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Letter to the Editor

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CD19 Expression in B-Cell Lymphomas and Clinical Considerations in the Evolving Landscape of CD19-Targeted Therapy

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To the Editor

Over the last decade, CD19-targeted therapies have transformed the treatment landscape for relapsed or refractory B-cell lymphoma. CD19-directed chimeric antigen receptor T-cells (CAR-Ts), including axicabtagene ciloleucel [1], lisocabtagene maraleucel [2], tisagenlecleucel [3] and brexucabtagene autoleucel [4], have proven to be highly efficacious in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma. Anti-CD19 monoclonal antibody tafasitamab is approved in the second-line setting, in combination with lenalidomide, for DLBCL patients with no intention to proceed to transplant [5]. Loncastuximab tesirine, a CD19-targeted antibody-drug conjugate, is also an option for relapsed or refractory DLBCL [6, 7]. As the use of CD19-directed therapies increases, it will be important to study patterns of CD19 expression, CD19 antigen escape, and the association between CD19 expression and the efficacy of CD19-targeted therapy. There is limited modern real-world data regarding CD19 expression and a lack of consensus regarding the optimal use and sequencing of CD19-directed therapies. Herein, we report a single-center retrospective study of CD19 expression in B-cell non-Hodgkin lymphoma patients and provide an up-to-date discussion on CD19-targeted therapies, including sequencing, CD19 loss and efficacy in cases with low or absent CD19 expression.

We identified 288 patients with B-cell non-Hodgkin lymphoma who were seen at Harbor-UCLA Medical Center in Torrance, CA, USA, from 2014 to 2023 (Table 1). The most common lymphoma histologies were DLBCL (49.7%), follicular lymphoma (13.2%), marginal zone lymphoma (7.6%), high-grade B-cell lymphoma (6.6%) and mantle cell lymphoma (4.2%). Biopsies were obtained per standard clinical practice, and CD19 testing was performed at the pathologist's discretion and not for the purpose of this study. Of the 228 patients with biopsy results available from the time of diagnosis, CD19 expression status was reported for 92 patients (40.4%). Flow cytometry (95.7%) was the primary modality of CD19 expression analysis, with immunohistochemistry (4.3%) used in a small number of cases.

At the time of diagnosis, three patients (3.3%) were CD19-negative (one with plasmablastic lymphoma, one with DLBCL and one with non-Hodgkin B-cell lymphoma not otherwise specified), and one DLBCL patient (1.1%) had dim CD19 expression by flow cytometry. At relapse, the rate of repeat biopsy was 48.4%. There were 75 biopsies performed at the time of relapse or refractory disease, with CD19 testing done in 46.7% of biopsies. The only CD19-negative relapse biopsy was for a patient with plasmablastic lymphoma, whose CD19 status was unknown at the time of diagnosis. There were no cases of CD19 expression loss. Three patients received anti-CD19 CAR-T therapy (without post-CAR-T biopsy results available), and no patients received tafasitamab or loncastuximab tesirine.

Previous studies have shown that 2-12% of all B-cell lymphomas are CD19-negative [1, 4, 6, 8-10], and 1-33% have low CD19 expression [3, 6, 11, 12]. Certain types of B-cell lymphomas (plasmablastic lymphoma and primary effusion lymphoma) are characterized by the lack of expression of mature B-cell markers, including CD19. In our single-center retrospective cohort of patients with B-cell non-Hodgkin lymphoma, CD19 expression was analyzed and reported in 41.9% of all biopsies, and less than 5% of all B-cell lymphomas had absent or dim CD19 expression. The rate of CD19 antigen escape in the present study was 0%, which is expected as there were no biopsies after CD19-targeted therapy. While the rate of repeat biopsy at relapse (48.4%) and the percentage of biopsies with CD19 expression reported (41.9%) are suboptimal, this may reflect real-world clinical practice. Additional limitations of this study include its modest sample size and lack of CD19 expression analysis after CD19-targeted therapy.

When a clinician is considering the implementation of CD19-directed therapy (CAR-T, tafasitamab, loncastuximab tesirine), it is reasonable to assume that the lymphoma will be CD19-positive in > 90% of cases in the absence of prior CD19-based therapy. Nevertheless, there is some evidence that CD19-targeted therapies may still be effective in lymphomas

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Table 1. CD19 Expression Analysis at Diagnosis and Relapse

	Number (%)
Patients with B-cell non-Hodgkin lymphoma	288
Diffuse large B-cell lymphoma	143 (49.7%)
Follicular lymphoma	38 (13.2%)
Marginal zone lymphoma	22 (7.6%)
High-grade B-cell lymphoma	19 (6.6%)
Mantle cell lymphoma	12 (4.2%)
Other	54 (18.7%)
Patients with diagnostic biopsy results available	228 (79.2%)
CD19 expression on diagnostic biopsy	92
CD19 positive	88 (95.6%)
CD19 dim	1 (1.1%)
CD19 negative	3 (3.3%)
Patients with relapsed or refractory disease	109 (37.8%)
Number of relapses across all patients	155
Relapses with biopsy performed	75
CD19 expression on relapse biopsy	35
CD19 positive	34 (97.1%)
CD19 dim	0 (0%)
CD19 negative	1 (2.9%)

with low or negative CD19 expression. In the ZUMA-1 trial of axicabtagene ciloleucel in relapsed/refractory high-grade B-cell lymphomas, there was no significant difference in overall response rate (ORR) (85% vs. 75%) or ongoing response rate (43% vs. 50%) between CD19-positive and CD19-negative lymphomas [1]. Similar results were demonstrated with tisagenlecleucel for relapsed high-grade B-cell lymphomas with comparable complete response rate (CRR) (40% vs. 29%), ORR (49% vs. 50%), and median overall survival (12.5 months vs. 10.3 months) observed between CD19-positive and CD19-negative/low lymphomas [3, 11]. In a translational study of tisagenlecleucel, there was no association between baseline CD19 expression and CAR-T cellular kinetics/expansion [11]. These findings indicate that axicabtagene ciloleucel and tisagenlecleucel may operate at least partially independently of CD19 and can be utilized in high-grade B-cell lymphomas with low or absent CD19 expression.

In the ZUMA-2 trial of brexucabtagene autoleucel for relapsed/refractory mantle cell lymphoma, there were no significant differences in ORR (95% vs. 100%), ongoing response rate (57% vs. 100%) or 6-month progression-free survival (79% vs. 100%) between CD19-positive and CD19-negative tumors, with all three patients with CD19-negative tumors achieving a complete remission with ongoing response [4]. These results suggest that brexucabtagene autoleucel can be effective in CD19-negative mantle cell lymphoma.

Lastly, loncastuximab tesirine has also demonstrated benefits in lymphomas with low or absent CD19 expression. In the phase 1 LOTIS-1 trial, pre-treatment CD19 expression correlated with pharmacodynamic parameters; however, there was no correlation between CD19 expression and response [6]. Among three patients with 0% CD19 expression at diagnosis, the ORR was 67%. In a subgroup analysis of 59 patients from the phase 2 LOTIS-2 trial, including nine patients with low or undetectable CD19 expression, there was no significant difference in ORR between CD19-positive lymphomas (ORR = 54%) and lymphomas with low or undetectable CD19 (ORR = 44%) [12].

With the multitude of management strategies available for relapsed or refractory B-cell lymphoma, the practical application of sequential CD19-targeted therapy is a topic of ongoing clinical investigation. Multiple studies have described success with re-infusion of CAR-T [1, 10, 13]; however, the optimal order for sequencing different CD19-directed therapies is unclear. In the phase 2 LOTIS-2 trial of loncastuximab tesirine for relapsed or refractory high-grade B-cell lymphoma in the third-line setting and beyond, 14 patients received prior CAR-T therapy, and 16 patients went on to receive CAR-T after loncastuximab tesirine [7]. In the 14 CAR-T treated patients (biopsy was required to ensure CD19 positivity prior to loncastuximab tesirine), loncastuximab tesirine had an ORR of 48% with a CRR of 25%, which was not statistically significantly different from CAR-T-naive patients. A subgroup analysis of 14 patients from LOTIS-1/2 who went on to receive CAR-T after disease progression on loncastuximab tesirine revealed an ORR of 50% and CRR of 43% with CAR-T therapy [14]. Together, these results demonstrate the efficacy of loncastuximab tesirine after CAR-T and CAR-T after loncastuximab tesirine.

There is no evidence to support the use of tafasitamab after CAR-T therapy; however, CAR-T has been used as an effective salvage therapy after progression on tafasitamab and lenalidomide. In the phase 2 L-MIND study of tafasitamab and lenalidomide, two patients received CAR-T therapy after progression on tafasitamab and lenalidomide, one of whom achieved a complete remission [5]. A compelling case series was published describing two patients with CD19-negative relapse after tafasitamab [15], both of whom later regained CD19 expression and went on to receive CD19-directed CAR-T. These results suggest that tafasitamab may result in prolonged CD19 blockade or downregulation, and while subsequent CD19-based therapy can be used, it should be used prudently and ideally after a CD19-targeting holiday. For instance, a CD20-directed bispecific antibody or a Bruton tyrosine kinase (BTK) inhibitor [16] could be used after the failure of CD19-based therapy.

The principle of CD19 antigen escape was initially a clinical concern after early trials for CAR-T therapy in B-cell acute lymphoblastic leukemia showed high rates of CD19-negative relapse [17]. Loss of CD19 expression after CD19-targeted therapy has been reported in B-cell lymphomas at a rate of 0-27% [1, 4, 14]. While further research regarding mechanisms of CD19 loss is warranted, the clinical ramifications of CD19 antigen escape may be less consequential, given the efficacy of axicabtagene ciloleucel, tisagenlecleucel, brexucabtagene maraleucel and loncastuximab tesirine in lymphomas with low or absent CD19 expression [1, 3, 4, 6, 11].

In conclusion, CD19 is expressed in > 90% of B-cell lymphomas, and CD19 antigen escape has been reported after CD19-targeted therapy. Multiple CD19-based therapies have

demonstrated efficacy in patients with low or negative CD19 expression. Evidence supports the use of CAR-T therapy after tafasitamab or loncastuximab tesirine, and loncastuximab tesirine after CAR-T failure. As CD19-targeted therapies expand in utilization and potentially move up in the treatment paradigm, further research is needed regarding their efficacy in CD19-negative lymphomas and the optimal sequencing of therapies.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Informed Consent

Harbor-UCLA Medical Center Institutional Review Board (IRB) approval was obtained (IRB number 18CR-32663-01). Informed consent was waived due to the retrospective nature of the study. Identifiable patient information was removed at the time of data analysis.

Author Contributions

ST designed the study and implemented the software for patient procurement. XQ analyzed biopsy samples. JM collected, analyzed, and curated data. JM prepared the original version of the manuscript. All authors were involved in manuscript editing. ST was responsible for project supervision. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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