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TO THE EDITOR:

CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy

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Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), with aggressive clinical behavior.¹ Approximately 40% to 50% of DLBCL patients are refractory to or relapse after frontline chemoimmunotherapies.² Management of relapsed/refractory DLBCL is challenging, and treatment options include salvage therapy followed by autologous hematopoietic cell transplantation (autoHCT), in younger, chemosensitive patients.³ CD19-directed chimeric antigen receptor (CAR) modified T-cell therapy is another potentially curative option for patients with relapse after autologous hematopoietic cell transplantation or those with refractory disease.⁴ Axicabtagene ciloleucel and tisagenlecleucel are 2 anti-CD19 CAR T-cell treatments approved by the US Food and Drug Administration for relapsed/refractory DLBCL.^{5,6}

The CD19 antigen is an attractive target for immunotherapy in B-cell non-Hodgkin lymphoma. It is expressed during B-cell development only after B-lineage commitment and is thus not present on hematopoietic stem cells.⁷ CD19 expression is lost during terminal plasma cell differentiation but maintained in hematologic B-cell malignancies.⁷ Several clinical trials using monoclonal antibodies,⁸ antibody-drug conjugates (ADCs),⁹ and bispecific T-cell engagers targeting the CD19 antigen are ongoing in B-cell non-Hodgkin lymphoma. Studies investigating CD19-directed CAR T-cell therapies in aggressive lymphomas frequently excluded patients previously treated with CD19 targeting immunotherapies. Hence, the feasibility and efficacy of anti-CD19 CARs in lymphoma patients with prior CD19-directed immunotherapies are not known. Loncastuximab tesirine is an ADC comprising a humanized anti-CD19 monoclonal antibody stochastically conjugated to a pyrrollobenzodiazepine dimer toxin, SG3199.¹⁰ A phase 1 first-in-human study of loncastuximab tesirine demonstrated encouraging clinical activity in patients with relapsed/refractory DLBCL,⁹ and a phase 2 study recently finished patient accrual (#NCT03589469).

We sought to evaluate the outcomes of anti-CD19 CAR T-cell therapy in relapsed, refractory DLBCL previously treated with CD19-directed immunotherapy. Adult (age ≥ 18 years) DLBCL patients were identified from 2 multicenter, open-label studies of loncastuximab tesirine (phase 1: #NCT02669017 and phase 2: #NCT03589469), who subsequently received anti-CD19 CAR T-cell therapy. This retrospective analysis was approved by the institutional review board. Deidentified patient data were collected in collaboration with 6 academic medical centers (US centers = 4; United Kingdom = 1; Italy = 1) involved in the loncastuximab tesirine trials. Cytokine release syndrome was graded using Lee et al 2014 criteria,¹¹ and neurotoxicity was graded as per Common Terminology Criteria for Adverse Events, version 5.0.

A total of 14 DLBCL patients with disease relapsing or progressing after treatment with loncastuximab tesirine and subsequently undergoing CD19-directed CAR T-cell therapy were identified (Table 1). Among the 14 patients, 11 patients (79%) were male, and 13 patients (93%) were white. The median age was 58.5 years (range, 27 to 86). Ten had de novo DLBCL (germinal center B-cell–like = 4; non–germinal center B-cell = 2; not known = 4), and 4 patients had DLBCL transforming from indolent histologies (marginal zone lymphoma = 1; follicular lymphoma = 1; nodular lymphocyte predominant Hodgkin lymphoma = 1). Five patients (36%) had a high-intermediate international prognostic index at the time of diagnosis. c-MYC gene rearrangement was identified in 3 patients (21%) (1 patient had triple-hit lymphoma), whereas c-MYC status was unknown in 3 patients (21%). The median interval between diagnosis of DLBCL and initiation of loncastuximab tesirine was 21.5 months (range, 6.8 to 258). These patients received a median of 2 cycles (range, 1 to 7) of loncastuximab tesirine.

Table 1. Patient demographics and disease characteristics

| | Patients (N = 14) |
|---|-------------------|
| Age, median (range), y | 58.5 (27-86) |
| Sex, n (%) | |
| Male | 11 (79) |
| Female | 3 (21) |
| Race, n (%) | |
| White | 13 (93) |
| African American/black | 1 (7) |
| Lymphoma subtype | |
| DLBCL* | 10 |
| Transformed DLBCL | 4 |
| IPI at diagnosis, n (%) | |
| Low (0, 1) | 3 (21) |
| Low-intermediate (2) | 3 (21) |
| High-intermediate (3) | 5 (36) |
| Unknown | 3 (21) |
| Advanced stage (III/IV) at diagnosis | 4 (29) |
| c-MYC rearrangement, n (%) | |
| Yes | 3 (21) |
| No | 8 (57) |
| Unknown | 3 (21) |
| Median interval between diagnosis and start of loncastuximab tesirine (range), mo | 21.5 (6.8-258) |
| Best response to loncastuximab tesirine, n (%) | |
| Complete response | 1 (7) |
| Partial response | 5 (36) |

Percentages may not add up to 100 due to rounding.
IPI, International Prognostic Index.
*One patient had mediastinal large B-cell lymphoma.

The antitumor response to loncastuximab tesirine in these 14 patients was as follows: 8 patients (57%) had refractory disease, 5 patients (36%) attained partial response, and 1 patient (7%) achieved a complete response (overall response rate [ORR] = 43%). All responding patients had progression of the disease before proceeding with CAR therapy.

Table 2 summarizes details of CAR T-cell therapy in these subjects. The median interval between loncastuximab tesirine and CAR T-cell therapy was 120 days (range, 22 to 600). Six patients received additional lines of therapy between loncastuximab tesirine and CAR T-cell treatment (median of 1 therapy line; range, 1 to 3). The CD19 expression was assessed by immunohistochemical staining on repeat biopsies in 10 patients (71%) in between loncastuximab tesirine and CAR administration. All 10 tested patients were positive for CD19 after ADC failure. This information was not available in 4 patients (29%). Before CAR T-cell administration, 13 patients had refractory or progressive disease, whereas 1 patient was in partial remission. All patients received standard lymphodepletion with fludarabine and cyclophosphamide before CAR T-cell therapy. The type of anti-CD19 CAR T-cell therapy received by the patients included axicabtagene ciloleucel (n = 5), tisagenlecleucel (n = 2), JCAR017 (n = 3), and investigational CARs targeting CD19 (n = 4; including 2 patients with CARs targeting dual antigens; Table 2).

Table 2. CAR T-cell therapy in DLBCL patients failing CD19-directed treatment

| | Patients (N = 14) |
|--|-------------------|
| CD19 expression on lymphoma cells after loncastuximab tesirine therapy, n (%) | |
| Positive | 10 (71) |
| Not checked | 4 (29) |
| Median interval between loncastuximab tesirine and CAR T-cell therapy (range), d | 120 (22-600) |
| Additional therapy between loncastuximab tesirine and CAR T-cell therapy, n (%) | |
| Yes* | 6 (43) |
| No | 8 (57) |
| Disease status before CAR T-cell therapy, n (%) | |
| Refractory disease | 5 (36) |
| Progressive disease | 8 (57) |
| Partial remission | 1 (7) |
| Flu/Cy lymphodepletion, n (%) | 14 (100) |
| Type of CAR T-cell therapy, n (%) | |
| Axicabtagene ciloleucel | 5 (36) |
| Tisagenlecleucel | 2 (14) |
| Investigational targeting CD19† | 4 (29) |
| JCAR017 | 3 (21) |
| Best response to CAR T-cell therapy, n (%) | |
| Complete response | 6 (43) |
| Partial response | 1 (7) |
| Refractory disease | 7 (50) |
| CRS grade, n (%) | |
| None | 6 (43) |
| 1 | 3 (21) |
| 2 | 4 (29) |
| 3 | 1 (7) |
| ICANS grade, n (%) | |
| None | 8 (57) |
| 1 | 4 (29) |
| 2 | 1 (7) |
| 3 | 0 (0) |
| 4 | 1 (7) |

CRS, cytokine release syndrome; Flu/Cy, lymphodepletion with fludarabine/cyclophosphamide.

*Additional therapy between loncastuximab tesirine and CAR T-cell therapy included radiation alone (n = 3), radiation, ifosfamide/vinblastine/etoposide (n = 1), radiation; rituximab/methotrexate (n = 1), lenalidomide, anti-CD47 antibody, ibrutinib (n = 1).

†One patient each received a CD19/CD22-directed CAR, and a CD19/CD20-directed CAR. Neither patient responded to CAR treatment.

The median follow-up of survivors was 6 months (range, 3 to 22). Grade 1 to 2 cytokine release syndrome was common (n = 7; 50%). Grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) was identified in 4 patients (29%), and only 1 patient had grade 4 ICANS. Following CAR therapy, the best response at 3 months included 6 patients (43%) with a complete response and 1 patient (7%) with a partial response (ORR = 50%). Seven patients had refractory disease following CAR therapy. Five of 6 complete

remissions are ongoing at a median of 6 months (range, 6 to 11). One patient with complete remission relapsed after 11 months and was alive at last follow-up (+22 months), whereas the patient achieving a partial remission subsequently died because of progressive lymphoma. Six out of the 7 patients not achieving a CR expired at a median of 5 months (range, 1 to 9) after CAR therapy. None of the 2 patients receiving dual-antigen targeting CARs (targeting CD19/CD22 and CD19/CD20) achieved a response. All 4 patients with unknown CD19 expression status after loncastuximab tesirine achieved a complete remission with anti-CD19 CAR T-cell therapy, making it unlikely that these patients had relapsed with a CD19-negative disease.

This is the first report, to our knowledge, evaluating the efficacy of anti-CD19 CAR T-cell therapy after anti-CD19 immunotherapy. In this series of 14 cases, favorable outcomes of CAR T-cell therapy (ORR = 50%) were seen in patients with relapsed/refractory DLBCL after anti-CD19-targeted treatment with a pyrrolobenzodiazepine dimer-based ADCs. The toxicity profile of CAR treatment in these subjects appears consistent with published data.^{5,6} CD19 expression on DLBCL was reassessed in 10 patients after relapse or progression on loncastuximab tesirine treatment; no cases of CD19 antigen-negative relapse were seen. We wish to acknowledge that this report is limited by small sample size and retrospective design. In conclusion, our report suggests that prior treatment with anti-CD19 ADCs in relapsed/refractory DLBCL does not preclude subsequent responses to anti-CD19 CAR T-cell therapies. Additional data on the feasibility of CAR therapy in patients receiving CD19 monoclonal antibodies and bispecific T-cell engagers are needed.

Send data sharing requests to the corresponding author, Mehdi Hamadani (mhamadani@mcw.edu).

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