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ORIGINAL REPORT

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

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ABSTRACT

Purpose

Blinatumomab is a CD19/CD3 BiTE (bispecific T-cell engager) antibody construct for the treatment of Philadelphia chromosome–negative acute B-lymphoblastic leukemia. We evaluated blinatumomab in relapsed/refractory B-cell non-Hodgkin lymphoma (NHL).

Patients and Methods

This 3 + 3 design, phase I dose-escalation study determined adverse events and the maximum tolerated dose (MTD) of continuous intravenous infusion blinatumomab in patients with relapsed/refractory NHL. Blinatumomab was administered over 4 or 8 weeks at seven different dose levels (0.5 to 90 $\mu g/m^2$/day). End points were incidence of adverse events, pharmacokinetics, pharmacodynamics, and overall response rate.

Results

Between 2004 and 2011, 76 heavily pretreated patients with relapsed/refractory NHL, who included 14 with diffuse large B-cell lymphoma, were enrolled; 42 received treatment in the formal dose-escalation phase. Neurologic events were dose limiting, and 60 $\mu g/m^2$/day was established as the MTD. Thirty-four additional patients were recruited to evaluate antilymphoma activity and strategies for mitigating neurologic events at a prespecified MTD. Stepwise dosing (5 to 60 $\mu g/m^2$/day) plus pentosan polysulfate SP54 (n = 3) resulted in no treatment discontinuations; single-step (n = 5) and double-step (n = 24) dosing entailed two and seven treatment discontinuations due to neurologic events, respectively. Grade 3 neurologic events occurred in 22% of patients (no grade 4/5). Among patients treated at 60 $\mu g/m^2$/day (target dose; n = 35), the overall response rate was 69% across NHL subtypes and 55% for diffuse large B-cell lymphoma (n = 11); median response duration was 404 days (95% CI, 207 to 1,129 days).

Conclusion

In this phase I study of relapsed/refractory NHL, continuous infusion with CD19-targeted immunotherapy blinatumomab at various doses and schedules was feasible, with an MTD of 60 $\mu g/m^2$/day. Single-agent blinatumomab showed antilymphoma activity.

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INTRODUCTION

Since the monoclonal antibody rituximab became an integral part of treatment regimens for B-cell non-Hodgkin lymphoma (NHL), patient outcomes have improved significantly.[1,2] However, both early relapse and refractory disease remain associated with a dismal prognosis. Furthermore, with the introduction of rituximab as first-line treatment, outcomes after salvage with autologous hematopoietic stem cell transplantation (HSCT) have been reported to be worse.[3,4] In diffuse large B-cell lymphoma (DLBCL), an aggressive lymphoma, the 3-year progression-free survival for patients who experience an early relapse after rituximab treatment is only 23%.[4,5] Complete remission rates (the prerequisite for cure in aggressive lymphoma and a predictor of survival in indolent NHL[6,7]) typically achieved

with current investigational agents administered as monotherapy remain low.[8]

Blinatumomab is a BiTE (bispecific T-cell engager) antibody construct that targets both the CD3ε subunit of the T-cell receptor complex and the B-cell differentiation antigen CD19.[9] CD19 is expressed throughout B-cell development and in corresponding B-cell malignancies except for plasma cell neoplasias.[10,11] Blinatumomab transiently links $CD3^+$ polyclonal T cells to $CD19^+$ B cells, which induces T-cell activation followed by T-cell–mediated serial B-cell lysis[12,13] and concomitant T-cell proliferation.[14] Blinatumomab has demonstrated antileukemia activity in patients with B-lineage acute lymphoblastic leukemia (ALL),[15,16] including relapsed/refractory ALL.[17,18]

The phase I study described here evaluated continuous intravenous dosing with single-agent blinatumomab in heavily pretreated patients with relapsed/refractory indolent B-lineage NHL. An interim analysis (n = 38) reported dose-dependent clinical activity.[19] We summarize final study results, which include preventive treatments aimed at reducing the incidence of neurologic events.

PATIENTS AND METHODS

Eligible patients were 18 years of age and older with a first or subsequent relapse of histologically confirmed NHL (World Health Organization classification[20]), which included follicular lymphoma (FL; grades 1 to 3A), marginal zone lymphoma, lymphoplasmocytic lymphoma, mantle cell lymphoma (MCL), and small lymphocytic lymphoma, requiring therapy but not eligible for curative treatment. Inclusion of patients with DLBCL (after failure of treatment with curative intent) and those with transformed disease was allowed per protocol amendment (February 2010). Other key eligibility criteria were measurable disease per computed tomography scan; Eastern Cooperative Oncology Group performance status of 2 or less; life expectancy 6 months or longer; and adequate liver, renal, and bone marrow function. Patients with known or suspected CNS involvement; history of or current relevant CNS pathologies, other malignancy within the past 5 years, active infection, or human antimurine antibodies were excluded. The study protocol was approved by an independent ethics committee at each institution. Patients provided written informed consent.

Study Design and Treatment

This multicenter (nine sites in Germany), open-label, single-agent, dose-escalation phase I study investigated the tolerability of blinatumomab in patients with relapsed NHL and determined the recommended dose and schedule for phase II assessment. The primary end point was overall incidence and severity of adverse events (AEs); secondary end points included pharmacokinetics, pharmacodynamics, and overall response rate (ORR).

Given its short serum half-life, blinatumomab was administered as a continuous intravenous infusion. With use of a portable minipump and intravenous port catheter, patients received doses of 0.5, 1.5, 5, 15, 30, 60, or 90 $\mu g/m^2$/day at a constant flow rate for 4 to 8 weeks until dose-limiting toxicity (DLT) or relevant disease progression occurred, followed by an additional 4-week consolidation treatment phase at the respective initial dose in case of clinical benefit. All treatments were followed by an end-of-study visit 4 weeks after infusion stop. Patients were offered retreatment after lymphoma relapse if they had initially responded to treatment (complete response [CR]/unconfirmed CR [CRu], or partial response [PR]).

Dose Escalation, Maximum Tolerated Dose, and Study Extension

DLTs were defined as all treatment-related, clinically relevant grade 3/4 AEs (to include neurologic events) that occurred in the first 14 days (21 days for two-step dosing) after the start of the first treatment, unless clinically transient and/or isolated in nature and expected on the basis of the blinatumomab mechanism of action or related to organ infiltration by the lymphoma. Forty-two patients were enrolled in the dose-escalation phase; all received blinatumomab plus concomitant corticosteroids of the investigator's choice. At least three patients were assigned sequentially to increasing dose levels. Additionally, stepwise and ramp-up dosing was tested in dose levels 4 and 5 (Appendix, online only). If none of three or no more than one of six patients experienced a DLT, the next-higher dose level was enrolled. If a DLT occurred in two of six patients, additional patients were enrolled in the next-lower dose level. If no more than one of six patients at that lower dose level had a DLT, the dose was considered the maximum tolerated dose (MTD). Dose escalation was based on Data Review Committee decisions.

Thirty-four additional patients were enrolled in the extension phase. All were to receive a target dose of 60 $\mu g/m^2$/day as either constant (flat) dosing or weekly dose escalation as a single step (5 $\mu g/m^2$/day, days 1 to 7, then 60 $\mu g/m^2$/day) or a double step (5 $\mu g/m^2$/day, days 1 to 7; 15 $\mu g/m^2$/day, days 8 to 14; then 60 $\mu g/m^2$/day). All patients also received one of two concomitant corticosteroid schedules: a corticosteroid of the investigator's choice, with type (which included prednisolone and dexamethasone), dose, and duration determined by the investigator on the basis of the patient's clinical presentation, or early dexamethasone prophylaxis (days 1, 8, and 15, 20 mg dexamethasone orally between 6 and 12 hours before the start of blinatumomab infusion and again 1 hour before the infusion start; days 2 and 3, 9 and 10, and 16 and 17, 8 mg dexamethasone three times a day). Three patients received pentosan polysulfate SP54 (PPS) at treatment start and during the 5 to 60 $\mu g/m^2$/day dose step.

Assessments

Pharmacokinetic and lymphocyte subpopulation analyses are described in the Appendix. AEs were classified as in the Medical Dictionary for Regulatory Activities[21]; severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).[22] Before protocol amendment, all grade 4 laboratory abnormalities were considered serious AEs.

Response was defined according to the International Working Group response criteria for NHL[23] and was assessed after 4 and 8 treatment weeks and at study end using centrally reviewed contrast-enhanced computed tomography scans (neck, thorax, and abdomen/pelvis) and bone marrow biopsy.

Statistical Analysis

Duration of response was defined as the time from first assessment of CR, CRu, or PR until disease progression (transplantation not evaluated as progression), initiation of new antitumor therapy, or death. Patients without events were censored on the last available visit date. Median duration of response was calculated using Kaplan-Meier estimates; corresponding two-sided 95% CIs were estimated using the sign test.[24]

RESULTS

Patient Characteristics

Between June 22, 2004, and July 18, 2011, 76 patients with relapsed/refractory NHL were enrolled. The majority (n = 62) had indolent (low-grade) lymphomas, which included FL (n = 28) and MCL (n = 24); 14 had DLBCL (Table 1). The median number of previous treatment regimens was three (range, one to 10);

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	All Patients (n = 76)	Patients in the Extension Phase* (n = 34)
Median (range) age, years	65 (20-80)	62 (20-80)
Sex, No. (%)		
Female	19 (25)	11 (32)
Male	57 (75)	23 (68)
Median (range) time from diagnosis, years	4.0 (1-28)	2.3 (1-28)
Median (range) time from last chemotherapy regimen, months	8.3 (0-100)	6.5 (1-81)
Median (range) number of previous treatment regimens	3 (1-10)	3 (1-8)
Type of prior treatment regimen,† No. (%)		
One or more rituximab treatments	71 (93)	33 (97)
Fludarabine	23 (30)	5 (15)
Autologous HSCT	23 (30)	15 (44)
Histology, No. (%)		
Indolent lymphoma	52 (68)	18 (53)
Follicular lymphoma	28 (37)	10 (29)
Mantle cell lymphoma	24 (32)	8 (24)
Refractory to previous rituximab treatment‡	20 (26)	8 (24)
Diffuse large B-cell lymphoma	14 (18)	13 (38)
Relapsed after previous therapy with CHOP	10 (13)	10 (29)
Relapsed after previous autologous HSCT	9 (12)	9 (26)
Other§	10 (13)	3 (9)

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; HSCT, hematopoietic stem cell transplantation.
*At time of enrollment.
†Individual chemotherapy regimens that were administered during the same time period were considered combination therapies.
‡Stop of last rituximab dose less than 6 months (182 days) before start of next therapy.
§Includes lymphoplasmocytic lymphoma (n = 2), small lymphoplasmocytic lymphoma, immunocytoma, Waldenström macroglobulinemia, marginal zone non-Hodgkin lymphoma, marginal zone B-cell lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia, and small lymphoplasmocytic lymphoma/chronic lymphocytic leukemia (protocol deviations).

71 (93%) patients had previously received rituximab. Fifty-one (67%) patients received at least 4 weeks of blinatumomab treatment; of those, 24 (32%) received 8 weeks of treatment.

Dose Escalation and MTD

Of the 76 enrolled patients, 42 were assigned to seven escalating dose levels, with at least three patients in each level. Five of the 42 patients experienced DLTs, all of which occurred at dose levels 4, 5, and 7 (Table 2). The incidence of DLTs, primarily neurologic events (three of four treated patients), was highest at the 90 $\mu g/m^2$/day dose level, which suggests a dose-response relationship for neurologic events. Consequently, 60 $\mu g/m^2$/day was established as the MTD for administration on day 1. During the dose escalation phase, three patients had neurologic events that led to permanent treatment discontinuation and were not considered DLTs because they occurred well outside the prespecified DLT window as follows: grade 3 headache (dose level 4, day 54); grade 3 cerebellar syndrome (dose level 5, day 25); and grade 3 dysarthria, tremor, and encephalopathy (dose level 5, day 50). During dose escalation, all neurologic events clinically resolved after treatment discontinuation.

Table 2. Blinatumomab Dose Levels and DLTs (Dose Escalation Phase)

Dose Level	Highest Intended Dose ($\mu g/m^2$/day)	Patients (No.)	Patients With DLTs (No.)	Nature of DLT
1	0.5	3	0	
2	1.5	3 + 3	0	
3	5	3	0	
4	15*	7 + 6	1	Mental disorder due to general medical condition (grade 2)†
5	30‡	6	1	Metabolic acidosis due to grand mal seizure (grade 4)
6	60	4 + 3	0	
7	90	4	3	Encephalopathy (grade 3; n = 2); seizure and aphasia (grade 3; n = 1)

NOTE. Total number of patients was 42. Total number of patients with DLT was 5.
Abbreviation: DLT, dose-limiting toxicity.
*The first seven patients received an initial dose of 5 $\mu g/m^2$/day followed by intraindividual escalation to 15 $\mu g/m^2$/day. Three of the six patients were treated after a ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. The remaining three patients received 15 $\mu g/m^2$/day constant dosing. Before protocol amendment to allow enrollment of patients with diffuse large B-cell lymphoma, one patient with follicular non-Hodgkin lymphoma that later transformed to diffuse large B-cell lymphoma was enrolled in this dose group (protocol deviation).
†Before protocol amendment, neurologic events of any grade were considered DLTs.
‡Three patients were treated after a ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. Over-recruitment was permitted per the data review committee for further evaluation of the adverse event profile.

Study Extension Phase

The study protocol was amended to develop strategies for mitigating neurologic events to achieve the target dose of 60 μg/m^2/day safely and to explore treatment of patients with DLBCL. Thirty-four additional patients were enrolled, which included 13 with DLBCL (Table 1 [patient disposition shown in Appendix Table A1, online only]). The planned target dose of 60 μg/m^2/day was administered as constant (n = 2), single-step (n = 5), single-step plus PPS (n = 3), or double-step (n = 24, which included all 13 patients with DLBCL) dosing with various concomitant corticosteroids. Seven patients did not reach the target dose. No treatment discontinuations occurred among patients who received single-step blinatumomab dosing plus PPS or double-step dosing with early dexamethasone prophylaxis (DLBCL, n = 4). Overall, seven of the 24 patients who received double-step dosing with corticosteroid comedication prophylaxis discontinued treatment due to neurologic events compared with three of seven patients who received constant or single-step dosing (Appendix Table A2, online only).

Adverse Events

The incidence of grade 3, 4, and 5 AEs, regardless of causality, was 90%, 66%, and 4%, respectively. The most common AEs were lymphopenia, an expected AE given the mode of action of blinatumomab but required to be reported per study protocol; pyrexia; increased C-reactive protein level; fatigue; leukopenia; increased weight; and headache. Frequent laboratory abnormalities included hematologic AEs, which were mostly transient (Table 3). Febrile neutropenia occurred in two (3%) patients. Hematologic AEs also accounted for most of the serious AEs (55% had lymphopenia, 9% had leukopenia, and 9% had neutropenia) along with pyrexia (9%) and encephalopathy (8%). The incidence of AEs decreased over the course of treatment. There were 200 AEs on day 1 (76 patient-days) after infusion start and 102 AEs between days 46 and 84 (403 patient-days). The overall incidence of infections was 50% (grade 3 or higher, 11%), which were mostly nasopharyngitis (16%) and catheter-site infection (9%). Three grade 5 AEs occurred. Two were considered possibly related to treatment: sepsis (dose level 4) and *Pneumocystis jirovecii* infection (extension phase). One patient (dose level 2) died of dyspnea related to pulmonary involvement due to disease progression.

The most clinically relevant AEs were neurologic events. The overall incidence regardless of causality was 71% (grade 3, 22%) with headache being the most common AE. Twenty percent of patients experienced serious neurologic events (encephalopathy, 8%; aphasia, 4%; headache, 3%). No grade 4 or 5 neurologic events occurred. The predominant treatment-related clinical symptoms were headache, tremor, and dizziness (Table 4). Two patients had a grade 3 seizure. Most neurologic events began within the first 2 days of the first infusion within each treatment cycle or dose step. Neurologic events resolved clinically to grade 1 or lower on treatment or after discontinuation (time to resolution was 1 to 29 days in one case of intermittent mild tremor). In five

Table 3. Incidence of Adverse Events Regardless of Causality (n = 76)

Adverse Event in > 20% of Patients	No. of Patients (%)	
	All Grades	Grade ≥ 3
Lymphopenia	61 (80)	60 (79)
Pyrexia	58 (76)	3 (4)
C-reactive protein increase	37 (49)	15 (20)
Fatigue	35 (46)	3 (4)
Leukopenia	35 (46)	15 (20)
Headache	32 (42)	3 (4)
Weight increase	32 (42)	0
Hyperglycemia	31 (41)	9 (12)
Thrombocytopenia	29 (38)	9 (12)
ALT increase	25 (33)	0
Weight decrease	25 (33)	0
Chills	21 (28)	0
γ-glutamyltransferase increase	21 (28)	7 (9)
Diarrhea	20 (26)	0
Fibrin D dimer increase	20 (26)	6 (8)
Neutropenia	20 (26)	13 (17)
Anemia	17 (22)	5 (7)
Serum immunoglobulin A decrease	17 (22)	4 (5)
Hematuria	17 (22)	0
Hypokalemia	17 (22)	5 (7)
Leukocytosis	17 (22)	1 (1)
Nausea	17 (22)	0
AST increase	16 (21)	0
Blood potassium decrease	16 (21)	1 (1)
Decreased appetite	16 (21)	1 (1)
Night sweats	16 (21)	0

Table 4. Incidence of Treatment-Related Neurologic Events (n = 76)

Neurologic Event	No. of Patients (%)	
	All Grades	Grade 3*
Headache	27 (36)	3 (4)
Tremor	14 (18)	2 (3)
Dizziness	11 (15)	0
Aphasia	9 (12)	3 (4)
Encephalopathy	6 (8)	6 (8)
Confusion	5 (7)	0
Apraxia	4 (5)	0
Ataxia	4 (5)	1 (1)
Intention tremor	4 (5)	0
Speech disorder	4 (5)	1 (1)
Cerebellar syndrome	2 (3)	1 (1)
Seizure	2 (3)	2 (3)
Disorientation	2 (3)	2 (3)
Dysarthria	2 (3)	1 (1)
Insomnia	2 (3)	0
Agitation	1 (1)	0
Allodynia	1 (1)	0
Cognitive disorder	1 (1)	0
Communication disorder	1 (1)	0
Disturbance in attention	1 (1)	0
Dysesthesia	1 (1)	0
Emotional distress	1 (1)	1 (1)
Hallucination, auditory	1 (1)	0
Hallucination, visual	1 (1)	1 (1)
Hemiparesis	1 (1)	1 (1)
Memory impairment	1 (1)	0
Mental disorder due to general medical condition	1 (1)	0
Paraesthesia	1 (1)	0
Peripheral sensory neuropathy	1 (1)	0
Polyneuropathy	1 (1)	0
Sleep disorder	1 (1)	0
Transient ischemic attack	1 (1)	1 (1)
VIIth nerve paralysis	1 (1)	0

*No grade 4 or 5 adverse events occurred.

patients, the neurologic events were deemed possibly related to blinatumomab treatment and were ongoing at the end of the study (grade 1 and 2 headache, grade 2 dizziness, grade 2 memory impairment, grade 3 distress). Across the study, 17 (22%) patients (dose escalation, n = 7; extension phase, n = 10) had neurologic events regardless of causality (grade 3, n = 12; grade < 3, n = 5) that resulted in permanent treatment discontinuation, primarily encephalopathy (n = 6) and aphasia (n = 4). Two patients discontinued due to grade 3 encephalopathy during retreatment (one each in the dose escalation and extension phase).

Pharmacokinetics

Blinatumomab steady-state concentration in the serum increased dose proportionally from 5 to 90 μg/m^2/day (Appendix Table A3, online only). The mean clearance was 2.0 L/h (coefficient of variation [CV%], 44). On the basis of a subset of patients with pharmacokinetic terminal phase, mean terminal half-life was 2.1 h (CV%, 53), and mean volume of distribution was 5.7 L (CV%, 47).

Pharmacodynamics

After infusion start, complete depletion of peripheral blood B cells was observed at doses of 5 μg/m^2/day or more, regardless of baseline levels. Peripheral blood B-cell depletion was sustained during treatment. A transient decrease of T-cell counts was observed immediately after infusion start and at each dose step, with nadirs within 24 hours. This previously described redistribution[14] was followed by a return to baseline levels within 1 to 2 weeks. In some patients, T-cell expansion was observed during treatment weeks 2 to 4. Analysis of T-cell subsets showed that mainly CD8 effector memory and terminally differentiated effector memory T cells and CD4 effector memory and central memory T cells contributed to this expansion.

Antilymphoma Activity

All 76 patients were included in the response analysis (intention-to-treat principle). On the basis of the highest actual dose received during the first cycle, no CRs or PRs occurred at doses less than 15 μg/m^2/day. Four CRs or PRs were observed at 15 and 30 μg/m^2/day (n = 21), with one confirmed CR at each dose (Table 5). At 60 μg/m^2/day (n = 35), the ORR was 69% (37% CR + CRu and 31% PR), which suggests a dose-response relationship up to the MTD. The 60 μg/m^2/day dose was selected as the target dose for efficacy. At this dose, blinatumomab showed notable single-agent activity in patients with FL (ORR, 80%), MCL (ORR, 71%), and DLBCL (ORR, 55%; Table 5). The ORR in patients with early relapse who received the target dose was 53%. Figure 1A shows remission in a patient with relapsed MCL and bulky disease who received blinatumomab 60 μg/m^2/day. Two responders with DLBCL proceeded to allogeneic HSCT; a third patient with FL who did not achieve the target dose proceeded to autologous HSCT.

Based on follow-up data (until June 22, 2012), the median response duration for patients who received the target dose of 60 μg/m^2/day during the first cycle was 404 (95% CI, 207 to 1,129) days. Median duration of CR/CRu was 508 (95% CI, 213 to not estimable) days; median duration of PR was 185 (95% CI, 28 to 754) days. Nine of 24 patients were in ongoing remission at the time of analysis, and 12 had long-term remissions of more than 1 year, which included two with DLBCL (639 and 658 days; Fig 1B). Three responders who experienced a relapse underwent retreatment at 60 μg/m^2/day: one patient with FL (initial response, PR)

Table 5. Clinical Response

	Dose (μg/m^2/day)	No. of Patients	No. of Responses						
			CR	CRu	CR/CRu	PR	ORR CR + CRu + PR, n (%)	SD	PD
Response at highest actual dose received*	0.5, 1.5	9	0	0		0	0 (0)	4	5
	5	7†	0	0		0	0 (0)	4	2
	15	15†	1	0		2	3 (20)	7	4
	30	6†	1	0		0	1 (17)	2	2
	60	35†	8	5		11	24 (69)	5	5
	90	4†	1	0		1	2 (50)	1	0
Response at target dose*									
By histology									
FL	60	15			6	6	12 (80)		
MCL	60	7			3	2	5 (71)		
DLBCL‡	60§	11			4	2	6 (55)		
Other	60	2			0	1	1 (50)		
By early relapse status‖									
Early relapse	60	19			5	5	10 (53)		
No early relapse	60	16			8	6	14 (88)		

Abbreviations: CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*During the first treatment period only (not including consolidation treatment).
†One patient did not have a response assessment. Five patients had no response data available (MCL, n = 4; FL, n = 1) but were included in the statistical response analysis calculations.
‡Three patients with DLBCL did not receive the target dose (study termination before dose step to target dose, n = 2; one patient was treated in the 30 μg/m^2/day dose group).
§One patient received 30 μg/m^2/day.
‖Early relapse: end of last chemotherapy less than 12 months before blinatumomab treatment start. No early relapse: end of last chemotherapy 12 months or more before blinatumomab treatment start.

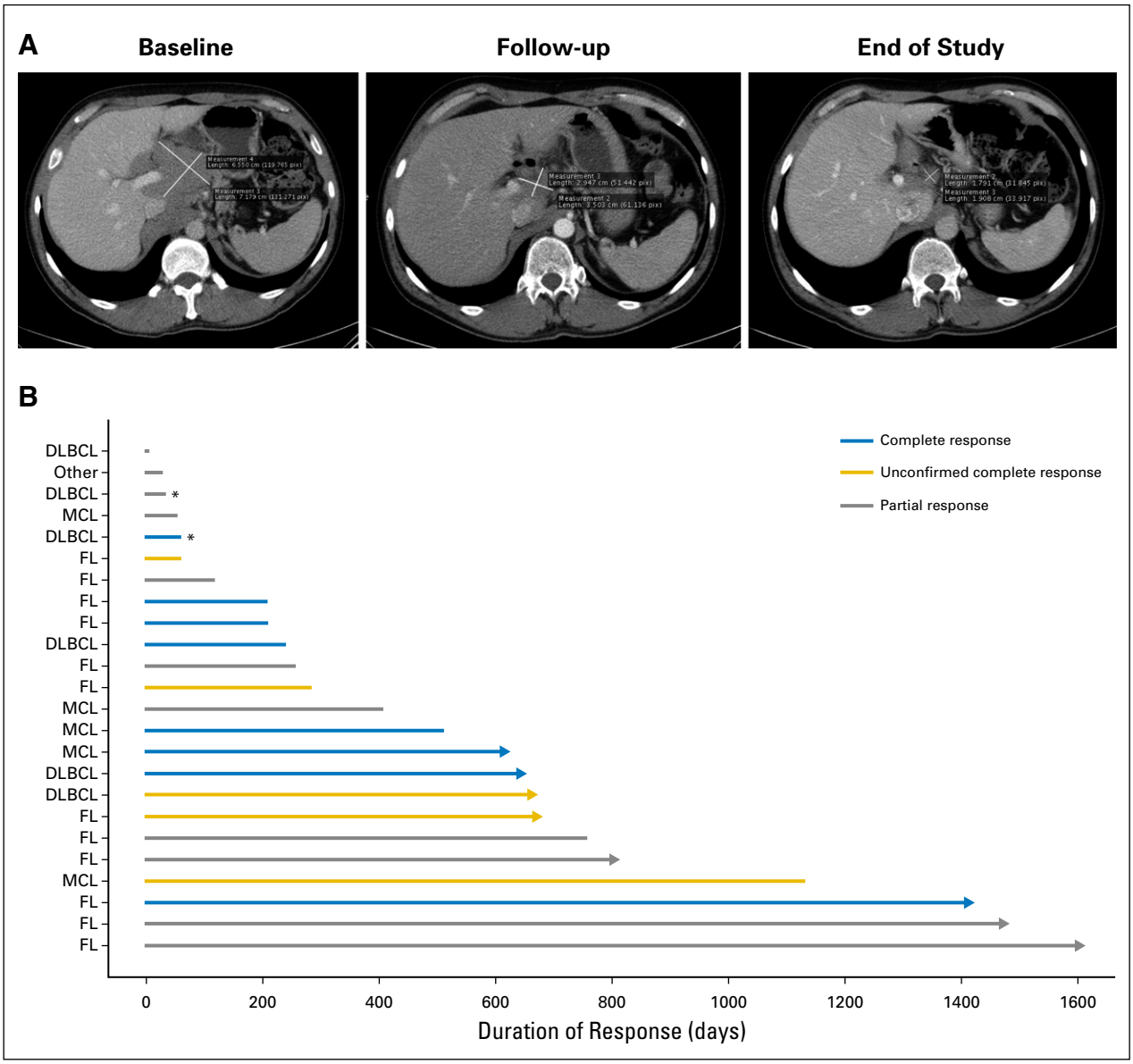

Fig 1. (A) Computed tomography scans of a patient with relapsed mantle cell lymphoma and mediastinal and abdominal lymph node enlargement who received continuous intravenous infusion of blinatumomab 60 μg/m^2/day. (B) Duration of response (in days) for all responding patients who received blinatumomab 60 μg/m^2/day (target dose) during the first cycle. Arrows represent ongoing responses. (*) Patient received allogeneic hematopoietic stem cell transplantation. DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma.

achieved CR for an additional 5 months and the other two (one with MCL and one with FL) did not respond to retreatment.

DISCUSSION

Our results confirm data from the study's interim analysis by showing that in this heavily pretreated population of patients with relapsed/refractory NHL, continuous intravenous infusion of single-agent blinatumomab is feasible up to the MTD of 60 μg/m^2/day and results in antilymphoma activity with durable CR and PR.

AEs associated with blinatumomab treatment were time and dose dependent. The rate was highest within the first days of infusion start and then declined over time (50% reduction in incidence rate by day 46 *v* day 1 after infusion start). Patients who received higher doses were more likely to experience DLTs, primarily neurologic events. The most frequent AEs (lymphopenia, which also accounted for most serious AEs; pyrexia; and increased C-reactive protein level) were consistent with the mode of action of a T-cell–activating antibody that depletes the CD19$^+$ B-cell compartment. In vitro, blinatumomab triggers transient release of proinflammatory cytokines upon first contact with unstimulated T cells,[25] which may explain flu-like symptoms. In the current study, transient proinflammatory cytokine elevations in the serum were seen during the first 48 h of treatment.[19] Two deaths due to infectious complications were deemed possibly related to treatment. However, despite blinatumomab-induced B-cell depletion and the ensuing hypogammaglobulinemia, the incidence of grade 3 or higher infections

was relatively low (11%) given the intense immunosuppression of the patient population caused by disease and previous treatment.

Blinatumomab-associated neurologic events were dose limiting and the most frequent cause for early treatment discontinuation. Such events, which included grade 3 encephalopathy, have also been reported in patients with relapsed ALL who received chimeric antigen receptor–modified T cells specific for CD19.[26-28] We speculate that neurologic events associated with blinatumomab treatment may be due to cytokine-releasing T-cells that migrate into the CNS; however, they cannot be correlated to the rather mild and transient cytokine elevations in serum at treatment start.

Several approaches for mitigating neurologic events were explored. Although the number of patients per group was small, intrapatient single-stepwise dose escalation to 60 $\mu g/m^2$/day plus PPS or double-stepwise dose escalation with corticosteroid prophylaxis was the most promising because few (double-step) or even no (PPS) treatment discontinuations due to neurologic AEs were necessary. Double-stepwise dosing with dexamethasone prophylaxis is currently under evaluation in a phase II study of relapsed/refractory DLBCL. The use of PPS was exploratory and requires further study. Corticosteroids have known anti-inflammatory properties by blocking synthesis and release of inflammatory cytokines and possibly have protective effects on the blood-brain barrier through reduction of barrier permeability.[29] Corticosteroids also have been shown in vitro to decrease blinatumomab-induced cytokine secretion by peripheral T cells without affecting redirected lysis.[25] The rationale for the use of the heparin-like agent PPS, a P-selectin antagonist,[30] was to decrease blinatumomab-induced adhesion of circulating T cells and other leukocytes to blood vessel endothelium through P-selectin blocking at treatment start and during dose steps,[19] which thus interferes with T-cell migration from the blood into the brain to reduce local cytokine release in the CNS. Agents that affect T-cell adherence to the endothelium may warrant further exploration as a mitigation strategy for blinatumomab-associated neurologic events.

Early testing of short 2- to 4-h intravenous blinatumomab infusions showed no objective responses.[31] Given the short half-life of blinatumomab, we hypothesized that antitumor activity requires sustained exposure through continuous infusion to achieve prolonged T-cell activation and T-cell penetration, enrichment, and expansion in target tissue with local effector-to-target cell ratios. Pharmacokinetic analysis showed that continuous infusion of blinatumomab results in stable serum levels during an extended time (4 to 8 weeks), with an average clearance of 2 L/h and mean terminal half-life of 2.1 h, which is comparable to previous reports in ALL.[14] Continuous blinatumomab infusion caused the T-cell activation and expansion, mostly of effector memory T cells, and B-cell depletion in peripheral blood, as desired. The latter was consistent across patients. These data are in line with results from a study in ALL.[14] Ongoing optimization of blinatumomab therapy aims to improve administration convenience and identify biomarkers of response and resistance, which may support use in more disease stages and settings.

Single-agent blinatumomab showed promising antilymphoma activity in relapsed/refractory NHL. At the target dose of 60 $\mu g/m^2$/day, the ORR of 69% was notably high, with many durable responses to include long-term remission independent of previous treatment or histologic subtype and a CR/CRu rate of 37%. The response assessment followed the original Cheson criteria,[23] which did not include positron emission tomography imaging for routine staging. In some NHL entities, positron emission tomography might have allowed for a better description of CR and differentiation between CR and CRu, although detailed efficacy assessment was not in the scope of this study. Responses were seen across all histologic subtypes (FL, MCL, and DLBCL) and in early relapse NHL. Importantly, the ORR (55%) and CR/CRu rate (36%) in patients with DLBCL are particularly promising given the phase I nature of the study, the intensity of previous therapies, and the modest single-agent activity of other newly emerging therapies (eg, lenalidomide, bortezomib, temsirolimus, pixantrone).[7,32] A phase II study of blinatumomab in the setting of relapsed/refractory DLBCL, which has a poor prognosis and constitutes a particular unmet medical need, is being conducted (ClinicalTrials.gov, NCT01741792).[33]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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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

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Appendix

Methods

Dose escalation. In the dose-escalation phase of the study, three modes of blinatumomab administration were evaluated, which included stepwise dosing, ramp-up dosing, and constant or flat dosing. Dose levels 1 through 3 used a dose (per time unit) that was below the lowest dose of initial exploratory dosing[31] by using a constant dose over the whole administration period. In dose levels 4 and 5, varying approaches to initial administration of study drug were explored to include stepwise dose increase, ramp-up dosing, and constant or flat dosing. In dose level 4, the first seven patients received an initial dose of 5 $\mu g/m^2$/day followed by intraindividual escalation to 15 $\mu g/m^2$/day. Three of the subsequently enrolled six patients were treated using ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. The remaining three patients received 15 $\mu g/m^2$/day constant dosing. In dose level 5, three patients were treated after ramp-up dose escalation to the target dose within 24 hours followed by constant target dose administration. Ramp-up dosing was achieved by programming the portable minipump used for blinatumomab administration such that the flow rate continuously increased within the first 24 hours of administration to achieve a steady increase in the administered dose from 0 $\mu g/m^2$/day to the target dose (15 or 30 $\mu g/m^2$/day) within the given period.

Decisions on whether to proceed to dose escalation, which mode of initial drug administration to apply, and patient treatment dose group assignment were made by the Data Review Committee, which reviewed the data of each dose group after all patients in that group had completed the first 14 days of treatment. Because no difference in the adverse event profile was observed among patients who received stepwise, ramp-up, or constant dosing in dose levels 4 and 5, constant dosing was used in dose levels 6 and 7 per Data Review Committee decision.

Pharmacokinetics. Serum samples were collected at regular intervals at baseline, during infusion, and after infusion stop. Blinatumomab concentrations in the serum were measured as described previously by using a validated bioassay with a lower limit of quantification of 100 pg/mL.[19] Serum concentration versus time profiles were visually inspected and steady-state concentration was calculated from concentrations between achievement of plateau and infusion stop. Pharmacokinetic parameters were estimated by using noncompartmental methods (WinNonlin version 5.3; Pharsight Corporation, Mountain View, CA).

Lymphocyte subpopulation analysis. Lymphocyte subpopulations were measured by fluorescence-activated cell sorting (FACS) at various time points during treatment and quantified as described previously.[19] Briefly, peripheral blood mononuclear cells from patients were isolated by using Biocoll (Biochrom, Berlin, Germany) density gradient centrifugation followed by staining with fluorescence-conjugated antibodies against multiple T-, B-, and natural killer cell–specific antigens. Cell acquisition was performed on either FACSCalibur or FACSCanto II (BD Biosciences, San Jose, CA) with subsequent analysis by CellQuest Pro (BD Biosciences) or FCS Express (De Novo Software, Los Angeles, CA). Absolute cell counts were obtained by combining FACS-based percentage data and absolute lymphocyte numbers from differential blood counts.

Table A1. Disposition of Patients in the Study Extension Phase and Adverse Events That Led to Permanent Treatment Discontinuation (n = 34)

	No. Patients (%)
Disposition	
Completed blinatumomab treatment and study	
End of study	13 (38)
Disease progression	3 (9)
Completed blinatumomab treatment; discontinued study	
Lost to follow-up	1 (3)
Other reason	1 (3)
Discontinued blinatumomab treatment and study	
Adverse event	13 (38)
Disease progression	1 (3)
End of study	1 (3)
Other reason	1 (3)
Adverse events that led to discontinuation of blinatumomab treatment and study	
Discontinued due to adverse events*	13 (38)
Aphasia	4 (12)
Encephalopathy	2 (6)
Dyspnea	2 (6)
Disorientation	2 (6)
Apraxia	2 (6)
VIIth nerve paralysis	1 (3)
Muscular weakness	1 (3)
Transient ischemic attack	1 (3)
Speech impairment	1 (3)
Visual hallucination	1 (3)
Dysarthria	1 (3)
Ataxia	1 (3)
Tremor	1 (3)
Pneumoperitoneum	1 (3)
Dysaesthesia	1 (3)

*More than one adverse event may have occurred in each patient.

Table A2. Blinatumomab Dose Levels and Neurologic Events in the Study Extension Phase

Intended Dose ($\mu g/m^2$/day)	Corticosteroid Comedication Prophylaxis	PPS	No. of Patients Enrolled	No. of Patients With Neurologic Events/Neurologic Events That Led to Treatment Discontinuation*
60 flat	Yes†	No	2	1/1 *Encephalopathy (grade 3)*
5-60 or 15-60 single step‡	Yes†	No	5	4/2 Headache, amnesic aphasia, apraxia, and (intermittent) tremulous and intermittent ataxia (5-60 $\mu g/m^2$/day) *Aphasia and VIIth nerve paralysis* (5-60 $\mu g/m^2$/day) Dizziness (15-60 $\mu g/m^2$/day) *Encephalopathy (grade 3*; 15-60 $\mu g/m^2$/day)
5-60 single step plus PPS§	Yes†	Yes	3	3/0 Kinetic tremor, speech impairment, and dizziness Dizziness Dysesthesia located on head, sadness, sleep disorder, and headache
5-15-60 double step‖	Yes†	No	11	7/3 Anomia Amnesic aphasia and kinetic tremor Intermittent headache Headache *Transient ischemic attack (grade 3)* *Speech impairment (grade 3)* *Apraxia*
Patients with DLBCL				
5-15-60 double step	Yes† Investigator choice, which included dexamethasone only (n=3)	No	9	8/4 Mild tremor, mild tremor both hands, and polyneuropathia lower extremities Headache Headache, apraxia, speech impairment, and (intermittent) kinetic tremor Headache, restless legs, and intensified headache *Apraxia* *Aphasia, disorientation, and visual hallucination (all grade 3)* *Aphasia, dysarthria, and dysaesthesia* *Aphasia, ataxia, disorientation, and tremor (all grade 3)*
5-15-60 double step	Yes† Early dexamethasone only	No	4	3/0 Intermittent headache, dizziness, and insomnia Headache, lymphocytic pleocytosis of the cerebrospinal fluid, ataxia, and confusion Tremor
Total			34	

Abbreviation: DLBCL, diffuse large B-cell lymphoma; PPS, pentosan polysulfate SP54.

*Neurologic events that led to treatment discontinuation are shown in italics.

†Corticosteroid comedication of the investigator's choice, with corticosteroid type (prednisolone and dexamethasone), dose, and treatment duration determined by the investigator on the basis of the patient's clinical presentation or early dexamethasone prophylaxis at least 12 h before blinatumomab treatment (days 1, 8, and 15, 20 mg dexamethasone orally twice a day 12-6 h and 1 h before blinatumomab infusion; days 2 and 3, 9 and 10, and 16 and 17, 8 mg dexamethasone three times a day).

‡All but two patients received the blinatumomab target dose of 60 $\mu g/m^2$/day as weekly dose escalation in a single step (5 or 15 $\mu g/m^2$/day on days 1-7, then 60 $\mu g/m^2$/day).

§Patients received blinatumomab along with PPS for 48 h during initiation of treatment and during dose increments. This was an exploratory treatment; therefore, the number of patients was limited to three per study protocol.

‖All but five patients received the blinatumomab target dose of 60 $\mu g/m^2$/day in a double step (5 $\mu g/m^2$/day on days 1-7; 15 $\mu g/m^2$/day on days 8-14, then 60 $\mu g/m^2$/day).

Table A3. Steady-State Exposure and Pharmacokinetic Parameters of Blinatumomab

	C_{ss} (pg/mL)					Across All Doses		
	5 μg/m^2/day	15 μg/m^2/day	30 μg/m^2/day	60 μg/m^2/day	90 μg/m^2/day	CL (L/h)	$t_{1/2}$ (h)	V_Z (L)
No.	26	37	8	40	4	72	37	37
Mean	234	734	1,357	2,869	3,567	2	2.1	5.7
SD	87	336	519	1,031	862	0.9	1.1	2.7
CV%	37	46	38	36	24	44	53	47

Abbreviations: CL, clearance; C_{ss}, steady-state concentration; CV%, coefficient of variation; SD, standard deviation; $t_{1/2}$, terminal half-life; V_Z, apparent volume of distribution during terminal phase.