REGULAR ARTICLE

blood advances

Impact of prior CAR T-cell therapy on mosunetuzumab efficacy in patients with relapsed or refractory B-cell lymphomas

Elise A. Chong,[1] Elicia Penuel,[2] Ellen B. Napier,[1] Rachel K. Lundberg,[1] Lihua E. Budde,[3] Mazyar Shadman,[4] Matthew J. Matasar,[5] Nancy L. Bartlett,[6] Ian W. Flinn,[7] Francesc Bosch,[8] Keith Fay,[9] Andre Goy,[10] Anita Kumar,[11] Loretta J. Nastoupil,[12] Michael C. Wei,[2] Mei Wu,[2] Shen Yin,[2] Joseph A. Fraietta,[13,14] Emeline R. Chong,[1] and Stephen J. Schuster[1]

[1]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [2]Genentech, Inc, South San Francisco, CA; [3]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [4]Clinical Research Division, Fred Hutchinson Cancer Center and Hematology and Medical Oncology Division, University of Washington, Seattle WA; [5]Division of Blood Disorders, Rutgers Cancer Institute, New Brunswick, NJ; [6]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; [7]Clinical Research, Tennessee Oncology and OneOncology, Nashville, TN; [8]Department of Hematology, Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [9]St. Vincent's Hospital and Royal North Shore Hospital, Sydney, Australia; [10]Lymphoma Division, John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ; [11]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [12]Department of Lymphoma and Myeloma, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX; and [13]Center for Cellular Immunotherapies and [14]Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Key Points

- A longer interval between prior CAR-T and mosunetuzumab is associated with a higher response rate to mosunetuzumab.
- After prior CAR-T, mosunetuzumab responders have greater increases in CD4 and CD8 T cells and longer CAR-T persistence than nonresponders.

Mosunetuzumab and other CD20/CD3 bispecific antibodies (BsAbs) have efficacy in B-cell lymphomas relapsing after or refractory to CD19-directed chimeric antigen receptor (CAR)–modified T cells (CAR-T). The optimal timing of BsAbs and biomarkers of BsAb response after CAR-T are unknown. We addressed these questions using clinical data and blood samples from patients previously treated with CAR-T and subsequently treated on a phase 1/2 study of mosunetuzumab. Thirty patients had paired samples at baseline and after 1 cycle of mosunetuzumab. The median time from CAR-T to mosunetuzumab was significantly longer for responding than for nonresponding patients (P = .006, unadjusted for multiple comparisons). Most patients (20/30) did not receive intervening therapy between CAR-T administration and mosunetuzumab. The remainder of patients received 1 intervening therapy after a protocol-mandated drug washout. After mosunetuzumab, responding patients had higher lymphocytes (995 vs 400 cells per μL; P = .02) and greater increases in CD4 and CD8 cells (median change, 73 vs –90 cells per μL [P = .005] and 243 vs –103 cells per μL [P = .004], respectively). Additionally, responding patients had an increase in activated CD8 cells (median fold change, 1.7; P = .02). Nonresponders had a relative decrease in CAR transgene levels (n = 16; P = .04). This is, to our knowledge, the first study to assess changes in lymphocytes, T cells, and CAR transgene levels in patients treated with BsAbs after CAR-T. These findings suggest an interaction between prior CAR-T and BsAb outcomes and have implications for optimal timing of BsAb after CAR-T. The trial was registered at www.ClinicalTrials.gov as #NCT02500407.

Submitted 13 May 2024; accepted 7 November 2024; prepublished online on *Blood Advances* First Edition 21 November 2024; final version published online 12 February 2025. https://doi.org/10.1182/bloodadvances.2024013640.

Qualified researchers may request access to individual patient-level data through the clinical study data request platform at https://vivli.org/.

Further details on Roche's criteria for eligible studies are available at https://vivli.org/ourmember/roche/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents (available at https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

The full-text version of this article contains a data supplement.

Introduction

Mosunetuzumab is a bispecific antibody (BsAb) that simultaneously engages CD20 on B cells and CD3 on T cells, thus activating and redirecting endogenous T cells to kill malignant B cells. A multicenter phase 1/2 trial of mosunetuzumab for the treatment of relapsed/refractory (R/R) B-cell non-Hodgkin lymphomas (B-NHLs), which included patients relapsed after or refractory to chimeric antigen receptor (CAR)–modified T-cells (CAR-T), led to the approval of mosunetuzumab for R/R follicular lymphoma after ≥2 lines of systemic therapy.[1-3] Mosunetuzumab is also active in R/R large B-NHLs (LBCL).[4] Two other BsAbs targeting CD20 and CD3, glofitamab and epcoritamab, are approved for R/R LBCL.[5-7]

CD19-directed CAR-T are also approved for R/R B-NHLs.[8-16] Patients with R/R B-NHLs after either CAR-T or BsAb therapy may receive the other T-cell–based immunotherapeutic approach. Approximately 35% of patients with LBCL R/R to CAR-T achieved a complete response (CR) after glofitamab or epcoritamab.[5,7] Similarly, 24% of patients with R/R LBCL had a CR after mosunetuzumab.[4] Critical questions when considering BsAb therapy for patients with R/R B-NHL previously treated with CAR-T include assessing the impact of BsAb on both CAR-T and endogenous T cells, determining the optimal timing of BsAb administration relative to prior CAR-T, and identifying biomarkers for BsAb response in this setting.

Table 1. Patient characteristics

Characteristic	N = 30 (100%)
Age, median (range), y	63 (18-82)
Sex, male, n (%)	19 (63)
ECOG PS, n (%)	
0	9 (30)
1	21 (70)
Ann Arbor stage, n (%)	
I-II	6 (20)
III-IV	24 (80)
B-NHL subtype, n (%)	
DLBCL	19 (63)
trFL	7 (23)
PMBCL	1 (3)
FL	3 (10)
Cell of origin (DLBCL, trFL), n (%)	
GCB	14 (54)
Non-GCB	12 (46)
Unknown	1 (4)
Double hit* lymphoma, n (%)	2 (7)
Bulky disease >10 cm, n (%)	1 (3)
Prior lines of therapy, median (range)	4 (3-8)
3 previous lines, n (%)	7 (23)
>3 previous lines, n (%)	23 (77)
Prior lymphoma therapies, n (%)	
Anti-CD20 antibody	30 (100)
Anthracycline	30 (100)
CAR-T	30 (100)
Prior ASCT	4 (13)
Response to prior therapies, n (%)	
Refractory† to last therapy	25 (83)
Relapsed after last therapy	5 (17)
Refractory to any prior anti-CD20	27 (90)
Refractory to CAR-T	24 (80)

ASCT, autologous hematopoietic stem cell transplantation; B-NHL, B-cell non-Hodgkin lymphoma; CAR-T, chimeric antigen receptor–modified T cells; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; GCB, germinal center B-cell-like subtype; PMBCL, primary mediastinal large B-cell lymphoma; trFL, large cell transformation of follicular lymphoma.

*MYC and BCL2 and/or BCL6 FISH translocations.

†Refractory is defined as stable or progressive disease after the indicated therapy.

Table 2. Treatment before mosunetuzumab

Therapy	n (% or range), N = 30
Lymphodepleting chemotherapy	20 (67)
Fludarabine/cyclophosphamide	18 (90)
Bendamustine	2 (10)
Unknown	10 (33)
Commercial anti-CD19 CAR-T	4 (40)
Investigational CAR-T	6 (60)
CAR-T product	
Commercial	20 (67)
Axicabtagene ciloleucel	10 (33)
Tisagenlecleucel	7 (23)
Lisocabtagene maraleucel	3 (10)
Investigational	8 (27)
Anti-CD19 CAR-T	6 (20)
Anti-CD20 CAR-T	2 (7)
Unknown anti-CD19 CAR-T	2 (7)
Bendamustine	11 (37)
Within 6 months of mosunetuzumab	1 (3)
Within 9 months of mosunetuzumab	2 (7)
Within 12 months of mosunetuzumab	4 (13)
Therapy administered between CAR-T infusion and mosunetuzumab	
No intervening therapy	20 (67)
Median number of therapies received	0 (0-1)
Investigational drugs, not otherwise specified	3 (10)
Lenalidomide-rituximab	2 (7)
Lenalidomide	1 (3)
Ibrutinib	1 (3)
Pembrolizumab	1 (3)
Copanlisib	1 (3)
R-ICE	1 (3)

CAR, chimeric antigen receptor–modified; CAR-T, chimeric antigen receptor-modified T-cells; R-ICE, rituximab, ifosfamide, carboplatin, etoposide.

Methods

Blood samples were prospectively collected from patients enrolled on a phase 1/2 study of mosunetuzumab (ClinicalTrials.gov identifier: NCT02500407). Mosunetuzumab was administered as previously described.[1,2,4] Post hoc analyses were performed on peripheral blood from the subset of patients with a history of prior CAR-T (N = 30). Before mosunetuzumab administration on cycle 1 day 1 (C1D1) and before mosunetuzumab dosing on C2D1, we measured absolute lymphocyte (ALC), CD4 T-cell, and CD8 T-cell counts. We also measured CAR transgene levels by quantitative polymerase chain reaction in those patients who had received commercially available CAR-T (supplemental Methods). Additionally, we characterized T cells by multicolor flow cytometry (supplemental Methods). Rank sum testing was used for continuous variables, and Fisher exact testing was used for binary variables. *P* values reported are unadjusted for multiple comparisons. This research was approved by each institution's review board, and all participants provided written informed consent. All authors had access to the primary clinical trial data.

Results

Thirty patients with a history of prior CAR-T were treated with mosunetuzumab and had peripheral blood samples obtained before mosunetuzumab infusion on C1D1 and C2D1; CD4 and CD8 T-cell counts were available for 29 patients at C1D1 and for 19 patients at C2D1. Patient characteristics are described in Table 1; 27 patients (90%) had LBCL, and 3 (10%) had low-grade (grades 1-3a) follicular lymphoma. Eighty percent of patients had

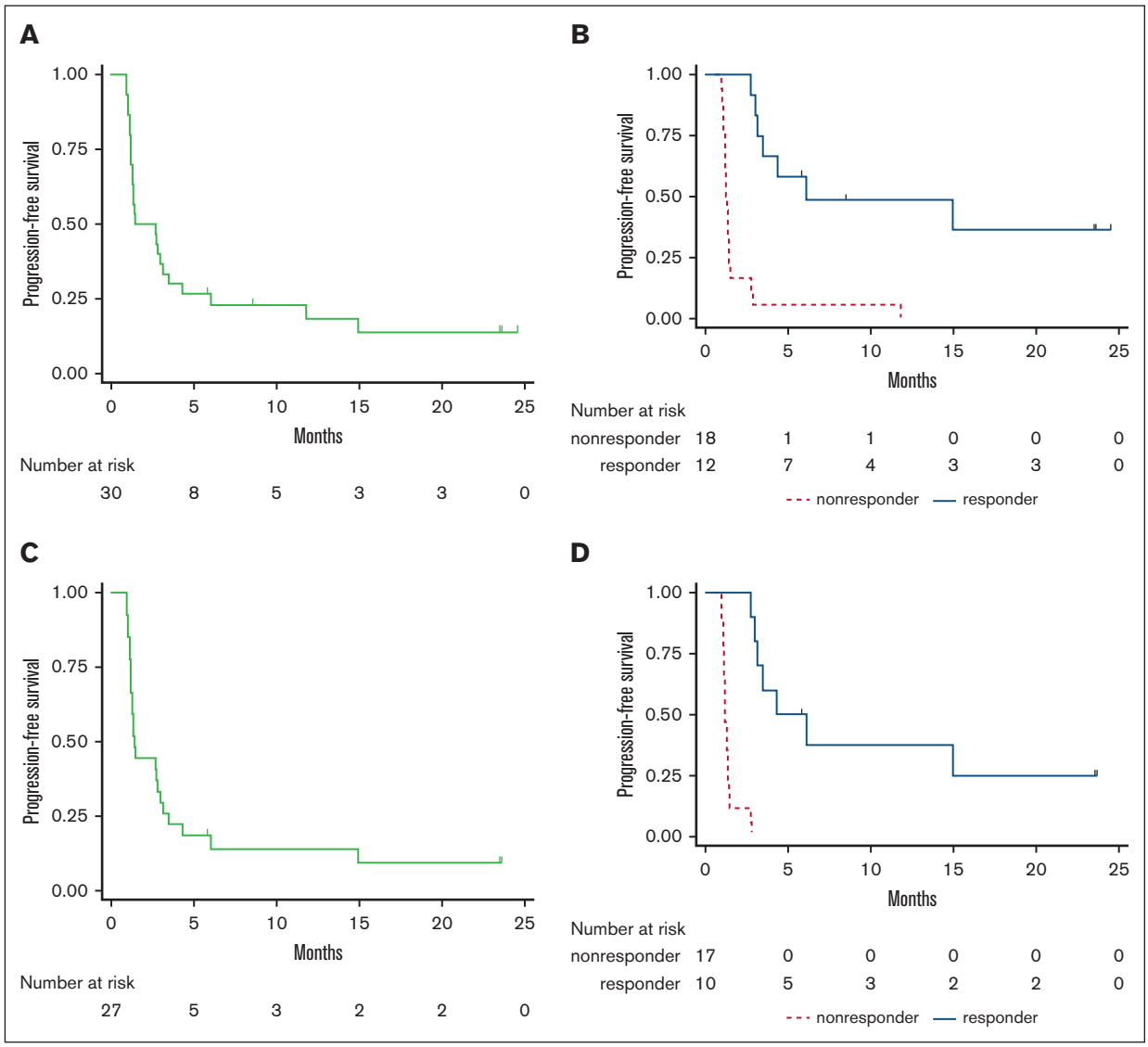

Figure 1. Progression-free survival. Blue solid lines indicate patients with lymphoma that responded to mosunetuzumab (complete response/partial response; responder), and red dashed lines indicate patients with lymphoma that did not respond to mosunetuzumab (stable disease/progressive disease; nonresponder). (A) Progression-free survival for the entire cohort (N = 30). (B) Progression-free survival all patients (N = 30) based on response to mosunetuzumab. (C) Progression-free survival for patients with large B-cell lymphomas (n = 27). (D) Progression-free survival for patients with large B-cell lymphomas (n = 27) based on response to mosunetuzumab.

B-NHL refractory to prior CAR-T, whereas the remainder had relapsed after prior response to CAR-T. Mosunetuzumab dosing ranged from 0.8/2/6 mg to 1/2/60 mg intravenously or 1.6 mg to 20 mg subcutaneously; most (17/30 [57%]) received the recommended phase 2 dose or higher (supplemental Table 1). Twelve patients (40%) responded (CR or partial response [PR]) to mosunetuzumab; 7 (23%) patients had a CR. Twenty patients had previously received standard-of-care, commercially available anti-CD19 CAR-T (10 axicabtagene ciloleucel, 7 tisagenlecleucel, and 3 lisocabtagene maraleucel), whereas 8 patients received investigational CAR-T products (6 anti-CD19 CAR-T and 2 anti-CD20 CAR-T; Table 2). Two patients received anti-CD19 CAR-T that could not be classified as commercial or investigational (Table 2). Progression-free survival was 6.1 months for patients who responded to mosunetuzumab and 1.2 months for patients without a response to mosunetuzumab; of note, 25% of responding patients with LBCL had durable responses at 1 year (Figure 1).

Before mosunetuzumab (C1D1), there was no difference in ALCs (n = 30), CD4 cell counts (n = 29), or CD8 cell counts (n = 29) between responding and nonresponding patients (Figure 2A-C supplemental Table 3). However, after 1 cycle of mosunetuzumab (C2D1), responding patients had significantly higher ALCs than patients without a response (n = 12; median, 0.995 x 10^3 cells/μL vs n = 18; median 0.400 x 10^3 cells/μL, respectively; $P = .023$; Figure 2A), likely reflecting changes in absolute CD4 and CD8 T-cell counts in responders and nonresponders at C2D1 (Figure 2D-E; supplemental Table 3).

Between C1D1 and C2D1, responding patients had significantly greater increases in their CD4 and CD8 cell counts than non-responders (n = 19), reflecting the changes in these T-cell subsets after cycle 1 of mosunetuzumab (median change in CD4 cells, 73 cells per μL vs −90 cells per μL; $P = .005$; median change in CD8 cells, 243 cells per μL vs −103 cells per μL; $P = .004$; Figure 2D-E; supplemental Table 3), as well as a larger fold change in CD4 cell counts (median CD4 fold change, 1.54 vs −0.56; $P = .003$) and CD8 cell counts (median CD8 fold change, 0.86 vs −0.24; $P = .020$; supplemental Figure 1C-D; supplemental Table 3).

We also examined CAR transgene levels in 20 patients who had received commercially available CAR-T; 16 patients had detectable

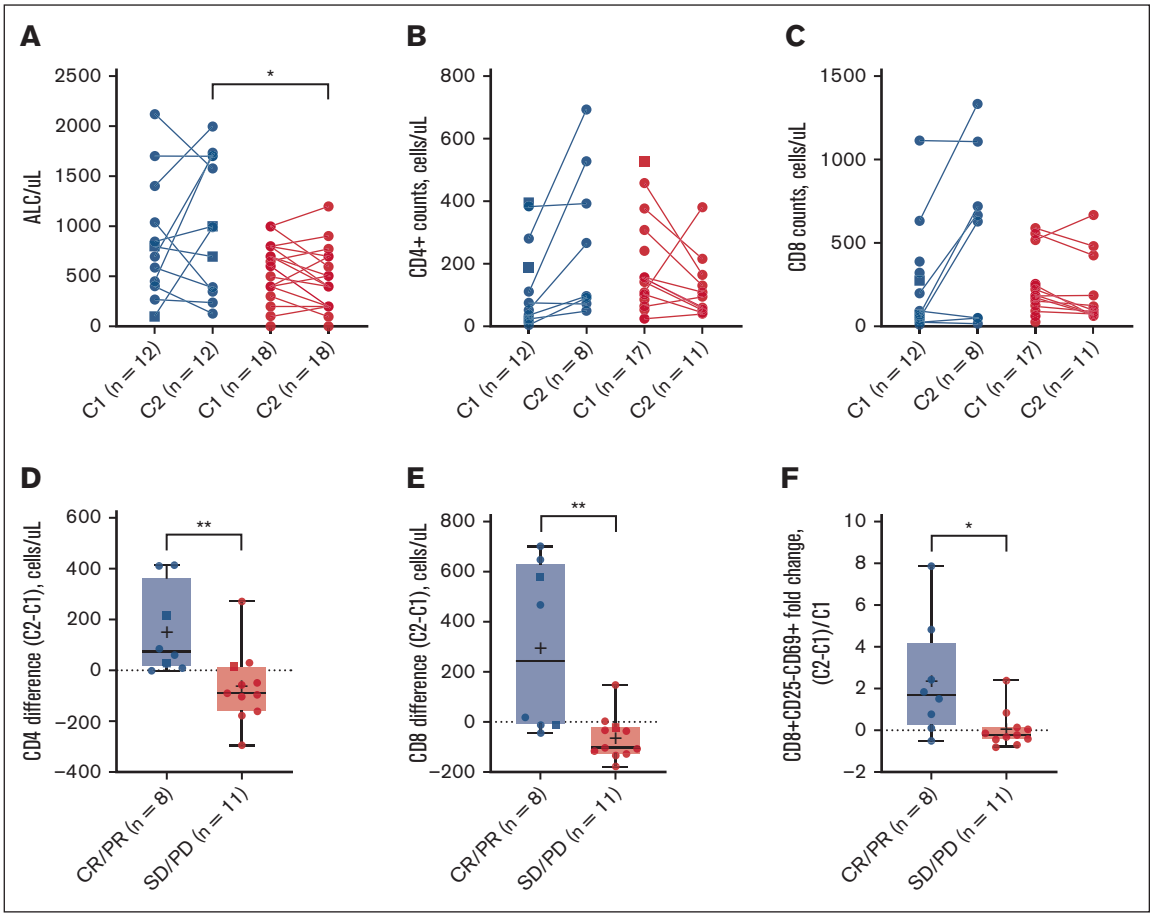

Figure 2. Change in lymphocyte counts, CD4 and CD8 T-cell counts, and activated CD8 T cells after 1 cycle of mosunetuzumab. All comparisons depict counts at baseline (C1D1) and after 1 cycle of mosunetuzumab (C2D1) for patients with responding and nonresponding lymphoma. Circles indicate a patient with large B-cell lymphoma, and square boxes indicate a patient with follicular lymphoma. Blue indicates patients with response (CR/PR), and red indicates patients with no response (SD/PD). (A) Absolute lymphocyte count (ALC). *$P = .02$, for C2D1 comparison. (B) CD4 counts. (C) CD8 counts. (D) Difference in CD4 counts. **$P = .005$. (E) Difference in CD8 counts. **$P = .004$. (F) Fold change in activated CD8 T cells ($CD8^+CD25^-CD9^+$). *$P = .02$. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

CAR transgene at any time. Fifteen had detectable CAR transgene levels before mosunetuzumab (transgene detected/total treated, 7/10 axicabtagene ciloleucel; 6/7 tisagenlecleucel; and 2/3 lisocabtagene maraleucel). Of note, 1 patient who had prior tisagenlecleucel with an undetectable baseline CAR transgene developed detectable CAR transgene after mosunetuzumab and had a best response of stable disease. Another nonresponding patient who had received axicabtagene ciloleucel lost CAR transgene persistence after mosunetuzumab and had a best response of progressive disease. The remaining 14 patients had detectable CAR transgene levels before and after mosunetuzumab. Among 16 patients with detectable CAR transgene at any time, there was no absolute difference between baseline and post-mosunetuzumab CAR transgene levels (Figure 3C). However, within individual

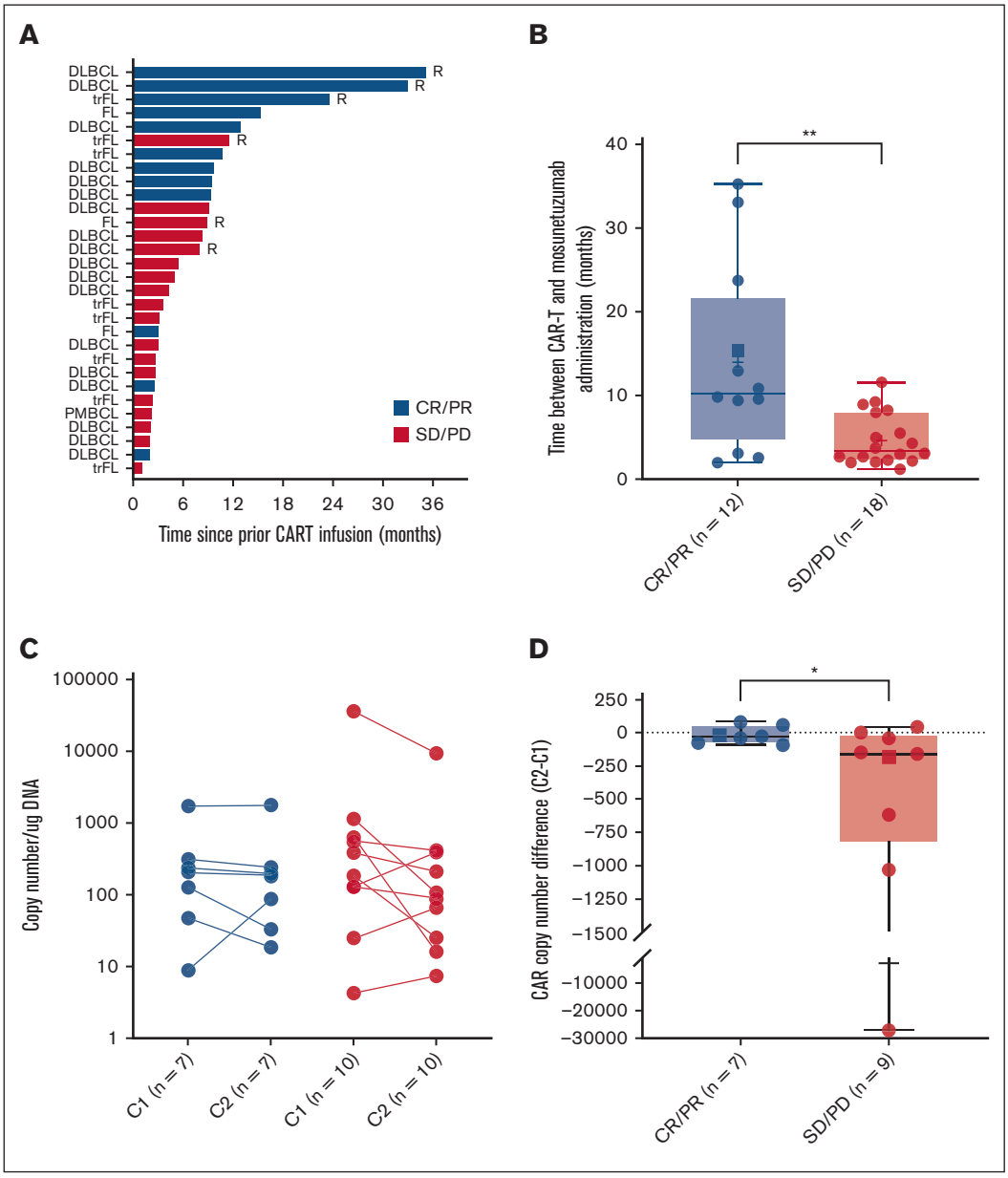

Figure 3. Time from CAR-T to mosunetuzumab administration and changes in CAR transgene levels. Blue bars and blue circles indicate CR/PR. Red bars and red circles indicate SD/PD. Circles indicate a patient with large B-cell lymphoma. Square boxes indicate a patient with follicular lymphoma. (A) Time from CAR-T to the start of mosunetuzumab. R indicates patients who responded to CAR-T and subsequently relapsed at least 6 months after CAR-T. The remainder of patients are CAR-T refractory, that is, they did not respond to CAR-T. (B) Comparison of responding and nonresponding patients' time from CAR-T to mosunetuzumab. $^{**}P = .006$. (C) CAR transgene copy number per µg genomic DNA for responding and nonresponding patients before and after mosunetuzumab. (D) Difference in CAR transgene copy number after 1 cycle of mosunetuzumab between responding and nonresponding patients. $^{*}P = .04$. C1, baseline prior to start of mosunetuzumab; C2, after one cycle of mosunetuzumab; CAR, chimeric antigen receptor-modified; CAR-T, chimeric antigen receptor–modified T-cell therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; trFL, large cell transformation of follicular lymphoma.

patients, nonresponders had a significantly greater decrease in CAR transgene levels after mosunetuzumab (n = 16; change after 1 cycle, −29 vs −159 copies per μg DNA; $P = .04$; Figure 3D).

Patients whose lymphoma relapsed after CAR-T (n = 6) had a longer time to treatment with mosunetuzumab than CAR-T refractory patients (n = 24; median, 537 vs 103 days; $P = .003$). However, response to prior CAR-T was not associated with subsequent response to mosunetuzumab; 3 of 18 nonresponders (17%) and 3 of 12 responders (25%) to mosunetuzumab had previously responded to CAR-T (Figure 3A).

For all patients, the median time from CAR-T to mosunetuzumab was 161 days (range, 35-1071). Of these 30 patients, 12 (40%) received mosunetuzumab within 100 days of CAR-T, 13 (43%) between 101 and 365 days after CAR-T, and 5 (17%) >1 year after CAR-T. We observed no clear differences in response based on the CAR-T product (supplemental Tables 2 and 4). The median time from CAR-T to mosunetuzumab initiation was significantly longer in patients with a CR/partial response after mosunetuzumab than in patients with stable or progressive disease (SD/PD; median, 313 days [range, 61-1071] vs 103 days [range, 35-353], respectively; $P = .006$; Figure 3A-B). When the time from CAR-T to mosunetuzumab was assessed as a predictor of mosunetuzumab response, we found that the receiver operating characteristic area under the curve for time from CAR-T to mosunetuzumab was 0.799 (95% confidence interval, 0.663-0.935). All patients, except 1 patient, who were treated at least 9.5 months after CAR-T responded to mosunetuzumab, although no single time point completely discriminated responders from nonresponders (Figure 3A).

To further understand this observation, we examined the lymphodepleting regimens received before CAR-T and the intervening therapies received between CAR-T and mosunetuzumab (Table 2). In most cases, lymphodepleting chemotherapy, predominantly fludarabine/cyclophosphamide, was the last chemotherapy received before mosunetuzumab. The median number of intervening therapies was 0 (range, 0-1). Twenty patients (67%) did not receive any intervening therapy between CAR-T and mosunetuzumab. We also examined bendamustine use before mosunetuzumab; 11 patients had received prior bendamustine, including 1 patient within 6 months of mosunetuzumab and 3 patients within 9 months of mosunetuzumab. Receipt of prior bendamustine was not associated with response to mosunetuzumab. However, the median time from the last dose of bendamustine to mosunetuzumab was longer for responders than nonresponders (median time for responders vs nonresponders, 10.0 months [range, 2.4-48.0] vs 41.6 months [range, 26.5-80.3]; $P = .02$).

Finally, we assessed markers of T-cell activation and proliferation (supplemental Table 5). We observed a larger fold increase in activated $CD8^+CD25^-CD69^+$ T cells in responding patients than nonresponding patients (median, 1.7 [range, −0.52 to 7.9] vs −0.23 [range, −0.79 to 2.34], respectively; $P = .02$; Figure 2F). There were no differences observed in activated CD4 cells or in proliferation of CD8 T cells between responding and nonresponding patients, although a trend toward fold increase in CD4 cell proliferation ($CD4^+Ki67^+$) was observed in responding patients (median, 1.72 [range, −0.42 to 40.9] vs −0.09 [range, −0.65 to 7.54]; $P = .09$; supplemental Figure 1E; supplemental Table 5).

Discussion

This is, to our knowledge, the first study to assess changes in lymphocyte counts, T-cell subsets, and CAR transgene levels in patients previously treated with CAR-T and subsequently treated with a BsAb, in this case, mosunetuzumab.

Other groups have investigated response rates to BsAb therapy after CAR-T[2,4,5]; however, to the best of our knowledge, the association of time interval between CAR-T and BsAb administration with response to BsAb has not been reported. We found that patients responding to mosunetuzumab had a longer duration of time between CAR-T infusion and mosunetuzumab initiation. This observation may reflect the time to lymphocyte recovery from lymphodepleting chemotherapy administered before CAR-T and/or disease biology with a preponderance of more refractory lymphomas among patients who received mosunetuzumab soon after CAR-T. Nonetheless, our data suggest a higher likelihood of response to BsAb when administered 9 to 12 months after CAR-T. However, it is important to note that 3 patients (3/20) who received mosunetuzumab less than 9 months from CAR-T also responded. A limitation of our findings is the relatively small sample size. It is also unknown whether these findings are applicable to other BsAb therapies.

We also observed that responding patients had higher ALCs than nonresponding patients on C2D1, as well as greater increases in both CD4 and CD8 cell counts. A similar phenomenon is described for other BsAbs, including blinatumomab, glofitamab, and epcoritamab.[1,6,17,18] These findings may indicate a class effect of T-cell–engaging BsAbs on T-cell proliferation. Furthermore, we also found that patients who relapsed after or were refractory to CAR-T and who subsequently responded to mosunetuzumab had a trend toward stable CAR transgene levels compared with patients not responding to mosunetuzumab. Hutchings et al found that responding patients had T-cell activation after glofitamab; interestingly, we observed the same phenomenon in patients responding to mosunetuzumab after CAR-T.[6] This suggests that a response to mosunetuzumab after CAR-T reflects the activation and expansion of T cells, which may include CAR T cells. Several hypotheses can be postulated to explain this observation. For example, it is possible that the T cells in nonresponding patients were more terminally differentiated, and thus, all T-cell counts including CAR T cells decreased or failed to expand after additional stimulation by mosunetuzumab (ie, by C2D1). This could account for the observed decrease in CAR transgene levels in nonresponding patients. Additionally, the observed stability or increase in CAR transgene levels in some patients may simply reflect the BsAb effect on T-cell expansion in general, rather than a unique CAR T-cell effect. This study was not designed to test these hypotheses, and future studies are needed.

It is notable that most patients did not receive additional therapy between CAR-T and mosunetuzumab. Those patients who had a longer time between CAR-T and mosunetuzumab start were more likely to have received an intervening therapy. The clinical trial exclusion criteria required a therapy washout of 5 half-lives or 4 weeks, whichever was shorter, before mosunetuzumab. Moreover, immune checkpoint inhibitors, such as pembrolizumab, required a 12-week washout before mosunetuzumab start. Based on these protocol requirements, we believe that the likelihood of these

intervening therapies affecting mosunetuzumab outcomes is low. Prior bendamustine was generally not administered in close proximity to mosunetuzumab in this patient cohort; however, patients who had received prior bendamustine and responded to mosunetuzumab also had a longer interval from bendamustine to mosunetuzumab than nonresponding patients. Whether this observation relates to lymphoma biology or bendamustine timing is unclear.

Finally, biomarkers of response to BsAb in post–CAR-T patients may differ from the reported biomarkers of response to the same BsAb administered in other therapeutic contexts.[1,2,4,5,7,19] Although we identified changes in ALC, T-cell counts, and time from CAR-T as potential biomarkers of BsAb response after CAR-T, an in-depth study of biomarkers for response to BsAb after CAR-T may be useful to optimize therapy for these patients. Further studies should also address the impact of specific antecedent therapies on both BsAb outcomes and biomarkers of response. Larger studies are also needed to determine whether differences between CAR-T products and/or lymphodepletion regimens[20-23] affect responses to BsAb.

This is, to our knowledge, the first study to suggest that prior lymphodepleting chemotherapy or CAR-T may affect responses to subsequent non–CAR-T, T-cell–engaging immunotherapy, such as mosunetuzumab. The optimal timing of BsAb therapy for LBCL after failing CAR-T may be at least 9 months after CAR-T. Further investigations, including studies of alternative BsAbs, are needed to understand the mechanisms and generality of our observations. These observations have potential implications for patients with B-NHL progressing after CAR-T with respect to the optimal timing of BsAb therapy and its effect on T-cell responses in these patients, which warrant validation.

Acknowledgments

E.A.C., E.R.C., and S.J.S. thank the Berman Family Center for Innovation in Chronic Lymphocytic Leukemia and Lymphoma.

E.A.C. was supported by a Lymphoma Research Foundation Clinical Investigator Career Development Award and the Brodie Lymphoma Research Fund. Research funding for this work was provided by Genentech/Roche.

Authorship

Contribution: E.A.C. designed the research and wrote the manuscript; E.A.C., S.J.S., and E.P. jointly analyzed data; E.P. created figures; E.R.C. assisted with assay development and collected data; S.J.S. conceived and designed the research, managed trial patients, and wrote the manuscript; J.A.F. developed and oversaw assays for chimeric antigen receptor (CAR)–modified T-cell detection; N.L.B., F.B., L.E.B., K.F., I.W.F., A.G., A.K., R.K.L., M.J.M., E.B.N., L.J.N., and M.S. managed trial patients and edited the manuscript; and M.C.W., M.W., and S.Y. oversaw the clinical trial and edited the manuscript.

Conflict-of-interest disclosure: E.A.C. reports research funding from Genentech/Roche, AbbVie, AstraZeneca, CARGO, and Nurix; and advisory board participation for AstraZeneca and BeiGene. E.B.N. reports travel support from Genentech. E.P., M.C.W., M.W., and S.Y. are employees of Genentech/Roche. A.K. reports research funding from AbbVie, Adaptive Biotechnologies, Celgene, Pharmacyclics, Loxo/Eli Lilly Pharmaceuticals, Seattle Genetics, Genentech, and Incyte; consulting/advisory from Adaptive Biotechnologies, Astra Zeneca, Kite Pharmaceuticals, Janssen, Genentech, and Loxo/Eli Lilly Pharmaceuticals; and consulting role with Genentech. S.J.S. reports research funding from Genentech/Roche; consulting fees from AbbVie, AstraZeneca, BeiGene, BioNTech, Genentech, Genmab Janssen, Kite Pharma, Legend Biotech, MorphoSys, and Novartis; and steering committee participation for Caribou Biotech and Novartis. The remaining authors declare no competing financial interests.

ORCID profiles: E.A.C., 0000-0001-8895-1625; E.B.N., 0000-0003-4019-6266; L.E.B., 0000-0003-1464-5494; M.S., 0000-0002-3365-6562; M.J.M., 0000-0002-4581-3721; I.W.F., 0000-0001-6724-290X; F.B., 0000-0001-9241-2886; A.G., 0000-0001-5125-6522; A.K., 0000-0002-1381-5810; L.J.N., 0000-0001-6071-8610; S.J.S., 0000-0002-3376-8978.

Correspondence: Stephen J. Schuster, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104; email: stephen.schuster@pennmedicine.upenn.edu.

References

1. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Oncol*. 2022;23(8):1055-1065.
2. Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose-escalation study. *J Clin Oncol*. 2022;40(5):481-491.
3. LUNSUMIO. Prescribing information. Genetech/Roche; 2022. Accessed 8 May 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf
4. Bartlett NL, Assouline S, Giri P, et al. Mosunetuzumab monotherapy is active and tolerable in patients with relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv*. 2023;7(17):4926-4935.
5. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(24):2220-2231.
6. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021;398(10306):1157-1169.
7. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell–engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. *J Clin Oncol*. 2023;41(12):2238-2247.

8. 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.
9. 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.
10. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852.
11. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342.
12. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654.
13. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. *N Engl J Med*. 2023;389(2):148-157.
14. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(1):91-103.
15. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med*. 2022;28(2):325-332.
16. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684.
17. Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. *Blood*. 2012;119(26):6226-6233.
18. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol*. 2021;39(18):1959-1970.
19. Bröske AME, Korfi K, Belousov A, et al. Pharmacodynamics and molecular correlates of response to glofitamab in relapsed/refractory non-Hodgkin lymphoma. *Blood Adv*. 2022;6(3):1025-1037.
20. Ghilardi G, Paruzzo L, Svoboda J, et al. Bendamustine lymphodepletion before axicabtagene ciloleucel is safe and associates with reduced inflammatory cytokines. *Blood Adv*. 2024;8(3):653-666.
21. Ghilardi G, Chong EA, Svoboda J, et al. Bendamustine is safe and effective for lymphodepletion before tisagenlecleucel in patients with refractory or relapsed large B-cell lymphomas. *Ann Oncol*. 2022;33(9):916-928.
22. Ong SY, Pak S, Mei M, et al. Bendamustine lymphodepletion is a well-tolerated alternative to fludarabine and cyclophosphamide lymphodepletion for axicabtagene ciloleucel therapy for aggressive B-cell lymphoma. *Am J Hematol*. 2023;98(11):1751-1761.
23. Chong EA, Chong ER, Therwhanger D, et al. Bendamustine as lymphodepletion for brexucabtagene autoleucel therapy of mantle cell lymphoma. *Transplant Cell Ther*. 2024;30(7):726.e1-726.e8.