original reports

Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

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abstract

PURPOSE Mosunetuzumab is a bispecific antibody targeting CD20 and CD3 that redirects T cells to engage and eliminate malignant B cells and is being developed for relapsed or refractory (R/R) B-cell non-Hodgkin lymphomas (B-NHLs).

METHODS This first-in-human trial (ClinicalTrials.gov identifier: NCT02500407) evaluated the safety and tolerability and efficacy of mosunetuzumab in patients with R/R B-NHL and established the recommended phase II dose. Data from dose escalation are presented. Single-agent mosunetuzumab was administered intravenously in 3-week cycles, at full dose in cycle 1 day 1 (group A) or with ascending (step-up) doses during cycle 1 on days 1, 8, and 15 (group B), for eight or 17 cycles on the basis of tumor response.

RESULTS Two hundred thirty patients were enrolled. Doses up to 2.8 mg and 60 mg were assessed in groups A and B, respectively; maximum tolerated dose was not exceeded. In group B (n = 197), common adverse events (≥ 20% of patients) were neutropenia (28.4%), cytokine release syndrome (27.4%), hypophosphatemia (23.4%), fatigue (22.8%), and diarrhea (21.8%). Cytokine release syndrome was mostly low-grade (grade ≥ 3: 1.0%) and mainly confined to cycle 1. Across the doses investigated (group B), best overall response rates were 34.9% and 66.2% in patients with aggressive and indolent B-NHL, respectively, and complete response rates were 19.4% and 48.5%. Among patients with a complete response, the median duration of response was 22.8 months (95% CI, 7.6 to not estimable) and 20.4 (95% CI, 16 to not estimable) in patients with aggressive and indolent B-NHL, respectively.

CONCLUSION Mosunetuzumab, administered with step-up dosing, has a manageable safety profile and induces durable complete responses in R/R B-NHL. The expansion stage of the study is ongoing at the dose level of 1/2/60/60/30 mg selected for further study.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Current standard of care for non-Hodgkin lymphoma (NHL) comprises an anti-CD20 monoclonal antibody in combination with chemotherapy. Despite recent advances, an unmet need remains for safe and effective therapies for progressive or relapsed disease.[1,2]

Redirecting T cells to target malignant cells is an effective therapeutic approach in B-cell malignancies.[3-6] CD19-directed chimeric antigen receptor T-cell (CAR-T) therapies have shown efficacy in relapsed or refractory (R/R) NHL,[5-8] although specialized manufacturing may limit widespread applicability. Antibody fragment–based T-cell–targeted bispecific molecules have also shown efficacy, but generally require continuous infusion because of a short half-life.[9,10]

Mosunetuzumab is a full-length, humanized, immunoglobulin G1–based bispecific antibody targeting CD20 (B cells) and CD3 (T cells).[11] Unlike anti-CD20 monoclonal antibodies that induce direct cell death and complement- and antibody-dependent cellular cytotoxicity,[12] mosunetuzumab redirects T cells to engage and eliminate malignant B cells.[11] Preclinical studies show that mosunetuzumab induces rapid and sustained T-cell activation and proliferation, and potent lysis of CD20-expressing B cells, including primary leukemia and lymphoma cells, both in vitro and in vivo, with the potential to circumvent resistance to rituximab.[11]

CONTEXT

Key Objective

This ongoing trial is the first-in-human study with mosunetuzumab. The dose-escalation study evaluated safety, tolerability, and efficacy of single-agent mosunetuzumab in patients with relapsed or refractory B-cell non-Hodgkin lymphomas (B-NHLs).

Knowledge Generated

When administered by step-up dosing, mosunetuzumab had a manageable safety profile; most adverse events were low grade, transient, and reversible and occurred early in the first cycle of treatment.

Mosunetuzumab achieved durable complete responses in patients with aggressive and indolent relapsed or refractory B-NHL.

Relevance (*J.W. Friedberg*)

Mosunetuzumab has a promising risk-benefit profile for patients with relapsed or refractory B-NHL, and ongoing single-agent and combination studies will better define the optimal role for this agent in patients with both indolent and aggressive lymphomas.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

Here, we report an analysis of the dose escalation of single-agent mosunetuzumab in patients with B-cell NHL (B-NHL) from the ongoing first-in-human study (NCT02500407).

METHODS

Patients

Patients were age ≥ 18 years with histologically confirmed R/R B-NHL expected to express CD20 and no available therapy expected to improve survival. Full eligibility criteria are available in the Protocol (online only).

Study Design

NCT02500407 is an ongoing phase I and Ib multicenter, open-label, dose-escalation, and expansion study of mosunetuzumab. Data for dose-escalation and interim expansion cohorts using fixed (group A) or cycle 1 step-up dosing (group B) are reported.

The trial initially used single-patient dose-escalation cohorts for group A (0.05-0.2 mg) before converting to a 3 + 3 design on the basis of an observed grade 2 cytokine release syndrome (CRS) event that met one of the predefined criteria (Protocol).[13] Dose escalation in group B used a 3 + 3 design. To further characterize safety and efficacy, additional patients were treated in histology-specific interim expansion cohorts at each dose level. In the diffuse large B-cell lymphoma (DLBCL) and transformed follicular lymphoma (FL) cohorts, patients must have failed ≥ 2 prior systemic therapies (including anthracycline and anti-CD20–directed therapy; Protocol). In the FL cohorts, patients must have grade 1-3a and failed ≥ 2 prior systemic therapies (including anti-CD20–directed therapy and an alkylating agent).

In group A, mosunetuzumab was administered intravenously on day 1 of each 21-day cycle. In group B, mosunetuzumab was administered intravenously as low and intermediate step-up doses on days 1 and 8 of cycle 1, with the target dose on day 15 and on day 1 of subsequent 21-day cycles. Mosunetuzumab was discontinued after eight cycles for patients with a complete response (CR) and after 17 cycles for those with a partial response or stable disease. Retreatment was permitted for patients who relapsed after a CR.

All patients in group A were hospitalized for at least 72 hours for cycle 1, day 1. In group B, 72-hour in-patient monitoring was implemented in the dose-escalation cohorts after the cycle 1 day 15 dose, but was not required in the interim expansion cohorts.

The primary objectives during dose escalation were to evaluate safety, tolerability, and pharmacokinetics (PK) and to determine the recommended phase II dose (RP2D), maximum tolerated dose (MTD), and dose-limiting toxicities of mosunetuzumab. A secondary objective was to assess antitumor activity. The ongoing expansion phase of the study will further evaluate the efficacy and safety of the selected RP2D in several histology-specific cohorts.

Adverse events (AEs) were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[14] CRS events were graded on the basis of 2014 Lee criteria.[15] Tumor responses were assessed by investigators using the Revised Response Criteria for Malignant Lymphoma.[16] Tumor assessments (diagnostic quality computed tomography scans with or without fluorodeoxyglucose positron emission tomography) were performed at screening, 3 months after the first mosunetuzumab infusion, and every 3 months thereafter, with an optional assessment at 6 weeks. Additional assessments are described in the Protocol. Area under the concentration-time curve (AUC; patients with indolent B-NHL) and average

CD20 receptor occupancy (RO%; patients with aggressive B-NHL) were used to characterize mosunetuzumab exposure-response relationships (Protocol).

The protocol was approved by institutional review boards at each center. The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable laws and regulations. All patients provided written informed consent.

Statistical Analysis

The sample size of the dose-escalation cohorts was based on dose-escalation rules. Interim expansion cohorts for R/R DLBCL and transformed FL, FL, and mantle cell lymphoma were opened to acquire additional safety and efficacy data at cleared dose levels to inform dose selection, whereas higher dose levels continued to be evaluated in dose-escalation cohorts. As determined by the Internal Monitoring Committee, more than one mosunetuzumab dose level and schedule could be assessed in interim expansion cohorts of up to approximately 20 patients before the identification of the RP2D. Expansion cohorts at a RP2D could enroll more than 20 patients. For patients who underwent intrapatient dose escalation, analyses were performed on the basis of the initial assigned dose level. The safety and efficacy populations comprised all patients who received any study treatment. Patients with missing or no response assessments were considered nonresponders. Exact 95% CIs (Clopper-Pearson method) are provided for response rates. Data are reported up to the clinical cutoff date of January 21, 2020. One patient assigned to Cohort B7 received the correct 1.0/2.0/13.5 mg dose; however, data were entered erroneously as Cohort B9. Analyses were performed on the basis of the correct dose level.

RESULTS

Patients

Group A enrolled 33 patients in eight different fixed-dose cohorts (1-8 patients per dose; 0.05-2.8 mg). MTD was not reached. Further enrollment into group A was stopped, and further escalation was conducted with a cycle 1 step-up dosing schedule in group B to expand the therapeutic index by CRS mitigation.[17] The cycle 1, day 1 and day 8 step doses were empirically selected at 1 mg and 2 mg for the majority of the group B escalation because they were safe, enabled escalation of the day 15 dose with minimal CRS risk (see PK and exposure-response relationships), and responses were first observed in group A beginning at 1.2 mg. Group B enrolled 197 patients with 60 patients treated in 11 dose-escalation cohorts (1-10 patients per dose). Interim expansion cohorts were initiated at seven group B dose levels, as approved by the Internal Monitoring Committee, and enrolled an additional 137 patients to allow robust exposure-response assessment for both safety and efficacy to inform the final RP2D selection (Data Supplement, Fig S1, Table S1, online only, Protocol). An initial RP2D of 1/2/13.5 mg was studied in 43 patients with FL. However, on the basis of additional data from dose-escalation and integrated exposure-response modeling, loading doses of 60 mg would be further along the plateau of the exposure-response curve for efficacy (Fig 3) and a RP2D of 1/2/60/60/30 mg was selected for further study in all histologies (see Discussion). The median time on study was 12.6 months (range, 0.7-52.1 months) in group A and 10.1 months (range, 0.4-39.5 months) in group B. All patients were evaluable for safety and efficacy.

The median treatment duration was 2.6 months (range, 0.3-5.3 months) in group A and 4.0 months (range, 0.3-12.1 months) in group B. In group B, patients received a median of five cycles (range, 1-17). In the 59 (29.9%) patients who completed study treatment in group B, 48 received eight cycles and 11 received more than eight cycles. The median duration of response follow-up was 11.9 months (95% CI, 9.3 to 13.8).

Patient characteristics are shown in Table 1 (group B) and the Data Supplement, Table S2 (group A) and Table S3 (group B, prior CAR-T therapy). The median age of group B patients was 61 years (range, 19-91 years); 65.5% had aggressive B-NHL (mainly DLBCL [41.6%]) and 34.5% had indolent lymphoma (mostly FL [33.0%]). Patients had received a median of three prior systemic therapies (range, 1-14), 75.6% were refractory to their last treatment, and 9.6% had received prior CAR-T therapy.

Safety

The MTD was not exceeded with either dosing schedule: 0.05-2.8 mg in group A and 0.4/1.0/2.8-1.0/2.0/60 mg (cycle 1 day 1/8/15) in group B. Dose-limiting toxicities are described in the Data Supplement, Table S4.

Treatment-emergent AEs are summarized in Table 2 (group B), Data Supplement, Table S5 (group A), and Table S6 (group B, prior CAR-T therapy). Most AEs (53.7%) occurred during the first 21 days (Data Supplement, Fig S2). Common any-grade AEs (≥ 20% of group B) were neutropenia (28.4%), CRS (27.4%), hypophosphatemia (23.4%), fatigue (22.8%), and diarrhea (21.8%; Fig 1). Grade ≥ 3 AEs occurred in 71.1% of group B, with neutropenia (25.4%), hypophosphatemia (15.2%), and anemia (9.1%) being the most frequent (≥ 5%). In group B, seven (3.6%) patients discontinued treatment because of AEs (Data Supplement, Fig S1).

Grade 5 (fatal) AEs unrelated to disease progression were seen in one group A and three group B patients. One patient with chronic active Epstein-Barr virus infection died from hemophagocytic lymphohistiocytosis (related to treatment) and one each from sepsis (unrelated), Candida sepsis (unrelated), and pneumonia (related).

CRS occurred in 27.4% of group B patients (20.8% grade 1; 5.6% grade 2; 1.0% grade 3; no grade 4; Table 2 and Data Supplement, Table S7) and included pyrexia (23.4%),

TABLE 1. Patient Demographics and Baseline Disease Characteristics (group B; safety population)

Characteristic	Aggressive NHL[a] (n = 129)	Indolent NHL[b] (n = 68)
Age, years		
Median	63.0	60.5
Range	19-91	27-85
Male sex, No. (%)	82 (63.6)	43 (63.2)
ECOG PS, No. (%)		
0	42 (32.6)	37 (54.4)
1	86 (66.7)	31 (45.6)
2	1 (0.8)	0
Ann Arbor stage at study entry, No. (%)		
No. of evaluable patients[c]	127	68
Stage I	4 (3.1)	1 (1.5)
Stage II	15 (11.8)	9 (13.2)
Stage III	26 (20.5)	24 (35.3)
Stage IV	82 (64.6)	34 (50)
Prior systemic therapies, No.		
Median	3	3
Range	1-14	1-11
Prior CAR-T therapy, No. (%)	15 (11.6)	4 (5.9)
Prior autologous stem-cell transplant, No. (%)	44 (34.1)	12 (17.6)
Refractory to last therapy, No. (%)[d]	106 (82.2)	43 (63.2)
Refractory to prior anti-CD20 therapy, No. (%)[d]	100 (77.5)	51 (75.0)

NOTE. Clinical cutoff date: January 21, 2020.

Abbreviations: CAR-T, chimeric antigen receptor T cell; ECOG PS, Eastern Cooperative Oncology Group performance status; NHL, non-Hodgkin lymphoma.

[a]Includes patients with diffuse large B-cell lymphoma (n = 82), transformed follicular lymphoma (n = 26), mantle cell lymphoma (n = 13), Richter's transformation (n = 5), follicular lymphoma grade 3B (n = 1), transformed marginal zone lymphoma (n = 1), and mixed diffuse large B-cell lymphoma and mantle cell lymphoma (n = 1).

[b]Includes patients with follicular lymphoma (grade 1-3A; n = 65), marginal zone lymphoma (n = 2), and small lymphocytic lymphoma (n = 1).

[c]Data not available for all patients by cutoff date.

[d]Defined as not achieving a response (complete or partial response) or progressing within ≤ 6 months of applicable treatment.

chills (10.2%), tachycardia (4.1%), and hypotension (3.6%). CRS onset most often occurred after day 1 and day 15 of cycle 1 (Data Supplement, Fig S3); the median duration was 2 days (range, 1-20 days). All CRS events resolved; tocilizumab was administered in three patients and vasopressor in one patient. In group A, all CRS events were grade 1 or 2 (Data Supplement, Table S5), occurred during cycle 1, and had a median onset of 1 day and a median duration of 2 days (range, 1-16 days). Serious CRS leading to new or prolonged hospitalization occurred in 7.1% of patients.

Any grade neurologic AEs (preferred terms from the Nervous System Disorder and Psychiatric Disorders System Organ Class) reported in ≥ 10% of group B patients were headache (17.8%), insomnia (11.2%), and dizziness (10.2%; Fig 1). In group B, most neurologic AEs were grade 1-2. Grade 3 neurologic AEs occurred in 4.1% of patients; however, only two (1.0%) were considered treatment-related (hepatic encephalopathy, unresolved; and increased drowsiness, resolved); there were no grade 4 or 5 neurologic events.

In group B, neutropenia occurred in 28.4% of patients, with 25.4% grade ≥ 3; the median duration was 9 days (range, 1-385 days); 92.8% of neutropenia events resolved by the cutoff date. Growth factor for neutropenia was given to 22.3% of patients. Febrile neutropenia was observed in 3.6% of group B patients, and anemia in 18.8% (grade 1: 4.6%; grade 2: 5.1%; grade 3: 9.1%); 51.4% (19 of 37) of patients received treatment for anemia. Other hematologic AEs were uncommon (thrombocytopenia [2.5%], lymphopenia [2.0%], and leukopenia [1.0%]).

Hypophosphatemia occurred in 23.4% of patients. Although 15.2% of patients had grade ≥ 3 hypophosphatemia, events were asymptomatic, transient (median duration 3 days; range, 1-64), not dose-limiting, and resolved with or without phosphate supplements.

Efficacy

Best responses in group A patients are described in the Data Supplement, Table S8; the first CR was observed at 1.2 mg. Among 129 evaluable group B patients with aggressive B-NHL, the best objective response rate (ORR) was 34.9% and the CR rate was 19.4% (Table 3 and Fig 2A). The median duration of response for all responders and complete responders was 7.6 (95% CI, 5.6 to 22.8) and 22.8 (95% CI, 7.6 to not estimable [NE]) months, respectively (Fig 2C; Data Supplement, Fig S5A; and Table 3). In 68 evaluable group B patients with indolent B-NHL, the ORR was 66.2% and the CR rate was 48.5% (Table 3 and Fig 2B). The median duration of response for all and complete responders was 16.8 (95% CI, 11.7 to NE) and 20.4 (95% CI, 16.0 to NE) months, respectively (Fig 2C; Data Supplement Fig S5B; and Table 3). The median time to first response was 1.4 (range, 1.1-13.8) and 2.6 (range, 1.2-7.5) months in aggressive and indolent B-NHL, respectively. The median progression-free survival across all dose levels for aggressive and indolent B-NHL was 1.4 (95% CI, 1.4 to 2.9) months and 11.8 (95% CI, 8.4 to NE) months, respectively (Fig 2D). Clinical response in both aggressive and indolent B-NHL was strongly associated with mosunetuzumab exposure (CD20 RO% and AUC, respectively) in both dosing groups (Figs 3A and 3B).

Responses were observed in high-risk subgroups. The ORR in all 19 patients with indolent (n = 4) or aggressive NHL (n = 15) and prior CAR-T therapy was 36.8% (26.3%

TABLE 2. Summary of AEs (group B; safety population)

No. of Patients (%)	Group B (n = 197)
Any AE	195 (99.0)
Treatment-related AE[a]	146 (74.1)
Serious AE, not including grade 5 malignant neoplasm progression[b]	69 (35.0)
Treatment-related serious AE[a]	36 (18.3)
Grade 5 (fatal) AE, not including grade 5 malignant neoplasm progression[b]	3 (1.5)
Any AE leading to mosunetuzumab treatment discontinuation	11 (5.6)
Treatment-related AE leading to mosunetuzumab treatment discontinuation[a]	7 (3.6)

Common (≥ 20% of Patients) Any-grade AEs or (≥ 2% of Patients) Grade ≥ 3 AEs by Preferred Term	Any Grade	Grade ≥ 3
Total	195 (99.0)	140 (71.1)
Neutropenia[c]	56 (28.4)	50 (25.4)
Febrile neutropenia	7 (3.6)	7 (3.6)
CRS	54 (27.4)	2 (1.0)
Hypophosphatemia	46 (23.4)	30 (15.2)
Fatigue	45 (22.8)	2 (1.0)
Diarrhea	43 (21.8)	2 (1.0)
Anemia	37 (18.8)	18 (9.1)
Malignant neoplasm progression[b]	26 (13.2)	26 (13.2)
Hypokalemia	26 (13.2)	4 (2.0)
Urinary tract infection	15 (7.6)	5 (2.5)
Hyperglycemia	11 (5.6)	4 (2.0)
Pneumonia	9 (4.6)	5 (2.5)
ALT increase	8 (4.1)	4 (2.0)
Thrombocytopenia	5 (2.5)	4 (2.0)
Lymphocyte count decrease	5 (2.5)	4 (2.0)
Lymphopenia	4 (2.0)	4 (2.0)
Common (≥ 2% of Patients) Serious AEs by Preferred Term	**Any Grade**	**Grade ≥ 3**
CRS	14 (7.1)[d]	2 (1.0)
Febrile neutropenia	5 (2.5)	5 (2.5)
Neutropenia	5 (2.5)	5 (2.5)
Pneumonia	5 (2.5)	5 (2.5)

NOTE. Clinical cutoff date: January 21, 2020. Serious AEs are defined as any untoward medical occurrence(s) that results in death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity or a congenital anomaly or birth defect, or any life-threatening or significant medical event in the investigator's judgment. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32.

Abbreviations: AE, adverse event; CRS, cytokine release syndrome.

[a]Relationship between each AE and study treatment was determined by investigator assessment.

[b]Death attributed to progression of cancer was a reportable AE if occurring within 90 days after the last dose of study treatment and before the initiation of another systemic anticancer therapy.

[c]Includes the MedDRA Preferred Terms, neutropenia and neutrophil count decreased. Available from https://www.meddra.org/how-to-use/basics/hierarchy.

[d]Serious CRS AEs in 14 patients (diffuse large B-cell lymphoma [n = 7], follicular lymphoma [n = 4], mantle cell lymphoma [n = 2], and transformed follicular lymphoma [n = 1]). New or prolonged hospitalization for CRS management occurred after cycle 1 day 1 in three patients (1.5%), after cycle 1 day 8 in three patients (1.5%), after cycle 1 day 15 in seven patients (3.6%), and after cycle 2 day 1 in one patient (0.5%).

CRs; Table 3). In patients with FL, consistent CR rates were observed in patients refractory to both a prior anti-CD20 antibody and alkylating agent (55.9%) and in those with progressive disease within 24 months of starting first-line therapy (54.5%; Data Supplement, Table S9). Responses were also seen across histology subtypes (Data Supplement, Table S10). No association was found between response and the occurrence of CRS (Data Supplement, Table S11).

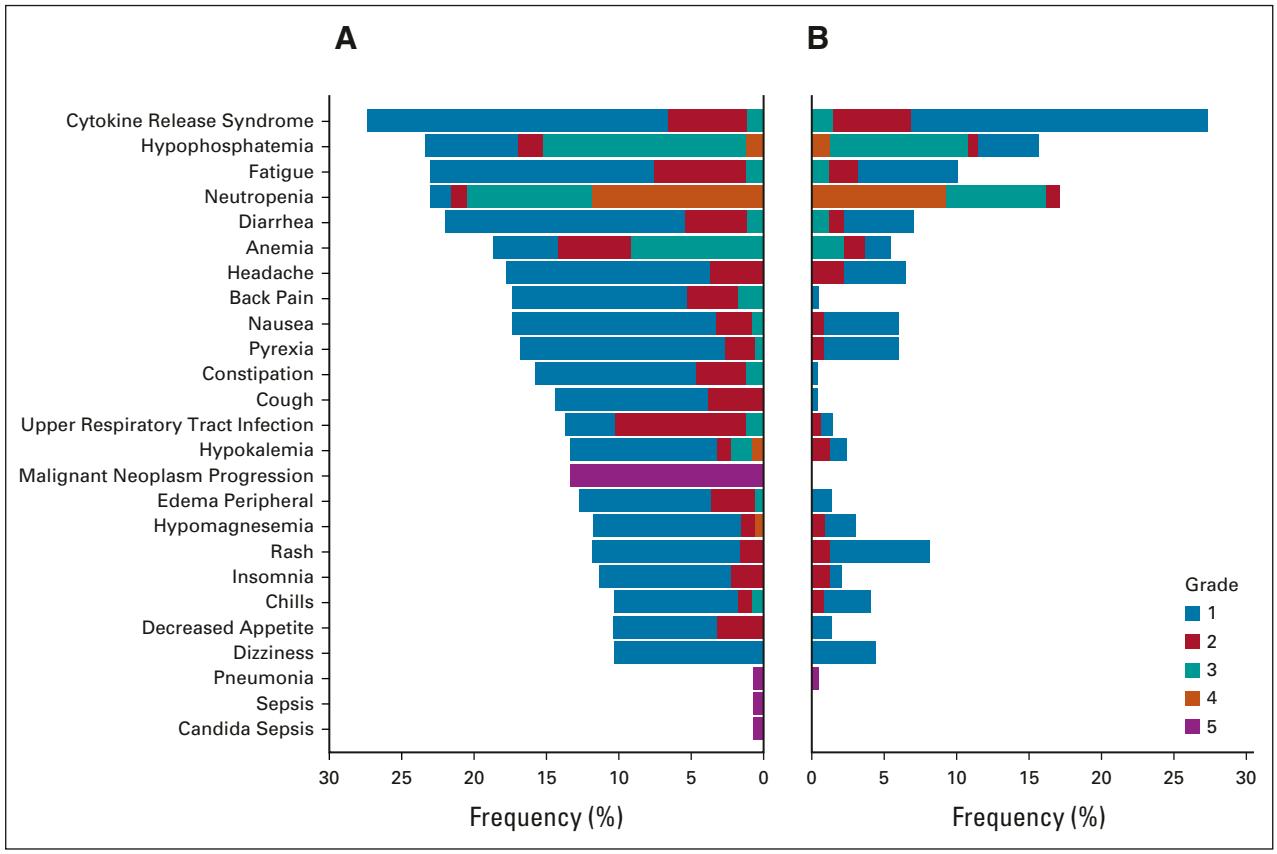

FIG 1. AEs with incidence ≥ 10% or National Cancer Institute-Common Terminology Criteria for AEs grade 5 (group B; safety population): (A) all AEs and (B) AEs related to mosunetuzumab. Clinical cutoff date: January 21, 2020. CRS events were graded and treated on the basis of the criteria published by Lee et al.[15] AEs, adverse events; CRS, cytokine release syndrome.

One patient in group A and five in group B who relapsed after achieving a CR were retreated with mosunetuzumab. Of the five evaluable for efficacy, four responded, including two CRs.

PK and Exposure-Response Relationships

The mosunetuzumab concentration increased in an approximately dose-proportional manner over the dose range of 0.05-60 mg. The apparent half-life was approximately 6-11 days. The PK profile of intravenous mosunetuzumab was described by a two-compartment PK model with time-dependent clearance. The estimated serum clearance was approximately 1 L/d at baseline and reduced to an average steady state of approximately 0.5 L/d over a transitional half-life of 21 days; this is higher than the expected range for a typical immunoglobulin G1 antibody, indicating a potential impact of target-mediated drug disposition.

Exposure-response analyses indicated positive relationships between PK exposure (CD20 RO% and AUC averaged over the initial 42 days of treatment for aggressive and indolent NHL, respectively) and CR rates or ORRs (Figs 3A and 3B). Observed CR rates and ORRs in the top exposure quartiles were 35% (n = 12/34) and 56% (n = 19/34), respectively, in patients with aggressive NHL, and 65% (n = 13/20) and 75% (n = 15/20), respectively, in patients with indolent NHL. In group A, there was a trend for an increase in grade ≥ 2 CRS with maximal RO% over the initial 42 days of treatment (RO_{max} days 0-42), which was largely mitigated when using cycle 1 step-up dosing, resulting in a broader therapeutic index (Fig 3C).

Pharmacodynamics

Mosunetuzumab treatment induced T-cell activation in peripheral blood (Data Supplement, Fig S4). Patients experiencing CRS had a trend for higher interleukin-6 peak induction, which was observed primarily after day 1 dosing (Data Supplement, Fig S6).

DISCUSSION

In this first-in-human study, mosunetuzumab exhibited a promising risk-benefit profile in heavily pretreated patients with R/R B-NHL. Across fixed dosing and cycle 1 step-up dosing groups, most AEs were low grade, transient, and reversible and occurred early in the first cycle, with few treatment discontinuations because of AEs. A comparison across dosing groups suggests that cycle 1 step-up dosing

TABLE 3. Summary of Efficacy (group B; efficacy population)

Best Objective Response[a]	Aggressive NHL[b] (n = 129)	Indolent NHL[c] (n = 68)	Post–CAR-T Therapy (n = 19)
ORR, No. (%) [95% CI]	45 (34.9) [26.7 to 43.8]	45 (66.2) [53.7 to 77.2]	7[d] (36.8) [16.3 to 61.6]
Complete response, No. (%) [95% CI]	25 (19.4) [13.0 to 27.3]	33 (48.5) [36.2 to 61.0]	5 (26.3) [9.2 to 51.2]
Partial response, No. (%) [95% CI]	20 (15.5) [9.7 to 22.9]	12 (17.6) [9.5 to 28.8]	2 (10.5) [1.3 to 33.1]
Stable disease, No. (%) [95% CI]	9 (7.0) [3.2 to 12.8]	13 (19.1) [10.6 to 30.5]	0 (0) [0.0 to 17.7]
Progressive disease, No. (%) [95% CI]	70 (54.3) [45.3 to 63.1]	9 (13.2) [6.2 to 23.6]	12 (63.2) [38.4 to 83.7]
Duration of response, median [95% CI], months	7.6 [5.6 to 22.8]	16.8 [11.7 to NE]	Not reported due to small sample size (n = 7)[d]
Duration of response in patients with complete response, median [95% CI], months	22.8 [7.6 to NE]	20.4 [16.0 to NE]	Not reported due to small sample size (n = 5)

NOTE. Clinical cutoff date: January 21, 2020.

Abbreviations: CAR-T, chimeric antigen receptor T-cell; NE, not estimable; NHL, non-Hodgkin lymphoma; ORR, objective response rate.

[a]Response by computed tomography with or without fluorodeoxyglucose positron emission tomography. At data cutoff, among patients who had at least one tumor assessment, 86% had at least one positron emission tomography scan performed.

[b]Includes patients with diffuse large B-cell lymphoma (n = 82), transformed follicular lymphoma (n = 26), mantle cell lymphoma (n = 13), Richter's transformation (n = 5), follicular lymphoma grade 3B (n = 1), transformed marginal zone lymphoma (n = 1), and mixed diffuse large B-cell lymphoma and mantle cell lymphoma (n = 1).

[c]Includes patients with follicular lymphoma (grade 1-3A; n = 68), marginal zone lymphoma (n = 2), and small lymphocytic lymphoma (n = 1).

[d]Post–CAR-T responders include patients with diffuse large B-cell lymphoma (n = 3; two patients maintained response by the clinical cutoff date, with durations of response of 0.03 and 4.47 months and one patient had a duration of response to death of 2.3 months) and follicular lymphoma (n = 4; one patient maintained response by the clinical cutoff date with a duration of response of 12.13 months and three patients had disease progression by the clinical cutoff date with durations of response of 9.37, 4.5, and 3.25 months).

enables dose escalation to higher subsequent and cumulative doses, while maintaining acceptable safety. The AE profile in patients who had received prior CAR-T-cell therapy was similar to the overall population.

Responses included durable CRs with a fixed treatment duration across a broad range of doses and in patients considered refractory to anti-CD20 therapy and other high-risk patients. Mosunetuzumab showed promise in patients who had progressed after prior CAR-T therapy, a population with limited treatment options. Although potentially subject to selection bias, 4 of 5 patients with previous CR responded to retreatment with mosunetuzumab, including two CRs.

CRS is a manageable, but significant inflammatory toxicity syndrome associated with T-cell–targeted immunotherapy.[15,16,18] To mitigate CRS, we used cycle 1 step-up dosing with mosunetuzumab. Pharmacodynamic analysis revealed that cytokine induction was primarily associated with the first dose and higher doses administered through step-up dosing did not further increase interleukin-6 levels. With step-up dosing (often administered in outpatient setting), any-grade CRS events were observed in 27.4% of patients with few grade 3 (1.0%) and no grade 4-5 events.[15] Most events occurred during cycle 1 and all resolved, with only 1.5% of patients requiring tocilizumab and 1.0% of patients requiring intensive care unit admission. Step-up dosing allowed higher target doses to be achieved while maintaining a tolerable safety profile, which combined with a positive exposure-response efficacy relationship, indicates a broad therapeutic index.[19] In addition, current safety monitoring guidance without mandatory hospitalization in the expansion cohorts appears reasonable and feasible, although RP2D data will be needed to describe optimal management in clinical practice.

The spectrum and severity of neurologic AEs observed in this study, including mostly grade 1-2 headache, insomnia, and dizziness, also compare favorably with the toxicities of encephalopathy and delirium reported with CD19-directed T-cell therapies.[20,21] The incidence of grade ≥ 3 neurologic AEs in B-NHL patients with CAR-T therapies and blinatumomab is 10%-32% and 22%, respectively.[5,7,10,22]

Multiple CD20-targeting bispecific antibodies (eg, glofitamab, epcoritamab, and odronextamab) are in development for B-NHL and as a class show promising antitumor activity.[23-25] Among studies of bispecific therapies, the present mosunetuzumab study enrolled the highest number of patients, allowing extensive exploration of the exposure-response relationship, dosing schedule, and early assessment of efficacy in high-risk subsets of patients. However, these phase I data are limited by lack of a control group, limited investigation of alternative scheduling options at similar doses, and modest follow-up. Mature data, including dose expansion in group B, are needed to better understand the treatment benefit at the RP2D.

This study suggests that the off-the-shelf CD20/CD3 bispecific immunotherapy, mosunetuzumab, has manageable safety and can achieve durable CRs in patients with R/R B-NHL. Although only three patients were treated

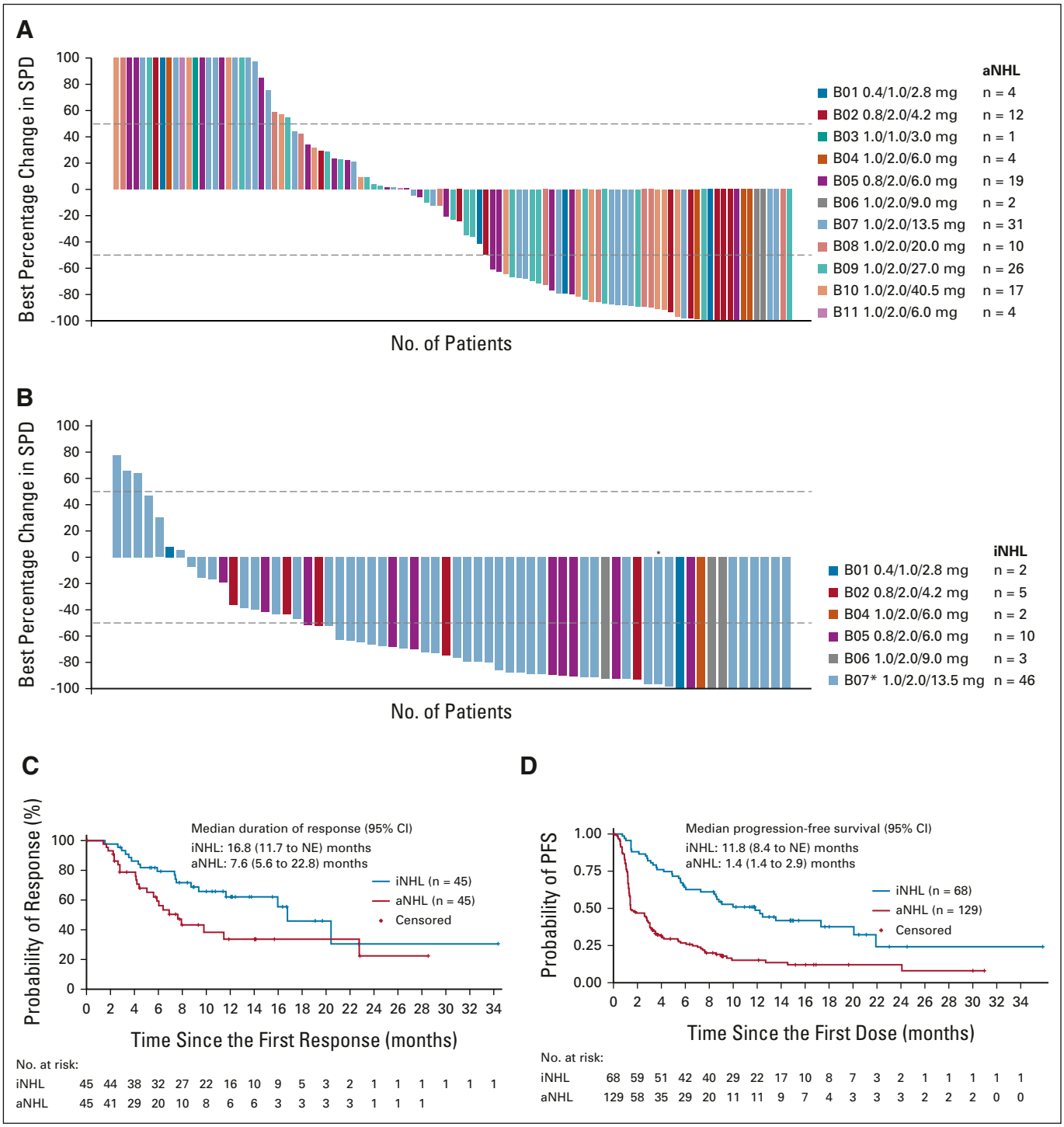

FIG 2. Best percentage change from baseline in the sum of the products of diameters in group B patients (efficacy population) with (A) aNHL (diffuse large B-cell lymphoma, transformed follicular lymphoma, mantle cell lymphoma, Richter's transformation, transformed marginal zone lymphoma, or grade 3b follicular lymphoma) and (B) iNHL (grade 1-3a follicular lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma). (C) Kaplan-Meier curves for duration of response (including complete and partial response) in aNHL and iNHL (group B; patients achieving complete response or partial response). (D) Kaplan-Meier curve for progression-free survival in group B patients with aNHL or iNHL. Clinical data cutoff: January 21, 2020. (A and B) Waterfall plots of the best overall change in the size of tumor target lesions according to the mosunetuzumab doses received. Plots of the best percentage changes in the sum of the products of diameters of target lesions are shown. The columns represent the results from individual patients, color coded according to the step-up doses of mosunetuzumab received. The dashed lines indicate 50% increase or decrease of the baseline SPD. The *y*-axis increase is truncated at 100%. aNHL, aggressive non-Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; NE, not estimable; SPD, sum of the products of diameters.

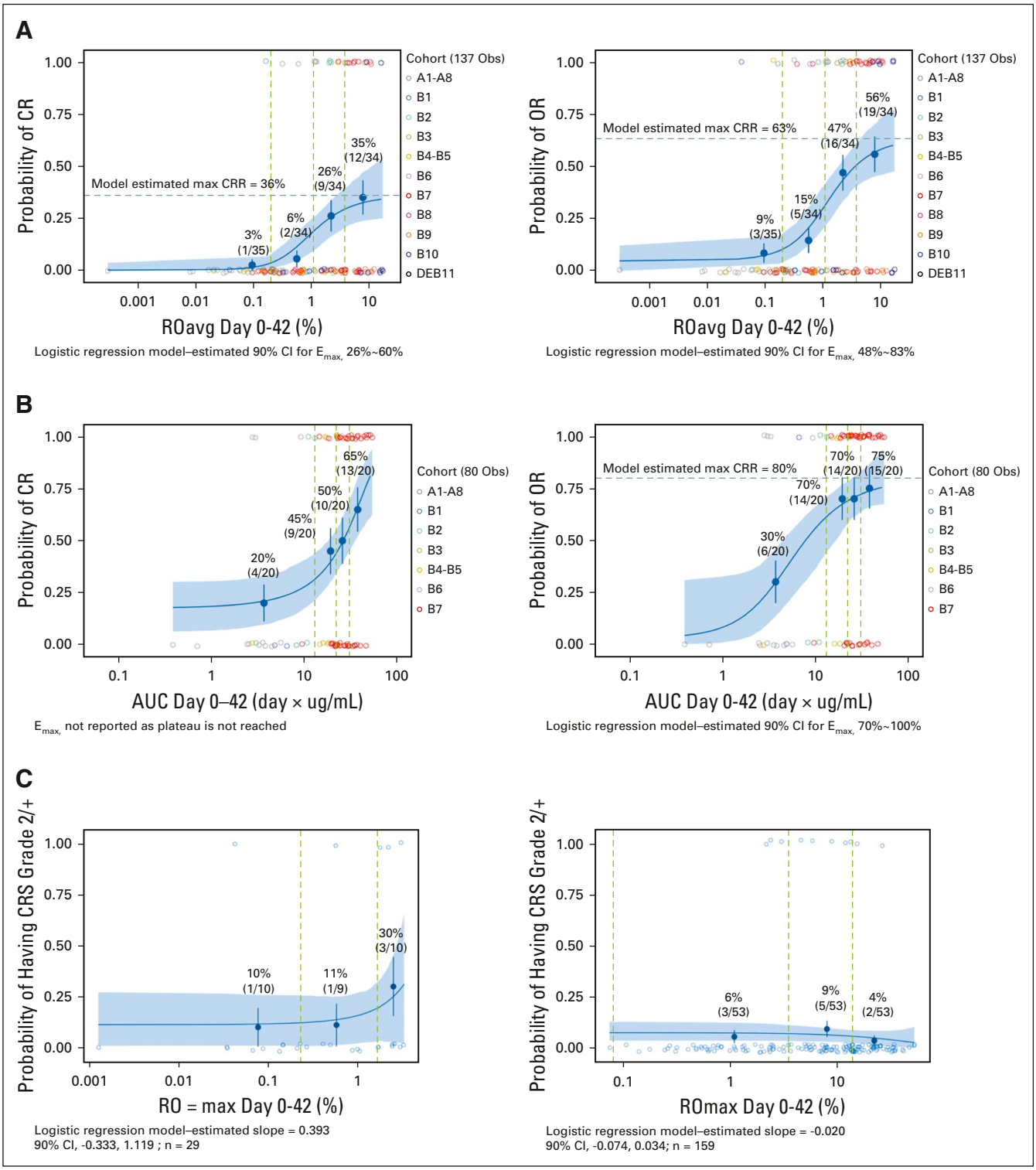

FIG 3. Exposure-response relationships of mosunetuzumab for clinical objective response and CRS: (A) for clinical response in group A and B patients with aggressive NHL (n = 137; left: CR; right: OR); (B) for clinical response in group A and B patients with indolent NHL (n = 80; left: CR; right: OR); (C) for occurrence of grade ≥ 2 CRS within the first 42 days of mosunetuzumab (mixed histology; left: group A fixed dosing; right: group B cycle 1 step-up dosing). PK data cutoff: November 12, 2019; clinical data cutoff: January 21, 2020. ROavg (%) represents the calculated CD20 RO% averaged over 0-42 days after cycle 1 day 1 administration of mosunetuzumab. ROmax (%) represents the maximal RO% value over 0-42 days after cycle 1 day 1 administration of mosunetuzumab. AUC represents the area under the serum concentration–time curve averaged over 0-42 days post cycle 1 day 1 administration of mosunetuzumab. Emax represents the maximal effect at infinite drug levels. (A and B) Open circles represent the observed clinical objective response for each patient (0 = nonresponder; 1 = responder), colored by dosing cohort. (C) Blue open circles represent the observed occurrence of grade ≥ 2 CRS

FIG 3. (Continued). event (0 = no event; 1 = event). (continued on following page)Exposure-response plots are divided into intervals (dashed green lines) indicating quartiles (for efficacy plots, A and B) or tertiles (for CRS plot, C) of the corresponding exposure metric; blue-filled circles at each interval indicate the observed response rates as indicated by (A and B) the numbers and associated sample sizes or (C) the observed probability of patients having a CRS event of grade ≥ 2 at the median exposure in each of the corresponding interval. Blue lines are the modeled average trend on the basis of logistic regression models; shaded areas represent the 90% CI of the modeled exposure-response relationship. Dashed horizontal lines represent (A) the model estimated maximal CR rate of 36% (90% CI, 26 to 60%) and the maximal ORR of 63% (90% CI, 48 to 83%) in patients with aggressive NHL and (B) the model estimated maximal ORR of 80% (90% CI, 70 to 100%) in patients with indolent NHL. Maximal response rate (Emax) was not estimated in patients with indolent NHL. A trend toward plateau at higher exposure levels was observed in the dose range studied (0.05-60 mg) in patients with aggressive NHL. In patients with indolent NHL, a trend toward plateau at higher exposure levels was observed for objective but not for CR rates in the dose range studied (0.05-13.5 mg). There was no statistically significant relationship between mosunetuzumab ROmax (%) and the occurrence of grade ≥ 2 CRS within the first 42 days of mosunetuzumab although a visual trend of increasing grade ≥ 2 CRS rate with increasing ROmax (%) exists for the fixed dosing group and not the step-up dosing group. AUC, area under the serum concentration-time curve; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; NHL, non-Hodgkin lymphoma; OR, objective response; ORR, objective response rate; RO%, receptor occupancy.

in the 1/2/60 mg dose-escalation cohort, a RP2D (1/2/60/60/30 mg) was selected on the basis of accumulated data and the well-characterized exposure-response analyses, with the goal of maximizing clinical efficacy, while mitigating the risk of acute CRS. On the basis of PK and exposure-response modeling for efficacy and safety, a 60-mg dose on cycle 1 day 15 and cycle 2 day 1 was selected because at 60 mg, the drug exposure was on the maximal plateau of the exposure-response curve for clinical response (Figs 3A and 3B), while on the flat exposure-response curve for CRS (Fig 3C). The two 60-mg loading doses increase RO% for patients with bulky disease and residual rituximab from prior therapies. After this initial debulking, a 30-mg dose on day 1 of subsequent cycles was selected to maintain RO% from cycle 3 onward. It is expected that this lower dose will maintain durable clinical responses, given the promising durability observed at the 13.5-27 mg doses, and minimize unnecessary overexposure and the potential for acute, chronic, or cumulative toxicity. Taken together, the clinical evidence of the step-up dosing for CRS mitigation combined with the exposure-response characterization for clinical response supported the selection of a RP2D that is being further studied in histology-specific expansion cohorts. The promising results of this phase I study raise the important question of the optimal use of bispecifics for both aggressive and indolent NHL, especially in relationship to CAR-T cell therapy. Forthcoming data for mosunetuzumab, at the RP2D, are needed to evaluate its optimal use. On the basis of favorable tolerability and encouraging activity, further single-agent and combination studies of mosunetuzumab in R/R and previously untreated B-NHL are ongoing (NCT03677154, NCT03671018, NCT04246086, NCT03677141, and NCT04313608).

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

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