patient populations too heterogeneous, and the study design not appropriate to evaluate the role of HSCT in relapsed or refractory ALL, and HSCT remains the standard of care.

One aim of our study was to explore a manageable dosing schedule for blinatumomab in adult relapsed or refractory ALL. Using a dose-finding run-in with sequential cohorts, we determined stepwise dosing with a lower dose for 7 days followed by a higher target dose for the remaining treatment time as the optimal schedule. The most frequent AEs that occurred during the study (eg, pyrexia, fatigue, and headache) are consistent with the blinatumomab mode of action (ie, local polyclonal T-cell activation). Clinically important AEs of specific interest included CRS and nervous system and psychiatric disorders. Recently, administration of an anti–interleukin-6 antibody was described as a feasible approach for the management of CRS in patients treated with CD19 CAR-modified T cells.[17] In our study, stepwise dosing, along with prephase treatment including cyclophosphamide and dexamethasone, for patients with high tumor burden seemed to be successful in the prevention of severe CRS. Nervous system and psychiatric disorders have previously been described with blinatumomab treatment.[6,18] Such AEs led to temporary or permanent treatment discontinuation in six patients; all resolved clinically within 72 hours of treatment stop. Of note, the three patients with epilepsy or convulsions successfully resumed treatment with antiseizure prophylaxis. The mechanism underlying the development of these clinically reversible nervous system and psychiatric disorder AEs during blinatumomab treatment remains hypothetical. Interestingly, such events have also been described in patients who were treated with CD19 CAR-modified T cells.[19,20] Additional studies to further evaluate the efficacy and tolerability of blinatumomab in larger populations of patients with B-precursor relapsed or refractory ALL are warranted and may also provide an opportunity to investigate determinants of response.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Table A1. Patient Characteristics and Prior Treatment

Patient No.	Cohort	Sex	Salvage or Primary Refractory	Prior HSCT	Age (years)	Blast Count (%)	LDH (U/L)	Time to Relapse From Diagnosis (months)	Dexamethasone (yes *v* no)	Cyclophosphamide (yes *v* no)
155002	1	Male	Salvage two at relapse > 12 months after initial diagnosis	No	77	9	281	27.9	No	No
155003	1	Female	Salvage two at relapse ≤ 12 months after initial diagnosis	Yes	34	76	316	7.0	No	Yes
155004	1	Male	Salvage two at second relapse	Yes	18	81	197	22.0	No	Yes
155005	2a	Male	Salvage two at relapse > 12 months after initial diagnosis	Yes	66	90	174	27.0	No	No
155006*	2b	Female	Salvage two at second relapse	Yes	38	86	408	48.9	Yes	Yes
155007	2b	Male	Salvage two at second relapse	Yes	25	91	249	29.7	Yes	Yes
155008	2b	Male	Salvage one at relapse > 12 months after initial diagnosis	No	71	40	254	23.3	Yes	No
155009	3	Female	Primary refractory	No	29	9	217	—	Yes	No
155010	3	Male	Salvage two at relapse ≤ 12 months after initial diagnosis	No	31	82	295	7.4	Yes	Yes
155011	3	Male	Salvage one at relapse > 12 months after initial diagnosis	No	44	90	199	21.9	Yes	No
155012	3	Male	Salvage one at relapse > 12 months after initial diagnosis	No	24	13	152	19.6	Yes	No
155013	3	Male	Salvage one at relapse > 12 months after initial diagnosis	No	24	80	213	29.0	Yes	No
155014	3	Male	Salvage one at relapse > 12 months after initial diagnosis	Yes	26	83	187	17.0	Yes	Yes
156001	1	Male	Salvage one at relapse ≤ 12 months after initial diagnosis	No	56	92	240	4.0	No	No
156002	2a	Female	Salvage one at relapse ≤ 12 months after initial diagnosis	No	60	36	162	3.1	No	No
156003	3	Female	Salvage one at relapse ≤ 12 months after initial diagnosis	No	55	86	597	8.2	No	No
157001	1	Female	Salvage two at second relapse	No	62	88	205	24.6	No	No
157002	1	Male	Salvage two at relapse > 12 months after initial diagnosis	No	24	41	129	18.7	No	No
157003	2a	Male	Salvage two at relapse ≤ 12 months after initial diagnosis	No	31	60	234	5.6	No	No
157004	2b	Female	Salvage one at relapse > 12 months after initial diagnosis	No	72	61	187	22.0	No	No
157005	3	Female	Salvage one at relapse > 12 months after initial diagnosis	Yes	23	93	247	17.0	Yes	Yes
157006	3	Male	Salvage two at second relapse	Yes	21	6	128	17.9	No	Yes
158001	3	Male	Salvage two at second relapse	Yes	21	51	162	26.9	Yes	Yes
159001	3	Male	Salvage two at second relapse	Yes	27	20	177	4.0	Yes	No
159002	3	Female	Salvage two at relapse ≤ 12 months after initial diagnosis	No	64	85	1708	9.0	Yes	No
159003	3	Male	Primary refractory	No	57	19	161	—	Yes	No
159004	3	Male	Salvage two at second relapse	Yes	21	8	299	23.9	Yes	Yes
159005	3	Female	Salvage two at second relapse	No	42	73	546	7.5	Yes	No
160001	2a	Female	Salvage one at relapse ≤ 12 months after initial diagnosis	No	66	8	246	6.4	No	No
160002	2b	Male	Primary refractory	No	20	9	210	—	Yes	No
160003	3	Female	Salvage one at relapse ≤ 12 months after initial diagnosis	No	32	78	772	8.5	Yes	No
160004	3	Male	Salvage two at relapse > 12 months after initial diagnosis	Yes	29	97	135	29.0	Yes	Yes

(continued on following page)

Table A1. Patient Characteristics and Prior Treatment (continued)

Patient No.	Cohort	Sex	Salvage or Primary Refractory	Prior HSCT	Age (years)	Blast Count (%)	LDH (U/L)	Time to Relapse From Diagnosis (months)	Dexamethasone (yes *v* no)	Cyclophosphamide (yes *v* no)
161001	1	Female	Salvage two at relapse ≤ 12 months after initial diagnosis	Yes	37	9	195	7.0	No	Yes
162001	2a	Female	Salvage two at second relapse	Yes	59	80	236	14.0	No	No
162002	2b	Male	Salvage one at relapse > 12 months after initial diagnosis	No	29	96	650	25.4	No	No
163001	3	Male	Salvage one at relapse > 12 months after initial diagnosis	Yes	23	84	164	13.0	Yes	No

Abbreviations: HSCT, hematopoietic stem-cell transplantation; LDH, lactate dehydrogenase.
*Patient underwent two donor lymphocyte infusions before study start (on days −278 and −350).

Table A2. AEs During the Dose-Finding Stage of the Study

Dose ($\mu g/m^2$ per day)	Cohort	No. of Patients	No. of AEs
15	1	7	260
5 to 15	2a	5	110
5 to 15 to 30	2b	6	145

Abbreviation: AE, adverse event.

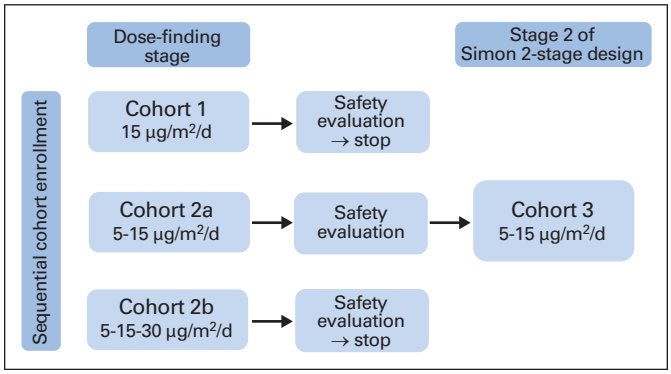

Fig A1. Study design. In cohort 1, patients were treated at a dose of 15 $\mu g/m^2$ per day over the entire treatment period. In cohort 2a, patients received blinatumomab at a dose of 5 $\mu g/m^2$ per day in the first week and then at a dose of 15 $\mu g/m^2$ per day for the remaining period of the first cycle and all following treatment cycles. In cohort 2b, patients were treated at a dose of 5 $\mu g/m^2$ per day for the first week, 15 $\mu g/m^2$ per day in the second week, and 30 $\mu g/m^2$ per day in weeks 3 to 4 of the first cycle and for remaining treatment cycles.