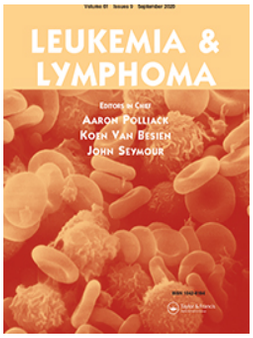

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ORIGINAL ARTICLE

Open-Label, phase 2 study of blinatumomab as second salvage therapy in adults with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma

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ABSTRACT

The phase 2 portion of this open-label phase 2/3 study assessed the efficacy and safety of blinatumomab as second salvage for aggressive relapsed or refractory (r/r) aggressive B-cell non-Hodgkin lymphoma (B-NHL) following platinum-based first salvage chemotherapy. Forty-one patients with aggressive disease (32% relapsed; 68% refractory) enrolled and received stepwise blinatumomab (9–28–112 μg/day) in a 70-day cycle 1 and an optional 28-day cycle 2; 19 (46%) completed cycle 1 and 3 (7%) completed cycle 2. The overall response rate after 12 weeks was 37%, including 9 (22%) complete metabolic responses. Eight (20%) patients (all responders) subsequently received stem cell transplants. Grade ≥3 adverse events were reported in 29 (71%) patients. Grade 3 cytokine release syndrome occurred in one patient. Grade 3 neurologic events occurred in 10 (24%) patients; all resolved. Blinatumomab monotherapy appears effective as second salvage therapy in patients with r/r aggressive B-NHL.

Trial registration: NCT02910063.

ARTICLE HISTORY
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KEYWORDS
B-cell non-Hodgkin lymphoma; B-NHL; salvage therapy; blinatumomab; phase 2 trial; DLBCL

Introduction

Between one-third to one-half of patients with diffuse large B-cell lymphoma (DLBCL), the most common type of B-cell non-Hodgkin lymphoma (B-NHL) are either refractory to or relapsed following first-line treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) [1]. Rituximab combined with platinum-based chemotherapy followed by autologous hematopoietic stem cell transplant (autoHSCT) is a commonly used first salvage regimen in transplant-eligible patients with relapsed or refractory (r/r) B-NHL. However, only 30–40% of patients with r/r B-NHL respond to first salvage and potentially benefit from autoHSCT, and half of the patients relapse after first salvage and autoHSCT [2–7]. Outcomes among patients with r/r B-NHL following first salvage or later lines of therapy are poor, with median overall survival (OS) of 6 months or less [8,9]. Although CAR-T cell therapy has recently been accepted as a second salvage for B-NHL, there is an unmet need for novel treatments.

Blinatumomab, a bispecific T-cell engager (BiTE®) immunotherapy that directs cytotoxic T cells to lyse B cells expressing CD19 [10], has demonstrated benefits in median OS and relapse-free survival benefit in patients with r/r B-cell precursor ALL, including those with minimal residual disease [11,12]. There is also early clinical evidence for blinatumomab activity in patients with aggressive r/r B-NHL. Among patients with r/r B-NHL who received the blinatumomab target dose (60 μg/m^2/day) in a phase 1 study, the overall response rate (ORR) was 69% across B-NHL subtypes ($n = 35$) and 55% for diffuse large B-cell lymphoma

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Supplemental data for this article can be accessed here.

(DLBCL; $n = 11$) [13]. In a phase 2 study of blinatumomab in patients ($N = 25$) with heavily pretreated r/r DLBCL, the ORR was 43% among 21 evaluable patients, with complete response (CR) in 19% [14].

The phase 2 portion of this open-label phase 2/3 study assessed the efficacy and safety of blinatumomab as second salvage in patients with aggressive r/r B-NHL who did not achieve complete metabolic response (CMR) with platinum-based first salvage.

Materials and methods

Patients

Patients aged ≥18 years with biopsy-confirmed B-NHL that was relapsed (prior CMR) or refractory (no prior CR or CMR) following first-line treatment with anthracycline-based chemotherapy and anti-CD20 therapy were eligible. Additional eligibility criteria were progressive metabolic disease (PMD), no metabolic response (NMR), or partial metabolic response (PMR) by centrally assessed PET/CT scan following ≥2 cycles of the standard of care platinum-based first salvage chemotherapy or PMD by centrally assessed PET/CT scan following ≥1 cycle of platinum-based first salvage chemotherapy; Eastern Cooperative Oncology Group performance status ≤2; intention to proceed to high-dose chemotherapy; absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, creatinine clearance ≥50 mL/min, aspartate aminotransferase and alanine aminotransferase <3 × upper limit of normal (ULN), and total bilirubin <2 × ULN within 14 days before enrollment and after last first salvage chemotherapy. A pre-salvage scan was submitted to the central reader for patients with only one cycle of pre-salvage chemotherapy. Patients with prior radiotherapy were required to be PET positive ≥6 weeks after the last treatment. Key exclusion criteria included lymphoblastic, Burkitt, or mantle cell lymphoma; prior anti-CD19 therapy, autologous hematopoietic stem cell transplant (HSCT) with high-dose chemotherapy, or allogeneic HSCT; investigational drug/device within 30 days before enrollment; and central nervous system (CNS) involvement of NHL or clinically relevant CNS pathology. All patients provided written, informed consent before enrollment. Institutional review board approval was obtained for all study procedures.

Study design and treatment

This is the primary analysis of the open-label, phase 2 portion of an adaptive phase 2/3 study (NCT02910063) that was conducted at 19 centers. The phase 3 portion of the study did not enroll. Blinatumomab was given by continuous intravenous infusion for a single 70-day cycle 1 (9 μg/day for 7 days, 28 μg/day for 7 days, and 112 μg/day for 42 days, followed by a 14-day treatment-free interval) and an optional 28-day second cycle (9 μg/day for 7 days, 28 μg/day for 7 days and 112 μg/day for 14 days) at the investigator's discretion. Dexamethasone 20 mg was required within one hour before each blinatumomab dose for the prevention of cytokine release syndrome (CRS) and within one hour before restarting blinatumomab after any interruption lasting >4 h due to an adverse event (AE). Dexamethasone was administered at a daily maximum of three doses of 8 mg (24 mg/day) for up to 3 days for symptoms of CRS. Dexamethasone was administered at a dose of at least 24 mg/day for up to 3 days for neurologic events (NEs), depending on the grade of NE. Patients could receive HSCT at the investigator's discretion at any time after primary endpoint assessment.

Blinatumomab treatment was interrupted for grade 3 NEs, CRS, or other clinically relevant AEs or certain liver enzyme increases (total bilirubin [TBL] > 2 × ULN; alkaline phosphatase >8 × ULN; aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 8 × ULN; AST or ALT >5 × ULN but <8 × for ≥2 weeks; AST or ALT >3 × ULN with clinical signs of hepatitis [e.g. right upper quadrant abdominal pain/tenderness, fever, nausea, vomiting, and jaundice) but could be restarted (after dexamethasone premedication) when the AE had resolved to grade 1 or baseline, either at the same dose or at 9 μg/day. If the grade ≥3 NE or CRS occurred while the patient was receiving blinatumomab 112 μg/day, the patient restarted at 28 μg/day; if it occurred while the patient was receiving blinatumomab 9 or 28 μg/day, the patient restarted at 9 μg/day. Blinatumomab was discontinued for grade 4 NEs, CRS, or other grade 4 AEs; grade 3 NEs or CRS that did not return to grade 1 or baseline within 7 days; grade 3 clinically relevant AEs not returning to grade 1 or baseline within 14 days; two or more seizures; TBL >2 × ULN or international normalized ratio >1.5; or AST or ALT >3 × ULN when baseline was < ULN, and when no cause for the elevations was apparent. Hematologic toxicity was managed at the discretion of the investigators.

Study assessments

Clinical tumor assessments based on changes in the size of previously abnormal lymph nodes or extranodal sites or the development of new lesions were performed at baseline, on days 1, 57, and 70 during cycle

1, and on days 1 and 42 of optional cycle 2. PET/CT was performed at baseline and on day 70 of cycle 1 and following optional cycle 2. Central assessment of diagnostic biopsies included fluorescent *in situ* hybridization (FISH) and immunohistochemistry. A bone marrow biopsy and aspirate was performed at baseline and on day 70 of cycle 1 if there was prior evidence of bone marrow involvement. Scans were assessed by central review. Response was assessed per Lugano classification (PET/CT response, CMR, PMR, NMR, or PMD) [15]. All AEs occurring during the study were recorded and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [16]. Determination of cell of origin (immunohistochemistry and gene expression profiling) and assessment of BCL-2, BCL-6, and MYC (FISH) and double expression (immunohistochemistry) was performed by NeoGenomics Laboratories, Inc., and was centrally reviewed.

Statistical analysis

The primary endpoint was CMR by central PET. Additional endpoints included median OS (time from enrollment to death), ORR (CMR plus PMR), progression-free survival (PFS; time from enrollment to disease progression or death, whichever occurred first), duration of response (time from earliest assessment of CMR or PMR to relapse or death, whichever occurred first), post-response HSCT rate, and the incidence and severity of AEs. Endpoints were assessed based on intent to treat (ITT).

The sample size was determined by a 1-sample test of the rate of CMR after 1 cycle of blinatumomab. With the 1-sided type I error rate of 0.025, a null hypothesis response probability of 15%, and an alternative response probability of 40%, a sample size of 36 patients was estimated to provide 90% power to reject the null hypothesis that the response probability is no more than 15%.

The proportion of patients achieving CMR after the first or second cycle was summarized with a two-sided 95% confidence interval (CI). Median OS, PFS, and duration of CMR were estimated using the Kaplan-Meier method and were summarized with hazard ratios and two-sided 95% CIs. All other data were summarized descriptively. SAS version 9.4 was used for all analyses.

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

Results

Patients

Between 23 January 2017 and 15 January 2018, 41 patients were enrolled in the phase 2 study. At enrollment, this population of patients manifested aggressive disease, given that 28 (68%) patients were refractory to first-line therapy and 27 (66%) had demonstrated progressive disease following first salvage (Table 1). Seventeen (42%) patients were nonresponsive to both first-line therapy and first salvage. At enrollment, R-CHOP was the most common first-line regimen received, and R-ICE was the most common first salvage regimen (Table S1).

Of 33 patients with known cell of origin using immunohistochemistry and gene expression profiling, 17 (42%) were germinal center B-cell (GCB), and 16 (39%) were non-GCB per central review (Table 1). High proportions of patients had double or triple expressor B-NHL ($n = 15$ [37%]). Nine (22%) patients had C-myc and Bcl-2 or Bcl-6 rearrangements, with five (12%) patients being double hit and four (10%) patients being triple hit.

Disposition and exposure

All 41 patients in the ITT analysis received blinatumomab (Figure 1). Overall, 19 (46%) patients completed cycle 1 of blinatumomab, and 22 (54%) discontinued due to disease progression ($n = 17$), AEs ($n = 4$), or death ($n = 1$). Four (10%) patients initiated the optional cycle 2 of blinatumomab, 3 (7%) completed the cycle, and 1 (2%) discontinued due to an AE. Treatment interruptions occurred in 23 (56%) patients: 13 due to AEs, two per protocol, and nine for unspecified reasons. In total, 24 (59%) patients received $\geq$80% of the intended dose of blinatumomab (Table S2). The mean dose received was 67% of the intended dose.

Response and survival

In the ITT analysis, 15 of 41 (37%; 95% CI, 22–53) patients had an objective response per central review after 12 weeks of treatment, including 9 (22%; 95% CI, 11–38) with CMR and 6 (15%; 95% CI, 6–29) with PMR (Table 2). Five (12%) patients had NMR and 12 (29%) had PMD. Median duration of response was not estimable; however, 64% (95% CI, 28–86) of objective responders and 86% (95% CI, 33–98) of patients achieving CMR were estimated to still be in response at 9 months. CMR was achieved by 5 of 13 (39%) patients who had relapsed disease following first salvage therapy, 4 of 28 (14%)

Table 1. Demographics and baseline disease characteristics.

Characteristics	Patients ($n = 41$)
Median (range) age, years	56 (19–75)
Sex, *n* (%)	
Men	28 (68)
Women	13 (32)
Race, *n* (%)	
White	38 (93)
Black	1 (2)
Asian	1 (2)
Not reported	1 (2)
ECOG performance status, *n* (%)	
0	19 (46)
1	18 (44)
2	3 (7)
Missing	1 (2)
Disease type, *n* (%)	
Diffuse large B-cell lymphoma	34 (83)
Primary mediastinal (thymic) large B-cell lymphoma	4 (10)
High grade B-cell lymphoma with C-myc, Bcl-2, and/or Bcl-6 rearrangements	2 (5)
T-cell/histiocyte–rich large B-cell lymphoma	1 (2)
Disease stage, *n* (%)	
I	1 (2)
II	4 (10)
IIE	3 (7)
III	10 (24)
IV	20 (49)
Missing	3 (7)
International Prognostic Index at study entry, *n* (%)	
Low risk	15 (37)
Low-intermediate risk	11 (27)
High-intermediate risk	11 (27)
High risk	4 (10)
Disease status after first-line therapy, *n* (%)	
Relapsed	13 (32)
Refractory	28 (68)
Response after first salvage, *n* (%)	
NMR	5 (12)
PMR	9 (22)
PMD	27 (66)
Prior indolent lymphoma, *n* (%)	6 (15)
Extranodal disease, *n* (%)	25 (61)
Cell of origin determination, *n* (%)	
Known	33 (81)
GCB	17 (42)
Non-GCB	16 (39)
Unknown[a]	8 (20)
C-myc, Bcl-2, and Bcl-6 rearrangement, *n* (%)	9 (22)
Double hit,[b]	5 (12)
Triple hit,[c]	4 (10)
Double or triple expressor, *n* (%)	15 (37)

GCB: germinal center B cell–like.
[a]Reasons for no cytogenetics reporting included no cytogenetics or FISH reports in hospital records; data not available; and cell of origin determination not performed by IHC or gene expression profiles/arrays.
[b]Defined as rearrangement of C-myc and either Bcl-2 or Bcl-6.
[c]Defined as rearrangement of C-myc, Bcl-2, and Bcl-6.

patients with disease refractory to first-line therapy, and 3 (8%) of patients who were non-responsive to both first-line therapy and first salvage. Six (15%) patients non-responsive to both first-line therapy and first salvage had objective responses (CMR or PMR). Among 36 patients who completed $\geq$7 days of infusion at the highest intended dose level, 13 (36%) had an objective response, including eight (22%; 95% CI, 10–39) with CMR and five (14%; 95% CI, 5–30) with PMR.

Treatment with blinatumomab led to CMR in 4 of 9 (44%) patients who had previously achieved PMR following first salvage, in 3 (33%) who had NMR following first salvage, and 2 (22%) who had PMD following first salvage. In a prespecified subgroup analysis, there was a trend toward CMR favoring patients who had relapsed versus refractory disease after first-line therapy, those who achieved PMR vs PMD following first salvage, and those with GCB versus non-GCB cell of origin (Figure 2).

Among patients with CMR after 12 weeks of treatment, 85.7% (95% CI, 33.4–97.9) were estimated to still be in CMR at 9 months (median follow-up, 8.8 months

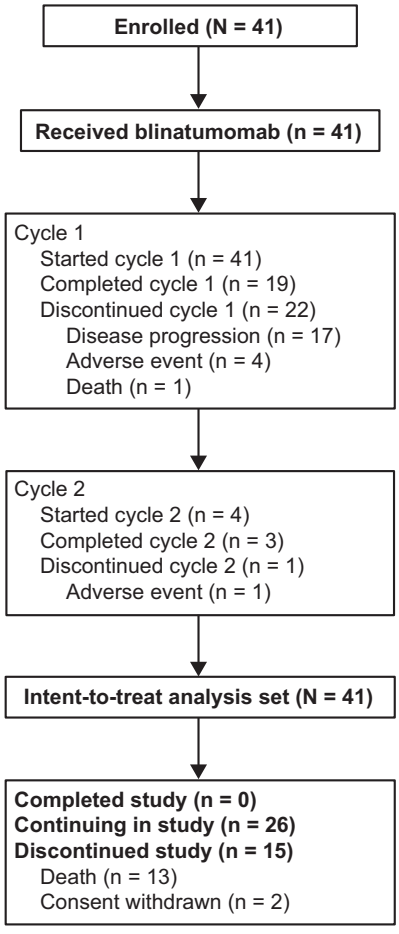

Figure 1. Patient disposition. [a]One patient with progressive disease also had an AE discontinuation event (superior vena cava occlusion). [b]Death attributed to sepsis.

[95% CI, 0.3–9.4]). Median PFS was 2.5 months (95% CI, 2.3–4.9), with a median follow-up of 2.4 months (95% CI, 2.3–4.7). At a median follow-up for OS of 4.9 months (95% CI, 3.5–9.7), 13 (32%) patients had died, and median OS was not estimable (Figure 3). At 9 months, 50.9% (95% CI, 28.3–69.6) of patients were estimated to be alive.

Stem cell transplant

Eight (20%) patients, who had responded to blinatumomab treatment (CMR, $n = 6$; PMR, $n = 2$), subsequently received HSCT, 5 (12%) within 30 days of first responding (Table 2). Three patients who achieved CMR did not receive HSCT: one due to investigator decision, one proceeding to cycle 2, and one for unknown reasons. One (2%) patient received allogeneic HSCT following PMR. Seven (17%) patients underwent autologous HSCT, 6 (15%) following CMR and 1 (2%) following PMR. Among the eight patients who received HSCT, 80.0% (95% CI, 20.4–96.9) were estimated to be alive at 9 months.

Safety and tolerability

All (100%) patients had an AE of any grade, the most frequent of which were back pain ($n = 10$ [24%]), pyrexia ($n = 10$ [24%]), headache ($n = 9$ [22%]), tremor ($n = 9$ [22%]), and peripheral edema ($n = 9$ [22%]; Table 3). Overall, 29 (71%) patients had grade $\geq$3 AEs,

Table 2. Response and transplant realization.

Characteristics	Patients	Proportion (95% CI)
Best response after 12 weeks of treatment		
Objective response rate (CMR + PMR)	15/41	37% (22–53)
CMR	9/41	22% (11–38)
PMR	6/41	15% (6–29)
NMR	5/41	12% (4–26)
PMD	12/41	29% (16–46)
Not performed[a]	9/41	22%
Patients with HSCT	8/41	20%
Autologous HSCT	7/41	17% (7–32)
Allogeneic HSCT	1/41	2% (<1–13)
Patients with HSCT within 30 days of first response	5/41	12%
Patients with delayed or not done HSCT	35/41	85%
No CMR (PMR only)	4/41	10%
NMR or unknown	1/41	2%
PMD	17/41	42%
Toxicity/adverse event	4/41	10%
Patient preference	1/41	2%
Missing	1/41	2%
Other[b]	8/41	20%

CI: confidence interval; CMR: complete metabolic response; HSCT: hematopoietic stem cell transplant; NMR: no molecular response; PMD: progressive metabolic disease; PMR: partial metabolic response.
[a]Reasons for missing post-baseline assessment were death ($n = 5$), withdrawn consent ($n = 2$), patient refusal ($n = 1$), and logistical issue ($n = 1$).
[b]Other includes more than 30 days to organize transplant ($n = 2$), logistical issue ($n = 2$), investigator decision ($n = 1$), initiated cycle 2 without transplant ($n = 1$), transplant 9 days after completion of cycle 2 ($n = 1$), and started another line of treatment without transplant ($n = 1$).

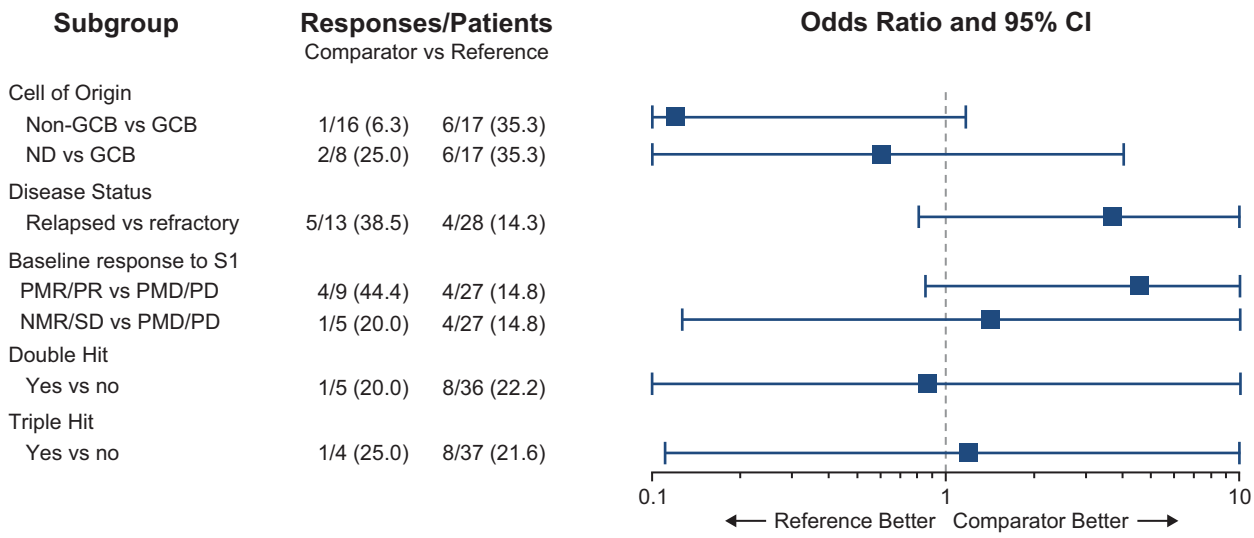

Figure 2. Response by baseline parameter.

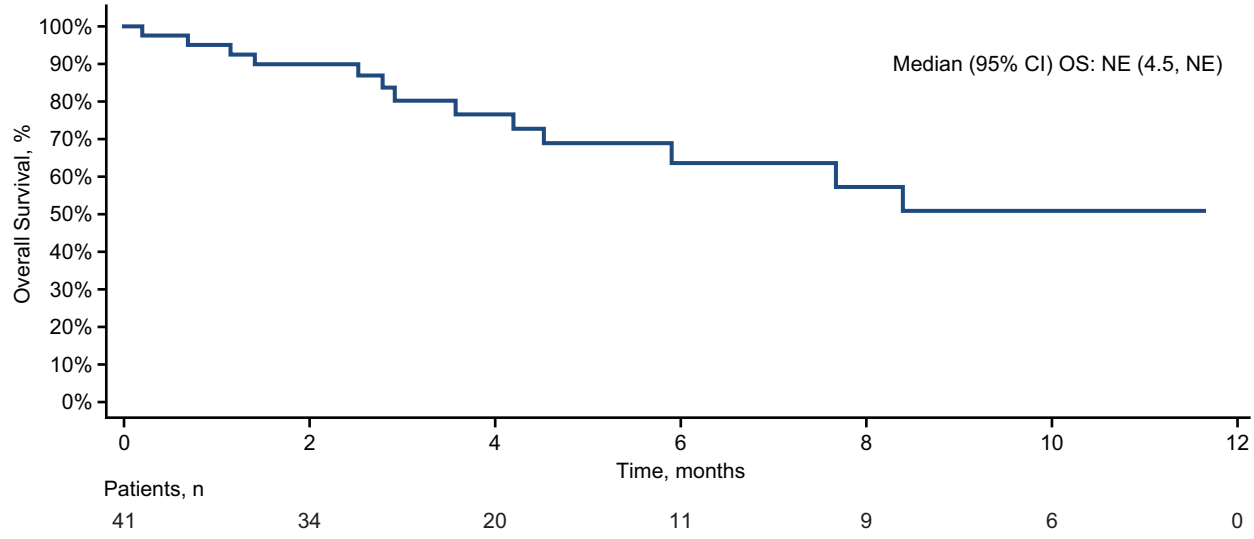

Figure 3. Kaplan–Meier estimated overall survival.

the most frequent of which were neutropenia ($n = 4$ [10%]), anemia ($n = 3$ [7%]), confusional state ($n = 3$ [7%]), aphasia ($n = 2$ [5%]), lower respiratory tract infection ($n = 2$ [5%]), lymphocyte count decreased ($n = 2$ [5%]), neurotoxicity ($n = 2$ [5%]), extremity pain ($n = 2$ [5%]), sepsis ($n = 2$ [5%]), and decreased white blood cell count ($n = 2$ [5%]). NEs were reported in 23 (56%) patients and were predominantly grades 1 or 2 ($n = 14$ [61%]). Grade 3 NE were reported in 10 (24%) patients; all resolved with dexamethasone and/or blinatumomab interruption ($n = 10$ [24%]) or discontinuation ($n = 3$ [7%]). The median duration of NEs was 26 days (95% CI, 7–NE) for any grade and 3 days (95% CI, 1–5) for grade $\geq$3. One patient (2%) had grade 3 CRS lasting 5 days that temporarily resolved before another event of grade 3 CRS lasting 5 days that resulted in blinatumomab discontinuation.

In total, 5 (12%) patients discontinued blinatumomab due to 6 AEs. In addition to discontinuations resulting from NEs ($n = 3$) and CRS ($n = 1$), blinatumomab was also discontinued following acute pancreatitis ($n = 1$), and chest pain ($n = 1$). No patients had grade 4 or fatal NEs.

Overall, nine (22%) patients had fatal treatment-emergent AEs, most ($n = 6$) of which were related to disease progression (Table 3). The other treatment-emergent fatal AEs were multiple organ dysfunction syndrome and pancytopenia. The only fatal AE considered potentially related to treatment with blinatumomab was sepsis.

Table 3. Summary of adverse events.

	Any grade	Grade ≥3
Patients with any treatment-emergent AE, *n* (%)	41 (100)	29 (71)
Patients with any treatment-emergent serious AE, *n* (%)	19 (46)	18 (44)
Patients with a fatal AE,[a] *n* (%)	9 (22)	
AEs occurring in ≥10% of patients, *n* (%)		
Back pain	10 (24)	1 (2)
Pyrexia	10 (24)	1 (2)
Headache	9 (22)	0
Tremor	9 (22)	1 (2)
Peripheral edema	8 (20)	1 (2)
Confusional state	6 (15)	3 (7)
Constipation	6 (15)	0
Nausea	6 (15)	1 (2)
Abdominal pain	5 (12)	1 (2)
Anemia	5 (12)	3 (7)
Neutropenia	5 (12)	4 (10)
Arthralgia	4 (10)	1 (2)
Diarrhea	4 (10)	0
Fatigue	4 (10)	1 (2)
Hypoalbuminemia	4 (10)	1 (2)
Hypomagnesemia	4 (10)	0
Insomnia	4 (10)	0
Pain in extremity	4 (10)	2 (5)
Patients with neurologic events, *n* (%)	23 (56)	10 (24)
Headache	9 (22)	0
Tremor	9 (22)	1 (2)
Confusional state	6 (15)	3 (7)
Insomnia	4 (10)	0
Aphasia	3 (7)	2 (5)
Lethargy	2 (5)	0
Neurotoxicity	2 (5)	2 (5)
Oral paresthesia	2 (5)	0
Agitation	1 (2)	0
Anxiety	1 (2)	0
Depression	1 (2)	0
Dissociative amnesia	1 (2)	0
Dizziness	1 (2)	0
Dysesthesia	1 (2)	1 (2)
Dysarthria	1 (2)	0
Facial paresis	1 (2)	0
Hemiparesis	1 (2)	1 (2)
Hypoesthesia	1 (2)	0
Intention tremor	1 (2)	0
Oral paresthesia	1 (2)	0
Presyncope	1 (2)	0
Somnolence	1 (2)	0
Speech disorder	1 (2)	0
Tension headache	1 (2)	0
Vertigo	1 (2)	0

[a]Diffuse large B-cell lymphoma ($n = 2$), lymphoma ($n = 1$), non-Hodgkin lymphoma ($n = 1$), squamous cell carcinoma of the lung ($n = 1$), pancytopenia ($n = 1$), multiple organ dysfunction syndrome ($n = 1$), treatment-related sepsis ($n = 1$), and adult failure to thrive ($n = 1$).

Discussion

In this open-label phase 2 portion of an adaptive phase 2/3 multicenter study, the ORR was 37% and the CMR rate was 22% after 12 weeks of treatment with single-agent blinatumomab as second salvage in patients with aggressive r/r B-NHL. As anticipated, fewer (15%) patients who were non-responsive to both first-line therapy and first salvage had objective responses during the study. Overall, responses were durable, with 85.7% of patients who achieved CMR estimated to have remained in remission at 9 months. Furthermore, eight (20%) patients, all of whom achieved CMR or PMR, went on to receive HSCT, including five within 30 days of response. Median OS was not reached at the follow-up of 4.9 months; however, 50.9% of patients were estimated to be alive at 9 months. Median PFS was 2.5 months. The activity of blinatumomab as second salvage therapy in this study is consistent with observations made in two earlier studies in which the ORR was 69% in patients with r/r B-NHL and 43% in patients with r/r DLBCL [13,14].

The 37% ORR and 22% CMR rates observed in this study are especially noteworthy considering the highly aggressive disease in this study population, of whom 68% had disease refractory to first-line therapy, 66%

had progressive disease following first salvage, 42% were nonresponsive to induction and first-line salvage, 37% were double or triple expressors, 12% had double hit disease, and 10% had triple hit disease. In contrast, in the SCHOLAR-1 pooled retrospective analysis of patients with r/r DLBCL ($n = 636$) treated with various standard of care chemotherapy regimens, the ORR was 26%, with a CR rate of 7%, and the ORR was only 20% among those who were refractory to first-line therapy and 26% among those who were refractory to second-line or later-line therapy [8]; however differences in the patient populations limit comparison with the present study. Given the subgroup analyses and the CMR rates of 39% among patients who had relapsed disease after first-line therapy and 14% among those with disease refractory to first-line therapy, it is plausible that patients with aggressive r/r B NHL might benefit from earlier salvage treatment (e.g. first salvage) with blinatumomab.

There is no standard of care second salvage regimen for patients with aggressive r/r B-NHL following platinum-based first salvage. Current strategies include alternate salvage chemotherapies (e.g. GDP, DHAP, ICE, and ESHAP) followed by autoHSCT for transplant-eligible patients, CAR-T cell therapy, and investigational therapies (e.g. brentuximab vedotin and polatuzumab vedotin) [17,18]. Comparison of the efficacy of blinatumomab as salvage in this study with that of other studies is not objectively possible due to inherent differences in study design, patient populations, and smaller number of patients. For example, efficacy with blinatumomab in this study (ORR, 37%; CR rate, 22%) is less than with the CAR-T cell therapies axicabtagene ciloleucel in the ZUMA-1 study (ORR, 83%; CR rate, 58%) [19] and tisagenlecleucel in the JULIET study (ORR, 52%; CR rate, 40%) [20]. However, unlike the present study, efficacy evaluation in ZUMA-1 and JULIET was not based on the ITT population, thereby inflating the response and survival rates. Patients enrolled in ZUMA-1 had less advanced/aggressive disease than the patients in the current study, with fewer being refractory to first-line treatment (26% vs 68%), and fewer patients had double-hit disease (9% vs 12%) and triple-hit disease (2% vs 10%). In JULIET, 45% of patients had relapsed and 55% were refractory to the last therapy. Furthermore, the degree of confounding of the apparent efficacy by mandatory condition regimens in ZUMA-1 (low-dose cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2) and JULIET (either fludarabine 25 mg/m^2 with cyclophosphamide 25 mg/mg^2 or bendamustine 90 mg/m^2) is unclear.

The AE profile of blinatumomab monotherapy in this study was consistent with that observed in previous studies of blinatumomab in patients with r/r B-NHL and in patients with B-ALL [11–14]. NEs have been previously documented during treatment with blinatumomab and typically resolve following interruption of treatment and/or with dexamethasone administration [21], as was the case in this study. In this study, grade 3 NEs occurred in 10 (24%) patients, consistent with prior phase 1 and phase 2 studies of blinatumomab in B-NHL in which grade 3 NEs occurred in 22% of patients who received stepwise dosing of blinatumomab [13,14]. Consistent with previous reports, all of the grade 3 NEs in this study resolved. CRS is another AE of interest that has been infrequently reported (2% to 3%) in patients treated with blinatumomab [11,12]. In this study, one (2%) patient experienced grade 3 CRS. Both NEs and CRS have been observed in real world practice and in studies of patients with r/r B-NHL treated with CAR-T cell therapy [22]. The incidences of both of these AEs were greater in the ZUMA-1 study of axicabtagene ciloleucel [23] than in this study (grade $\geq$3 NEs, 32% vs 24%; grade $\geq$3 CRS, 11% vs 2%), as was the incidence of grade $\geq$3 CRS in the JULIET study of tisagenlecleucel (22% vs 2%) [20]. Notably, CRS in ZUMA-1 and JULIET was scored using the Lee grading system [24], potentially underestimating the incidences compared with this study, which graded CRS using CTCAE. These data highlight the greater manageability of NEs and CRS with blinatumomab, especially through the temporary interruption of treatment, which is not an option after administration of CAR-T cells.

This study was limited by a relatively high rate of treatment discontinuation during the first treatment cycle, primarily due to disease progression ($n = 17$) rather than to AEs ($n = 4$). Overall, 46% of patients completed cycle 1 and 7% completed the optional cycle 2. Consequently, exposure to blinatumomab was lower than anticipated, with 34% of patients receiving $<$50% of the intended dose, and only 59% receiving $\geq$80% of the intended dose. Although at least 1 week of treatment at the target dose of 112 μg/d appears necessary for efficacy [13,14], investigating other dosing strategies may be appropriate. Despite this limitation, the ORR and CMR rates seen with blinatumomab were encouraging given the aggressive nature of heavily pretreated r/r disease in this population of patients. The longer follow-up period at the final analysis will allow for better estimation of the effects of blinatumomab on OS and relapse-free survival in this cohort.

In conclusion, the results of this study suggest considerable single-agent activity and a manageable safety profile with blinatumomab as second salvage in patients with aggressive r/r B-NHL following platinum-based first salvage regimens. These results imply a potential for effective use of blinatumomab earlier in the salvage treatment continuum and raise the question of whether efficacy could be improved in combination with other conventional or experimental therapies; however, additional investigation is needed. In the primary analysis of an open-label phase 2 study (ClinicalTrials.gov, NCT03023878), blinatumomab treatment after first-line rituximab-based chemotherapy led to an 89% ORR in patients with newly diagnosed DLBCL [25]. Blinatumomab combined with pembrolizumab is also under investigation in patients with r/r DLBCL (ClinicalTrials.gov, NCT03340766).

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References

[1] Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do?. Hematology Am Soc Hematol Educ Program. 2016;2016(1):366–378.

[2] Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. JCO. 2014;32(31):3490–3496.

[3] Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. JCO. 2010;28(27):4184–4190.

[4] Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. JCO. 2012;30(36):4462–4469.

[5] Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51–57.

[6] Hamadani M, Hari PN, Zhang Y, et al. Early failure of frontline rituximab-containing chemo-immunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2014;20(11):1729–1736.

[7] van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. JCO. 2017;35(5):544–551.

[8] Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800–1808.

[9] Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. Am J Hematol. 2013;88(10):890–894.

[10] Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. Science. 2008;321(5891):974–977.

[11] Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015;16(1):57–66.

[12] Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522–1531.

[13] Goebeler ME, Knop S, Viardot A, et al. Bispecific T-Cell Engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. JCO. 2016;34(10):1104–1111.

[14] Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood. 2016;127(11):1410–1416.

[15] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. JCO. 2014;32(27):3059–3068.

[16] National Cancer Institute. NCI common terminology criteria for adverse events (CTCAE), v. 4.0. Bethesda, MD: National Cancer Institute; 2014.

[17] Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. Br J Haematol. 2018;182(5):633–643.
[18] Hashmi H, Hamadani M, Awan FT. Choosing the appropriate salvage therapy for B-cell non-Hodgkin lymphoma. Expert Opin Pharmacother. 2018;19(15): 1631–1634.
[19] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–2544.
[20] Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45–56.
[21] Stein AS, Schiller G, Benjamin R, et al. Neurologic adverse events in patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab: management and mitigating factors. Ann Hematol. 2019;98(1):159–167.
[22] Grigor EJM, Fergusson D, Kekre N, et al. Risks and benefits of chimeric antigen receptor T-cell (CAR-T) therapy in cancer: a systematic review and meta-analysis. Transfus Med Rev. 2019;33(2):98–110.
[23] Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1): 31–42.
[24] Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–195.
[25] Katz DA, Chu MP, David KA, et al. Open-label, phase 2 Study of blinatumomab after first-line rituximab-chemotherapy in adults with newly diagnosed, high-risk diffuse large B-cell lymphoma. Blood. 2019; 134(Supplement_1):4077–4077.