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RESEARCH ARTICLE

Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia

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Abstract

Blinatumomab is a BiTE® (bispecific T-cell engager) molecule that redirects $CD3^+$ T-cells to engage and lyse $CD19^+$ target cells. Here we demonstrate that subcutaneous (SC) blinatumomab can provide high efficacy and greater convenience of administration. In the expansion phase of a multi-institutional phase 1b trial (ClinicalTrials.gov, NCT04521231), heavily pretreated adults with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) received SC blinatumomab at two doses: (1) 250 μg once daily (QD) for week 1 and 500 μg three times weekly (TIW) thereafter (250 μg/500 μg) or (2) 500 μg QD for week 1 and 1000 μg TIW thereafter (500 μg/1000 μg). The primary endpoint was complete remission/complete remission with partial hematologic recovery (CR/CRh) within two cycles. At the data cutoff of September 15, 2023, 29 patients were treated: 14 at the 250 μg/500 μg dose and 13 at 500 μg/1000 μg dose. Data from two ineligible patients were excluded. At the end of two cycles, 12 of 14 patients (85.7%) from the 250 μg/500 μg dose achieved CR/CRh of which nine patients (75.0%) were negative for measurable residual disease (MRD; $<10^{-4}$ leukemic blasts). At the 500 μg/1000 μg dose, 12 of 13 patients (92.3%) achieved CR/CRh; all 12 patients (100.0%) were MRD-negative. No treatment-related grade 4 cytokine release syndrome (CRS) or neurologic events (NEs) were reported. SC injections were well tolerated and all treatment-related grade 3 CRS and NEs responded to standard-of-care management, interruption, or discontinuation. Treatment with SC blinatumomab resulted in high efficacy, with high MRD-negativity rates and acceptable safety profile in heavily pretreated adults with R/R B-ALL.

1 | INTRODUCTION

Long-term survival for patients with B-cell acute lymphocytic leukemia (B-ALL) has improved over recent decades. Novel immune therapies have contributed to this improvement.[1] However, the outcome for relapsed or refractory (R/R) B-ALL in adult patients remains poor, with randomized controlled trials evaluating targeted therapies reporting an approximate median overall survival of 7 months.[2,3]

Many treatment regimens in adult patients with R/R B-ALL now consists of different antibody-based therapeutics and chimeric antigen receptor (CAR) T-cell therapies. The goal of salvage therapy is to induce remission and proceed to allogeneic hematopoietic stem cell transplantation (HSCT). Treatment-related toxicity is frequent.[4] Thus, despite advances, better therapies are needed for R/R B-ALL.

The B-lineage surface antigen cluster designation (CD)-19 is expressed on more than 90% of B-cell precursor ALL blasts. Blinatumomab is a bispecific T-cell engager (BiTE®) molecule that binds simultaneously to CD3-positive cytotoxic T-cells and CD19-positive B-cells. This unique feature of blinatumomab allows it to transiently connect malignant cells with T-cells, thereby inducing T-cell mediated lysis of malignant cells.[5] Blinatumomab with continuous intravenous infusion (cIV) has become a standard treatment regimen utilized in R/R B-ALL.[2,6–8]

The subcutaneous (SC) delivery of blinatumomab was developed to evaluate higher doses aiming to further improve efficacy and simplify administration to enhance convenience for patients. Here, we report the results of the expansion phase of a global, multicenter phase 1b trial in heavily pretreated adults with R/R B-ALL to determine the safety, efficacy, and pharmacokinetics (PK) of SC blinatumomab.

2 | METHODS

2.1 | Trial design and patients

This multicenter, single-arm, open-label, phase 1b trial consisted of dose escalation and dose-expansion and evaluated the safety, tolerability, PK, and efficacy of SC blinatumomab as monotherapy in adult patients with R/R B-ALL. Investigators at 17 centers in six countries enrolled patients as follows: (1) refractory to primary induction therapy or at least one salvage therapy, (2) in untreated first or greater relapse or refractory relapse, or (3) relapse any time after HSCT. Patients with Philadelphia-chromosome positive B-ALL intolerant or refractory to prior tyrosine kinase inhibitors were also eligible. Patients had ≥5% blasts in the bone marrow (BM) and Eastern Cooperative Oncology Group performance status ≤2. Key exclusion criteria

were other active malignancies, clinically relevant (or history of) central nervous system (CNS) pathology, active leukemia in the CNS, (if cerebrospinal fluid [CSF] leukemia was present, intrathecal therapy and negative CSF result were required before enrollment), isolated extramedullary disease, autoimmune disease, active acute or chronic graft-versus-host disease requiring systemic immunosuppressive therapy, HSCT within 12 weeks, chemotherapy or radiotherapy within 2 weeks, immunotherapy within 4 weeks, or ongoing investigational treatment. Prior CD19-directed immunotherapy, such as blinatumomab or CAR T-cell therapy, received more than 4 weeks before enrollment was allowed. The dose escalation and dose-expansion phases of this trial have been completed.[9,10] Here, we report the results of the dose-expansion phase.

2.2 | Treatments

Patients in this study could receive at least one and up to five cycles of SC blinatumomab. Each cycle was 34 days and included a 26-day treatment period followed by an 8-day treatment-free interval. SC blinatumomab was administered once daily (QD) for the first week of cycle 1 and three times weekly (TIW) for rest of the cycle, and all subsequent cycles. The volume administered per injection of SC blinatumomab was 0.3–1.2 mL. Patients were hospitalized for the first 12 days of cycle 1. Subsequent doses were administered as outpatients with a minimum observation period of 1 h. Dose escalation consisted of four dose cohorts of increasing doses of SC blinatumomab (Figure S1). The expansion phase was designed to compare the two active doses from dose escalation, which is consistent with the Food and Drug Administration Project Optimus initiative to reform the dose optimization and dose selection paradigm in the development of oncologic drugs.[11] The two active doses were (1) 250 μg QD/500 μg TIW (250 μg/500 μg) or (2) 500 μg QD/1000 μg TIW (500 μg/1000 μg). Prior to starting SC blinatumomab, low-dose chemotherapy, and/or dexamethasone was recommended (to reduce tumor burden and the incidence of tumor lysis syndrome), at the investigator's discretion but mandatory for patients with BM blasts percentage (determined by cytomorphology) ≥50%, or peripheral blood blast count ≥15 000/μL (see Supplementary Materials for dose and schedule). In addition, patients received premedication with 20 mg of dexamethasone within 6 h of first dose of SC blinatumomab in cycle 1. Low-dose chemotherapy was given within 5 days of start of cycle 1 and evaluation of BM was not required immediately before the start of SC blinatumomab.

2.3 | Assessments

Hematologic remission was defined as <5% BM blasts, no evidence of extramedullary disease, and peripheral blood count recovery as follows: complete remission (CR), platelets>100 000/μL, and absolute neutrophil count (ANC) >1000/μL; CR with partial hematologic recovery (CRh), platelets >50 000/μL, and ANC >500/μL. Hematologic remission was based on local assessment. Measurable residual disease (MRD) analysis was performed locally using either multiparameter flow cytometry (MPFC) or real-time quantitative polymerase chain reaction (RQ-PCR) with a sensitivity of $\geq 10^{-4}$. Central MRD was performed using RQ-PCR of clonal immunoglobulin, T-cell receptor, or gene rearrangements and next-generation sequencing (NGS) using clonoSEQ assay. This assay (Adaptive Biotechnologies Co., Seattle, WA) is an in vitro diagnostic that uses multiplex PCR and NGS to analyze DNA extracted from the patient's BM.[12,13] All patients with BM evaluation had MRD performed at treatment sites. Central MRD was used to confirm local results when available. Evaluation of BM blasts was performed on days 12 (optional) and 27 of cycle 1 and day 27 of subsequent cycles. Lumbar puncture was performed at screening and at the end of each cycle to evaluate CNS leukemic involvement. Blood samples were collected for PK at pre-dose and/or scheduled time points post-dose following QD and TIW dosing in cycle 1. Details of collection times and serum PK analysis are provided in Supplementary Materials. Serum samples were tested at specified timepoints for the presence of anti-drug antibody (ADA) formation. Lymphocyte subset analysis was performed at set time points as outlined in Supplementary Materials.

2.4 | Statistical analysis

Primary endpoint for the expansion phase was CR/CRh within the first two cycles.

These results include all eligible patients. Analysis in the dose-expansion phase included all treated patients except two, both treated at the 500 μg/1000 μg dose, who were found to be ineligible post-enrollment. No formal statistical hypotheses were tested. The protocol and statistical analysis plan are included in Supplementary Materials.

2.5 | Role of the funding source

Amgen conducted statistical analyses and contributed to the writing of the manuscript. Amgen designed the study in collaboration with the study investigators.

3 | RESULTS

3.1 | Patients

Patients in the expansion phase were enrolled between October 24, 2022, and July 31, 2023. The data cutoff was September 15, 2023. Thirty-eight patients were screened: 29 enrolled and two patients were found to be ineligible after enrollment (Figure S2), due to prior history or presence of CNS pathology. Due to ineligibility, all data for these two patients were excluded from the analysis. All patients received open-label study treatment, and nine patients were continuing treatment at the time of this analysis. The treatment

groups had similar demographic and disease characteristics at baseline (Table 1). Median age was 52 years (range, 19–78); 12 patients (44.4%) were aged ≥55 years. Median number of prior therapies was 2 (range, 1–5), including stem cell transplant (eight patients [29.6%]), anti-CD19 CAR T-cell therapy (four patients [14.8%]), and cIV blinatumomab (five patients [18.5%]). Five patients (18.5%) were refractory to first-line therapy. Median number of SC blinatumomab cycles received was 2 (range, 1–4). Median BM blast percentage at screening was 74% (5%–98%).

TABLE 1 Demographics and baseline clinical characteristics of patients treated in the dose-expansion phase who were eligible for analysis.

Characteristics	250 μg/500 μg dose ($N = 14$)	500 μg/1000 μg dose ($N = 13$)
Age, years		
Median	46	56
Range	19–78	25–74
Sex, *n* (%)		
Male	8 (57.1)	8 (61.5)
Female	6 (42.9)	5 (38.5)
Race, *n* (%)		
White	12 (85.7)	7 (53.8)
Asian	0	1 (7.7)
Black	0	0
Other	2 (14.3)	5 (38.5)
Ethnicity—Hispanic, *n* (%)	8 (57.1)	5 (38.5)
ECOG performance status, *n* (%)		
0	6 (42.9)	8 (61.5)
1	6 (42.9)	5 (38.5)
2	2 (14.3)	0
Prior lines of therapy, *n* (%)		
1	4 (28.6)	6 (46.2)
2	4 (28.6)	3 (23.1)
3	4 (28.6)	2 (15.4)
4	1 (7.1)	1 (7.7)
5	1 (7.1)	1 (7.7)
Refractory to first-line therapy, *n* (%)	2 (14.3)	3 (23.1)
Previous allogeneic stem cell transplantation, *n* (%)	5 (35.7)	3 (23.1)
Previous anti-CD19 CAR T-cell therapy, *n* (%)	4 (28.6)	0 (0.0)
Previous cIV blinatumomab, *n* (%)	2 (14.3)	3 (23.1)
Maximum bone marrow blasts, *n* (%)		
5% to <10%	0 (0.0)	2 (15.4)
10% to <50%	3 (21.4)	2 (15.4)
≥50%	11 (78.6)	9 (69.2)

Abbreviations: CAR T-cell, chimeric antigen receptor T-cell; cIV, continuous intravenous; ECOG, Eastern Cooperative Oncology Group.

3.2 | Efficacy

At the data cutoff, 14 patients were treated with the 250 μg/500 μg dose and 13 patients were treated with the 500 μg/1000 μg dose. At the end of two cycles of SC blinatumomab, 12 of 14 patients (85.7%) at the 250 μg/500 μg dose achieved CR/CRh of which nine of 12 (75%) patients were MRD-negative ($<10^{-4}$ leukemic blasts; Table 2). For patients treated with the 500 μg/1000 μg dose, 12 of 13 patients (92.3%) achieved CR/CRh, of which 12 of 12 patients (100%) were MRD-negative. All patients who had a BM assessment at day 12 ($n = 18$) and day 27 ($n = 24$) of cycle 1 had blast-free BM (<5%). At 250 μg/500 μg, six of the seven patients who had central MRD RQ-PCR assessment achieved MRD negativity ($<10^{-5}$); four of the five patients who had central clonoSEQ assessment achieved MRD negativity ($<10^{-6}$). At 500 μg/1000 μg, 5 of the 6 patients who had central MRD RQ-PCR assessment achieved MRD negativity ($<10^{-5}$); five of the five patients who had central clonoSEQ assessment achieved MRD negativity ($<10^{-6}$). At data cutoff, 9 of 27 patients (33.3%) with MRD-negative CR/CRh after SC blinatumomab went on to receive allogeneic HSCT. One patient (3.7%) at the 500 μg/1000 μg dose developed CD19-negative relapse. Nine patients remained in the study.

3.3 | Safety

The median (range) number of treatment cycles was 2 (1–4) for both groups. Treatment-emergent adverse events were reported in 14 of 14 patients (100.0%) at the 250 μg/500 μg dose and in 12 of 13 patients (92.3%) at the 500 μg/1000 μg dose (Table 3). Serious treatment-related adverse events were reported in nine patients (64.3%) at the 250 μg/500 μg dose and in 10 patients (76.9%) at the

TABLE 2 Best hematologic response within two cycles after treatment initiation.

Response category	250 μg/500 μg dose ($N = 14$)	500 μg/1000 μg dose ($N = 13$)
CR	10 (71.4)	12 (92.3)
CRh	2 (14.3)	0
CR/CRh	12 (85.7)	12 (92.3)
MRD-negative in patients with CR/CRh	9 (75.0)	12 (100.0)
Not evaluated	2 (14.3)	1 (7.7)

Note: Data are presented as *n* (%). Complete remission was defined as 5% or less bone marrow blasts and no evidence of disease and was further characterized according to the extent of recovery of peripheral blood counts as follows: complete remission with full recovery (platelet count >100 000/μL and absolute neutrophil count >1000/μL) and complete remission with partial recovery (platelet count of >50 000/μL and absolute neutrophil count of >500/μL). MRD was reported based on a minimum sensitivity of $<10^{-4}$.
Abbreviations: CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; MRD, measurable residual disease.

TABLE 3 Incidence of adverse events for patients treated with a dose of 250 μg/500 μg or 500 μg/1000 μg.

Adverse event	250 μg/500 μg (*N* = 14) No. of patients (%)	500 μg/1000 μg (*N* = 13)
Any grade adverse events	14 (100.0)	12 (92.3)
Adverse events related to SC blinatumomab		
Serious adverse event	9 (64.3)	10 (76.9)
Fatal adverse event	0	0
Grade ≥3 adverse events	12 (85.7)	8 (61.5)
Leading to discontinuation of treatment	2 (14.3)	1 (7.7)
Due to cytokine release syndrome	1 (7.1)	0 (0.0)
Due to neurologic event	1 (7.1)	0 (0.0)
Leading to interruption of treatment	11 (78.6)	9 (69.2)
Due to cytokine release syndrome	7 (50.0)	5 (38.5)
Due to neurologic event	6 (42.9)	4 (30.8)
Grade ≥3 adverse events of interest		
Cytokine release syndrome	3 (21.4)	3 (23.1)
Neurologic event	6 (42.9)	3 (23.1)
Aphasia	0	1 (7.7)
Delirium	0	1 (7.7)
Headache	1 (7.1)	0
Immune effector cell-associated neurotoxicity syndrome	3 (21.4)	2 (15.4)
Neurotoxicity	1 (7.1)	1 (7.7)
Somnolence	1 (7.1)	0
Any decrease in platelet count	3 (21.4)	3 (23.1)
Any decrease in white-cell count	0	1 (7.7)

Abbreviation: SC, subcutaneous.

500 μg/1000 μg dose (Table 3). Grade ≥3 treatment-related events were reported in 12 patients (85.7%) at the 250 μg/500 μg dose and in eight patients (61.5%) at the 500 μg/1000 μg dose. Cytokine release syndrome (CRS) and neurologic events (NE) including immune effector cell-associated neurotoxicity syndrome (ICANS) were events of interest. While treatment-related grade ≥3 CRS events occurred equally in three (21.4%) patients at 250 μg/500 μg and three patients (23.1%) at 500 μg/1000 μg, treatment-related grade ≥3 NE including ICANS occurred less frequently at 500 μg/1000 μg (three patients [23.1%]) versus (six patients [42.9%]) at 250 μg/500 μg (Table 3). Of note, of the six patients at 250 μg/500 μg who had NEs, one had a grade 3 headache, associated with lumbar puncture. For both doses combined, median time to onset for grade ≥3 CRS events was 2 days (range 1–7 days) and for grade ≥3 NE, it was 7 days (range 2–50 days). One grade 3 CRS event at 250 μg/500 μg occurred on day 7, 1 day after restarting SC blinatumomab following 5 days of interruption due to a grade 1 CRS. Two grade 3 NEs occurred in cycle 2, one at 250 μg/500 μg (cycle 2 day 8) and one at 500 μg/1000 μg (cycle 2 day 3). No grade 4 treatment-related events CRS or NE including ICANS were reported. Treatment interruption and discontinuation were required by the protocol for the management of certain adverse events. At 250 μg/500 μg, SC blinatumomab-related treatment discontinuation was reported in two patients (14.3%), and treatment interruption in 11 patients (78.6%). At this dose, the treatment was interrupted in six patients with NE and in seven patients with CRS events (two patients had both NE and CRS requiring treatment interruption) and was discontinued in one patient for NE and one patient for CRS. At 500 μg/1000 μg, the treatment was interrupted in nine patients (69.2%) for treatment-related adverse events, of which therapy was interrupted due to CRS in five patients, NE in four patients, and discontinued due to cholestasis unrelated to SC blinatumomab in a single patient with prior liver injury. All patients for whom treatment was interrupted resumed at the same dose prior to the interruption. Overall, the drug interruption or discontinuation rates were lower at 500 μg/1000 μg (nine patients [69.2%]) than at 250 μg/500 μg (11 patients [78.6%]). Treatment-emergent fatal adverse events were reported in two patients up to 30 days from the last dose of administration. One patient at 250 μg/500 μg developed cerebral edema; the patient relapsed after multiple rounds of therapy, including (chemotherapy, cIV blinatumomab, CD19 CART [the latter with discontinuation because of toxicity], and allogeneic HSCT [all within 6 months of receiving SC blinatumomab]). No serious adverse events had been reported with prior cIV blinatumomab. The patient's history showed ongoing coagulopathy with history of thrombosis and embolism, the patient had an indwelling Ommaya shunt, had developed chemical meningitis possibly related to intrathecal therapy (4 weeks prior to receiving SC blinatumomab). Due to multiple confounding comorbidities and unsuccessful prior treatment attempts and with the lack of CNS symptoms commonly observed with blinatumomab, the event was not assessed as attributed to the use of SC blinatumomab. The other patient at 500 μg/1000 μg developed disease progression with hepatic failure; the patient had preexistent liver injury prior to blinatumomab treatment. The event was not attributed to the use of SC blinatumomab.

3.4 | Pharmacokinetics

Pharmacokinetic profiles of SC blinatumomab are shown in Figure 1. To present a full characterization of blinatumomab PK, results from dose escalation (discussed in Supplementary Materials) and expansion were presented. Median time to maximum concentration ranged from approximately 6–12 h. Dose-related increase in exposure was observed over the dose range. Mean apparent elimination half-life was approximately 8–12 h after repeat dosing. Observed exposures (mean steady-state average concentration [$C_{avg,ss}$]) following QD and

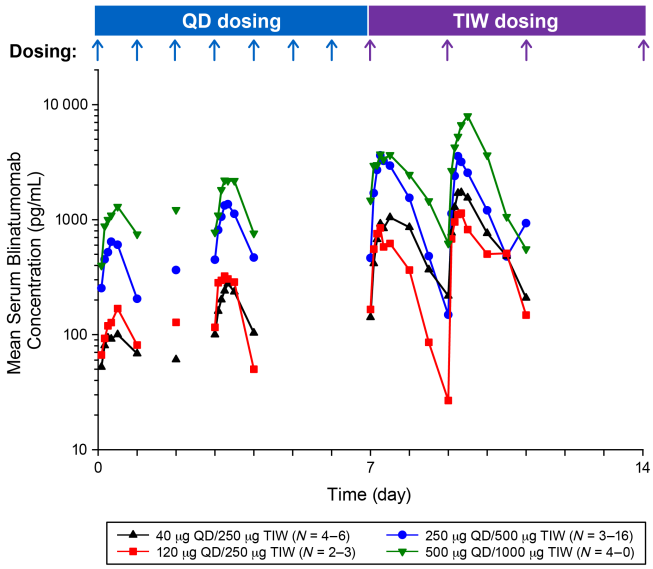

FIGURE 1 Pharmacokinetics of blinatumomab following subcutaneous administration. Mean serum concentration-time profiles of once daily (QD) and three times weekly (TIW) dosing over the first 14 days of cycle 1 are presented.

TIW dosing for the expansion doses generally exceeded exposures (mean steady-state concentration [C_{ss}]) of 28 µg/day cIV (efficacious cIV dose for R/R B-ALL).[14]

3.5 | Immunogenicity and pharmacodynamics

Aggregate data across dose escalation show no evidence for immunogenicity for SC blinatumomab. SC blinatumomab resulted in profound CD19-positive B-cell depletion observed with both 250 µg/500 µg and 500 µg/1000 µg doses in patients with quantitative baseline data. Further pharmacodynamic analysis is presented in Supplementary Materials (Figures S3–S5A,B, and S6A,B).

4 | DISCUSSION

This study has demonstrated for the first time that T-cell engagement as treatment for B-ALL is possible by the SC administration of a single agent. In the expansion phase of this multi-institutional phase 1b trial in adults with R/R B-ALL, treatment with SC blinatumomab as monotherapy resulted in higher CR and MRD response rates than that reported with cIV, and with comparable toxicity.[2] CR/CRh rates after two cycles of SC blinatumomab were 85.7% with 75.0% MRD response rate and 92.3% with 100.0% MRD response rate at the 250 µg/500 µg dose and the 500 µg/1000 µg dose, respectively. All patients received the efficacious dose from day 1 (no lower initial dose as with cIV formulation) and all 18 patients assessed on day 12 achieved CR/CRh.

SC blinatumomab dosing exhibited a favorable PK profile that included a gradual increase in exposure compared with cIV, allowing for higher doses and earlier exposures and an apparent increase in half-life for SC blinatumomab (~8–12 h vs. ~2 h for cIV) allowing for convenient TIW dosing after the first 7 days.[13] Both expansion dosing regimens resulted in observed exposures (mean $C_{avg,ss}$) from QD and TIW doses that generally exceeded the exposures (mean C_{ss}) of the cIV dose (28 µg/day).[10,15] This favorable SC PK profile and higher first week exposures than in cIV may have contributed to the high efficacy with faster and deeper responses compared with the cIV regimen.

While the rate of treatment-related grade 3 CRS events at dose levels 250 µg/500 µg and 500 µg/1000 µg were 21.4% and 23.1%, respectively, the rates of treatment-related grade 3 NE including ICANS were 42.9% and 23.1%, respectively. The reason for the higher rate of NE in the lower dose level is unclear. A larger sample size of patients may be needed for further evaluation. All grade 3 CRS and NE responded to standard-of-care treatment and dose interruption and were completely reversible. Treatment could be resumed without dose reduction. In patients with NE, no change in imaging was observed after the event and all resolved without sequelae (data not shown). There were no grade 4 or 5 CRS or NE related to SC blinatumomab. In contrast, grade 4 NE is associated with cIV blinatumomab.[8,16,17] There was no hepatic toxicity related to SC blinatumomab. No ADA was identified during SC blinatumomab treatment. The PK profile of SC blinatumomab with slow gradual increases in exposure may contribute to the observed acceptable safety profile.

The safety and efficacy data of SC blinatumomab compare favorably with other targeted therapies used in R/R B-ALL.[1,18] In the Ino-Vate trial, when adult patients were treated with inotuzumab ozogamicin (INO), a CR/CRi rate of 80.7% and an MRD-negativity rate of 78.4% among responders was observed.[3] The rate of grade ≥3 treatment-emergent sinusoid obstruction syndrome (SOS) was 11%. In the multicenter ZUMA-3 study evaluating KTE-X19 CAR T-cell therapy for adults with R/R ALL, 71% of patients had CR/CRi, with 97% of responders having MRD-negative disease.[19] Grade ≥3 CRS rate was 24% including 11% grade 4 CRS. The NE rate was 25% and included a grade 4 encephalopathy and a grade 5 brain herniation. This modality of treatment with the production of the CAR T-cells is laborious and may only be available for patients at selective centers. Fourteen of the enrolled patients (20%) did not receive KTE-X19 for reasons including unsuccessful manufacturing of the product. SC blinatumomab is available off-the-shelf and overcomes this limitation.

Even in combination therapies used in R/R B-ALL, SC blinatumomab data also compare favorably. In a recent phase 1 trial of dose-adjusted EPOCH chemotherapy plus INO, the CR/CRi rate was 85%, and 70% achieved MRD negativity. The rate of SOS was 4%.[20] In the study by Kantarjian et al., salvage therapy with mini-hyper-CVD and INO with or without cIV blinatumomab in R/R B-ALL resulted in a CR of 63%, CRp (CR without platelet recovery) of 19%, and CRi of 3%, with MRD negativity in 82% of the responders.[21]

Intravenous blinatumomab is beneficial for patients with R/R B-ALL,[2,7,8,16,22] but early data from SC blinatumomab suggest improved efficacy with a more convenient delivery profile.

TABLE 4 Treatment response with MRD status within first two cycles in patients treated with 250 μg/500 μg and 500 μg/1000 μg dose of SC blin.

Patient no.	BM%	C1D12[a] Treatment response (CR/CRh[c]): BM-MRD (l/c/n)[d]	C1D27	C2D27	Patient disposition[b]
Dose of SC blinatumomab: 250 μg/500 μg					
1	93	CRh: l−/c−/n(−)	CR: l−/c−	CR: l−/c−/n−	HSCT after C2
2	74	CR	CR: l+	CR	HSCT after C2
3	15	CR	CR	CR	Ended SC blin after C2: patient request, no SAE, no FU
4	58	CR: l−/c+/n+	CR: l−/c−/n(−)	CR: l−/c−/n−	HSCT after C3
5	41	CR: l−/c−/n−	CR: l−/c−/n−	CR: l−/c−	HSCT after C2
6	66	CR: l−	CR: l−	CR: l−	HSCT after C2
7	57	NP	CR: l−	CR: l−	HSCT after C2
8	95	CRh: c−	IE: c−/n(−)	CRh: l−/c−/n(−)	HSCT after C4
9	83	IE: c−	CR: l−/c−	-	Ended SC blin in C1: SAE
10	74	NP	-	-	Death in C1[e]
11	29	NP	CRh: l−	NP	Ended SC blin after C1D12: patient request, death from PD in FU
12	58	NP	CR: l−/c+/n+	-	Ended SC blin in C1: SAE , received HSCT
13	90	NP	NP	NP	Ended SC blin in C1W1: patient decision AMA, lost to FU
14	90	CR: l−/c−	CR: l−/c−	-	HSCT after C1
Dose of SC blinatumomab: 500 μg/1000 μg					
15	5	CR	CRh	CR: l−	Completed C5
16	94	CRh	CR: l−	-	End in C1: SAE[e]
17	85	CR: l−	CR: l−	ON	HSCT after C2
18	10	CRh: c−/n(−)	CR: c−/n−	ON	HSCT after C2
19	81	CRh: l−	CR: l−	CR: l−	C5 Ongoing
20	6	CR: l−/c−/n+	CR: l−/c+/n+	CR: l−/c−/n(−)[f]	C5 Ongoing
21	97	CRh: l−	CR: l−	CR: l−	HSCT after C2
22	97	NP	-	-	Death in C1[e]
23	70	CR: c+	CRh: l−	CRh: l−/c+/n−	CART after C4
24	98	NP	CR: l−	CR: l−	HSCT after C2
25	80	CR: l−/c+/n+	CR: l−/c−/n−	CR: l−/c−/n−	HSCT after C3
26	30	CR: l−/c−	CR: l−/c−/n−	Relapse	Relapse after C2
27	72	NP	CR: l−/c−/n−	CR: l−/c−/n−	C4 ongoing

Abbreviations: AE, adverse events; AMA, against medical advice; BM, bone marrow; BM% percentage of BM blasts at enrollment, blin, blinatumomab; c, central measurable residual disease analysis performed by RQ-PCR at central laboratory (sensitivity $<10^{-5}$); c+, central measurable residual disease-positive; c−, central measurable residual disease-negative; C, cycle; CART, chimeric antigen receptor T-cell therapy; CR, complete remission; CRh, CR with partial count recovery; D, day; FU, follow up; HSCT, hematopoietic stem cell transplant; l, local measurable residual disease analysis result performed by either multiparameter flow cytometry or RQ-PCR at the site (sensitivity of $<10^{-4}$); l+, positive local measurable residual disease; l−, negative local measurable residual disease; IE, cytomorphology reported as inevaluable; MRD, measurable residual disease; n, measurable residual disease analysis done by next-generation sequencing (sensitivity $<10^{-6}$); n+, next-generation sequencing measurable residual disease-positive; n−, next-generation sequencing measurable residual disease-negative; n(−), next-generation sequencing measurable residual disease indeterminate-a copy of the dominant sequence was detected in the sample, but the rearrangement was present below the limit of detection for the given sequence; NGS, next-generation sequencing; NP, bone marrow evaluation was not performed; ON, cycle ongoing at data cut; SAE, serious adverse event; SC, subcutaneous.

[a]All patients with C1D12 BM evaluation achieved a blast percentage of <5% at data cut. Some treatment responses results (CR/CRh) were entered after data cut.

[b]Patient disposition: patient status as of October 30, 2023. Most patients proceeded to HSCT after MRD-negative CR/CRh or completed the protocol maximum of 5 cycles. Patient data on post SC blinatumomab HSCT or post C5 blinatumomab outcome not available at data cut.

[c]CR and CRh were reported by investigators.

[d]MRD assessment done locally (l), centrally by RQ-PCR (c), centrally by NGS (n).

[e]Unrelated to SC blinatumomab.

[f]C2D27 NGS data point n (−) added after data cut.

Subcutaneous blinatumomab is delivered in a small-volume injection (0.3–1.2 mL per dose), is easy to prepare and administer, and has been tolerated by patients without any local reaction or pain.[10,23] The observed high efficacy with SC blinatumomab as monotherapy supports further exploration in earlier lines of therapy which may spare the need for intensive chemotherapy and/or transplantation. It has been demonstrated that the efficacy of blinatumomab is higher in earlier than in later treatment lines.[24,25] Approximately one third of patients proceeded to allogeneic HSCT after achieving MRD negativity with SC blinatumomab; however, four patients at the 500 μg/1000 μg dose and one patient at the 250 μg/500 μg dose completed four cycles with persistent MRD-negative CR suggesting durability of the deep response achieved with SC blinatumomab (Table 4). The combination of convenience, ease of delivery, and high efficacy could have tremendous global impact making this effective treatment modality available to more patients in different healthcare eco-systems.

Limitations of this trial include the small sample size. However, the corroborating PK evidence of dose-dependent increase in exposure validates the clinical findings. The early large reduction of tumor load and the combination of CR with deep MRD responses further provide evidence of efficacy. Another limitation is that only 50% of the patients had MRD evaluation performed centrally. Local MRD testing however was performed using MPFC or RQ-PCR with a sensitivity of at least $<10^{-4}$.

In summary, this multi-institutional phase 1b trial, in heavily pretreated adults with R/R B-ALL, treatment with SC blinatumomab demonstrated high efficacy with an acceptable safety profile. These encouraging results could be practice-changing and warrant further exploration for patients with B-ALL. Randomized controlled trials are warranted to test these hypotheses.

AUTHOR CONTRIBUTIONS

EJ, VA, PM-S, JJRR, RDC, BB, AR, MA-H, FH, TC, MTD, VV, JG-C, AR, SS, CB, JMH-R, MB, and HK contributed toward data collection, data analysis, and data interpretation. GZ, PRG, AH, YC, HLW, BP, YK, and AM contributed toward study design, data collection, data analysis, data interpretation, preparation of figures, and writing of the manuscript. EJ, PRG, GZ, and AM directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication.

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CONFLICT OF INTEREST STATEMENT

EJ reports research grants from Pfizer, Takeda, Amgen, AbbVie, Novartis, Astex, Adaptive Biotechnologies, and Ascent AG and consultancy to Pfizer, Takeda, Amgen, AbbvVie, BMS, Novartis, Genentech, Adaptive Biotechnologies, and Ascentage. GZ is employed by Amgen and holds stock and reports issue of patents (20190300609, 20130323247, and 20110262440), and has patents pending (10696744, 10662243, 20190142846, 20190142846, 20170327581, 10130638, 9688760, 20170122947, 9486475, 20160208001, 9192665, 20150071928, 8840888, 20140228316, 20140227272, 20130287778, and 20130287774). PM reports honoraria from Pfizer, Jazz Pharmaceuticals, and Incyte and support for attending meetings from Jazz Pharmaceuticals, AbbVie, Pfizer, and BMS. JJRR reports honoraria from Amgen for an online lecture at "Escuela de Leucemia" in Mexico; support from Amgen to attend ALL Assembly (Madrid 2023); RDC reports grant funding to his institution and honoraria for the current study from Amgen, grants from Kite/Gilead, Incyte, Pfizer, Merck, Servier, and Vanda Pharmaceuticals; consulting fees from Pfizer, Kite/Gilead, and Jazz; honoraria from Pfizer and Kite/Gilead; support for attending meetings from Pfizer; participation on advisory board for Autolus and PeproMene Bio; and stock options from Seagen. BB reports consulting fees from Pfizer and Amgen; honoraria from Gilead, Pfizer, and Amgen; and support for attending meetings from Gilead, Amgen, and Novartis. AR reports honoraria from BMS and Servier. MA-H reports honoraria from Jazz, Servier, and Takeda and participation on a Data Safety Monitoring Board for Kite, Rigel, Daiichi, Incyte, and Takeda. FH reports honoraria from Amgen, Incyte, Novartis, Pfizer, Clinigen, Servier, and Amgen and support for attending meetings from Amgen, Novartis, and Incyte. TC reports consulting fees from Celgene/BMS, AbbVie, Jazz Pharmaceuticals, Servier, and Novartis; honoraria from Novartis, Syros, Celgene/BMS, Takeda, Servier, and Keros; support for attending meetings from Pfizer, Celgene/BMS, Novartis, AbbVie, and Gilead; and participation on a Data Safety Monitoring Board for Novartis and Celgene/BMS. MTD reports honoraria from AbbVie, Gilead, Pfizer, Astellas, and BMS, support for attending meetings from Jannsen, AbbVie, and Jazz, and participation on Data Safety Monitoring Board for SOBI. AR reports honoraria from Novartis, Amgen, Pfizer, Astellas, Jazz, Jannsen, Incyte, Kite-Gilead, Roche, and Omeros; support for attending meetings from Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Roche, and Omeros; and participation on a Data Safety Monitoring Board for Novartis, Amgen, Pfizer, Astellas, Jazz, Janssen, Incyte, Kite-Gilead, Roche, and Omeros. SS reports honoraria from CSi Hamburg and Amgen; support for attending meetings from Amgen; and participation on a Data Safety Monitoring Board for Amgen and Pfizer. JMH-R reports grants from Celgene, Novartis, and Pfizer; consulting fees from GSK; honoraria from Amgen, Novartis, Pfizer, and BMS; payment for expert testimony from Novartis, Pfizer, Amgen, and BMS; and support for attending meetings from Pfizer and BeiGene. MB reports support for this article

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DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Complete details are available at https://www.amgen.com/datasharing. The study protocol and statistical analysis plan are included as Supplementary Materials.

PATIENT CONSENT

All patients provided written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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