Prognostic value of early positron emission tomography in patients with large B-cell lymphoma treated with anti-CD19 chimeric antigen receptor T-cell therapy

The prognostic implications of early (at 1 month) metabolic response on long-term outcome after anti-CD19 autologous chimeric antigen receptor (CAR) T-cell therapy remain poorly defined. We conducted a multicenter, retrospective study of 329 patients with large B-cell lymphoma who received commercial CAR T-cell therapy at six academic medical centers. We found that outcomes were excellent in patients with an early complete metabolic response, and did not vary by Deauville score (DS). Patients with a partial metabolic response or stable disease, with a DS 4 or 5, had inferior responses. Among early responders, univariable and multivariable analyses demonstrated that elevated baseline lactate dehydrogenase, grade 3 or higher cytokine release syndrome, and DS 4 and 5 were associated with inferior progression-free survival (PFS). Based on these findings, a risk score was developed that could stratify patients into four groups at significantly different risks of progression or death. The 24-month PFS in the four groups was 67%, 49%, 38% and 8% (P<0.001). This score has the potential to predict outcome more accurately based on early response and guide response-adapted treatment approaches after CAR T-cell infusion.

While response rates to CAR T-cell therapy are high, the majority of patients will ultimately relapse. One potential strategy to improve outcomes is through consolidation therapy for high-risk patients. While prior studies have demonstrated that patients with a partial metabolic response or stable disease at an early assessment of response have inferior outcomes and thus could be potential candidates for this type of approach, the majority were single-institution studies or included relatively small numbers of patients.[1-4] We therefore analyzed long-term outcomes based on early positron emission tomography (PET) and other clinical variables in patients with large B-cell lymphoma treated with commercial CAR T-cell therapy across six academic medical centers. To our knowledge this is the largest real-world experience to evaluate predictors of response among early responders.

We performed a retrospective, multicenter study of adult patients with large B-cell lymphoma treated with commercial anti-CD19 CAR T-cell therapy between July 2018 and May 2021. This analysis was approved by the Institutional Review Boards at participating centers. The selection of patients and products, supportive care, toxicity management, and response assessment followed institutional practice. The use of bridging therapy and the timing of imaging were according to the prescribers' discretion. Bulky disease (defined as a mass >10 cm), performance status, International Prognostic Index, lactate dehydrogenase level, and C-reactive protein concentration were evaluated prior to lymphodepletion. All patients included in this analysis had a PET scan 30 (±15) days following CAR T-cell infusion (range, 15-45 days). Cytokine release syndrome was graded according to the modified Lee criteria and the American Society for Transplantation and Cellular Therapy (ASTCT) criteria once available.[5,6] Neurotoxicity was graded according to the Common Terminology Criteria for Adverse Events version 4 and ASTCT criteria once available. Response was determined by PET scan using the 5-point DS based on local readings (not centrally reviewed) applying the Lugano criteria.[7] Kaplan-Meier analysis was used to estimate PFS and overall survival and Cox proportional hazards models were applied to identify predictors of PFS. A risk score was developed based on the hazard ratios for PFS determined in the multivariable models.

The baseline characteristics of the 329 patients are shown in Table 1. The median duration of follow-up after CAR T-cell administration was 24 months. The median PFS for the entire cohort was 10 months. The 12- and 24-month PFS was 48% (95% confidence interval [95% CI]: 43-54) and 42% (95% CI: 37-49), respectively (Figure 1A). There was no significant difference in PFS between patients who received axicabtagene ciloleucel or tisagenlecleucel (Figure 1B).

We evaluated PFS based on the metabolic response at the time of the 1-month response assessment. Among patients with a complete metabolic response at 1 month (n=169), the 24-month PFS was 61% (95% CI: 53-70) (Figure 1C). This did not vary by DS, as patients with DS 1/2 (n=108) had a 24-month PFS of 65% (95% CI: 56-76) as compared to 59% (95% CI: 47-75) in patients with a DS 3 (n=55), with a hazard ratio (HR) of 1.23 (95% CI: 0.68-2.23; P=0.49) (Figure 1D). Patients with a patial metabolic response (n=92) or stable disease (n=7) had a 24-month PFS of 37% (95% CI: 28-49) and 14% (95% CI: 28-49), respectively (Figure 1C). Responses varied by DS, with a 24-month PFS of 46% (95% CI: 34-61) in patients with a DS 4 (n=62) as compared to 11% (95% CI: 3-39) in pa-

tients with a DS 5 (n=20) (Figure 1D). The DS was missing from the PET report in 4% of patients with a complete response and 11% of patients with a partial response or stable disease. PFS was inferior among patients with a DS 4 (HR=1.87 [95% CI: 1.09-3.19], *P*=0.23) and DS 5 (HR=4.65 [95% CI: 2.14-10.1], *P*<0.001) as compared to patients with DS 1/2/3. Overall survival was also inferior among patients with partial metabolic response or stable disease at the time of early imaging (*Online Supplementary Figure S1*).

We also evaluated the timing of progression. The median PFS in patients who subsequently relapsed with complete metabolic response (n=45), partial metabolic response (n=49), and stable disease (n=3) at the 1-month response was 5.3 (95% CI: 4.2-6.8), 3.0 (95% CI: 2.6-3.5), and 1.6 (95% CI: 1.6-not reached) months, respectively. Twenty-seven percent of patients with an initial partial metabolic response or stable disease subsequently converted to a complete response without further therapy. The median time to conversion to a complete response was 111 days.

We next examined potential predictors of relapse using a variety of variables previously evaluated in prior CAR T-cell studies.[8] A univariable Cox regression analysis showed that elevated baseline lactate dehydrogenase, development of grade 3 or higher cytokine release syndrome, and DS 4 or 5 on the 1-month PET were associated with increased risk of progression (*Online Supplementary Figure S2A*). Patients with a DS 5 had inferior outcomes (HR=4.65 [95% CI: 2.14-10.1], *P*<0.001); within this group, there was limited impact of other prognostic variables. Given this, a decision tree was used to first separate patients with DS less than or equal to 4 and DS 5. In a multivariable Cox regression model restricted to patients with DS 4 or less, elevated baseline lactate dehydrogenase (HR=1.59 [95% CI: 1-2.51], *P*=0.049), grade 3 or higher cytokine release syndrome (HR=2.39 [95% CI: 1.05-5.41], *P*=0.037), and DS 4 (HR=2.02 [95% CI: 1.28-3.18], *P*=0.002) remained independently associated with risk of progression (*Online Supplementary Figure S2B*). Based on the hazard ratios within the latter model, we developed a risk score with one point each assigned for each of these variables. DS 5 was designated high risk and assigned 3 points. The score separated patients into a low-risk group (score=0; 41% of patients; 24-month PFS 67% [95% CI: 58-77]); low-intermediate-risk group (score=1; 30% of patients; 24-month PFS 49% [95% CI: 39-62]); high-intermediate-risk group (score=2; 21% of patients; 24-month PFS 38% [95% CI: 24-59]); and high-risk group (score=3+; 8% of patients; 24-month PFS 8% [95% CI: 2-30]) (Figure 2A). The risk score was also associated with overall survival (Figure 2B).

This study is to date the largest real-world experience to evaluate the prognostic role of early metabolic response following CAR T-cell therapy in patients with relapsed/refractory large B-cell lymphoma. As expected, we found that patients with a complete metabolic response, with a DS 1/2/3, had improved outcomes as compared to those with a partial metabolic response or stable disease, with a DS 4

Table 1. Baseline characteristics of the 329 patients studied.

Characteristic	
Product, N (%)	
Axicabtagene ciloleucel	297 (90)
Tisagenlecleucel	32 (10)
Gender, N (%)	
Female	111 (34)
Male	218 (66)
Histology, N (%)	
DLBCL	221 (67)
HGBCL	11 (3)
PMBCL	13 (4)
Richter syndrome	4 (1)
THRLBCL	4 (1)
Transformed lymphoma	76 (23)
Age in years, median (range)	61 (19-83)
N of prior therapies, median (range)	3 (1-9)
IPI, N (%)	
0-1	88 (27)
2	84 (25)
3-5	151 (46)
Unavailable	6 (2)
Bulky disease, N (%)	
Yes	32 (10)
No	231 (70)
Unavailable	66 (20)
Elevated LDH, N (%)	
Yes	145 (44)
No	184 (56)
Elevated CRP, N (%)	
Yes	57 (17)
No	132 (40)
Unavailable	140 (43)
Bridging therapy, N (%)	160 (49)
Chemotherapy, %	66
Steroids alone, %	15
Radiation, %	12
Targeted therapy, %	6
Anti-CD20 therapy, %	1
Grade 3+ CRS, N (%)	
Yes	17 (5)
No	303 (92)
Unavailable	9 (3)
Grade 3+ neurotoxicity, N (%)	
Yes	61 (19)
No	214 (65)
Unavailable	54 (16)

DLBCL: diffuse large B-cell lymphoma; HGBCL: high-grade B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; THRLBCL: T-cell histiocyte-rich large B-cell lymphoma; IPI: International Prognostic Index; LDH: lactate dehydrogenase; CRP: C-reactive protein; CRS: cytokine release syndrome.

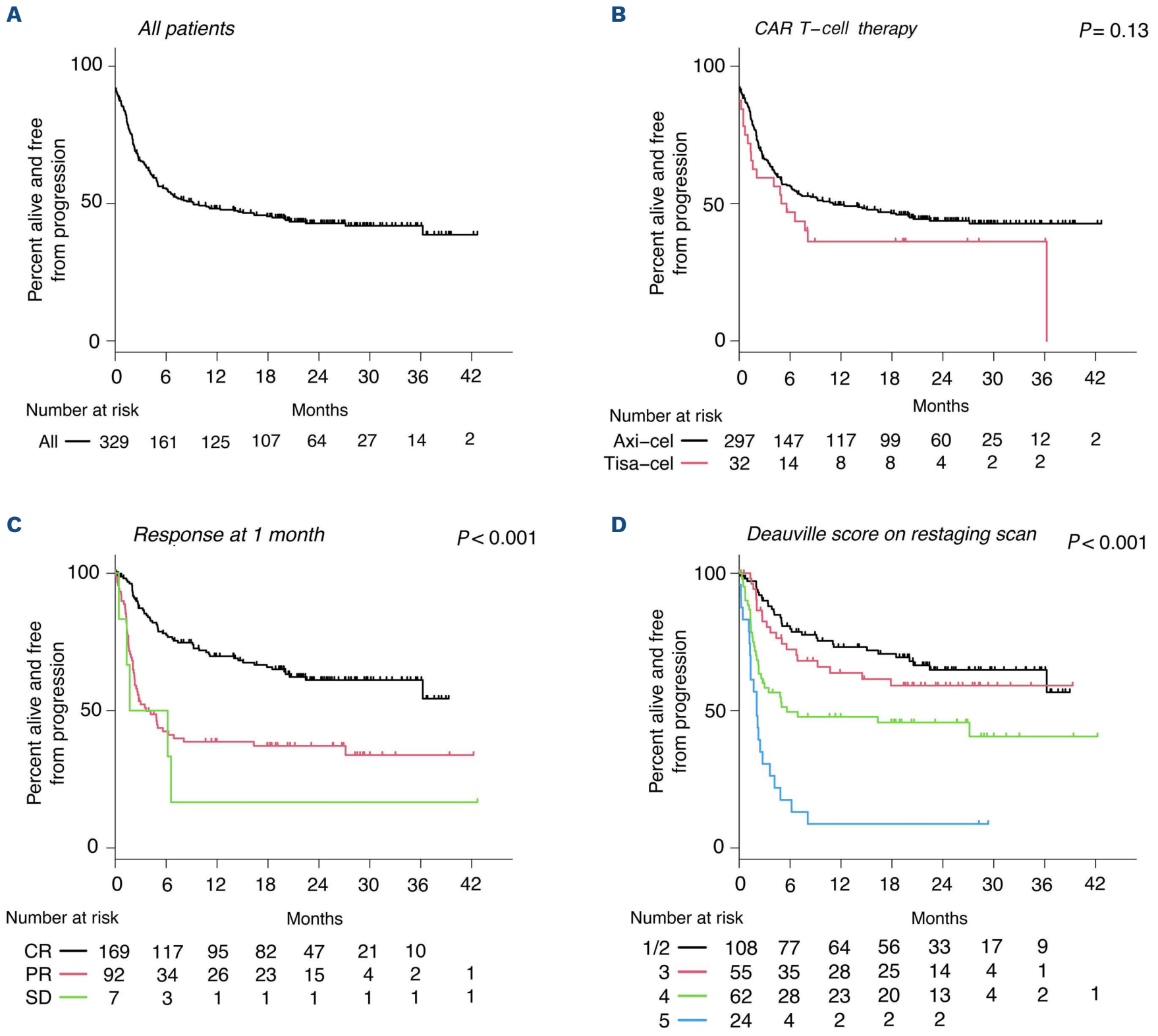

Figure 1. Progression-free survival following chimeric antigen receptor T-cell therapy. (A) Progression-free survival (PFS) among the entire cohort. (B) PFS among patients who received axicabtagene ciloleucel *versus* tisagenlecleucel. (C) PFS among patients with a complete metabolic response, partial metabolic response or stable disease at the 1-month assessment. (D) PFS among patients with a Deauville score of 1/2, 3, 4, or 5. CAR: chimeric antigen receptor; axi-cel: axicabtagene ciloleucel; tisa-cel: tisagenlecleucel; CR: complete response; PR: partial response; SD: stable disease.

or 5. Furthermore, within this group, patients with DS 5 had dismal outcomes, even if they did not have progressive disease at the 1-month timepoint.

We also sought to identify readily available clinical features that could discriminate patients at greatest risk of subsequent progression, particularly among patients with a partial response at the time of the 1-month PET. In our cohort, elevated baseline lactate dehydrogenase, grade 3 or higher cytokine release syndrome, and DS 4 or 5 were all associated with inferior PFS. We therefore used these variables to develop a risk score that could stratify patients into four groups with significantly different PFS and overall survival. We hope that this risk score, especially if validated in other datasets, may be used for prognostication for individual patients, for the selection of patients for clinical trials evaluating consolidative strategies after CAR T-cell therapy, and as a tool to define the null hypothesis in such trials. Of note, our data also suggest that maintenance or other response-adapted strategies, if employed, should be initiated soon after the 1-month response assessment, as the majority of patients who relapsed did so soon after the initial response.

This study has limitations based on its retrospective nature and the lack of centralized PET review. Additionally,

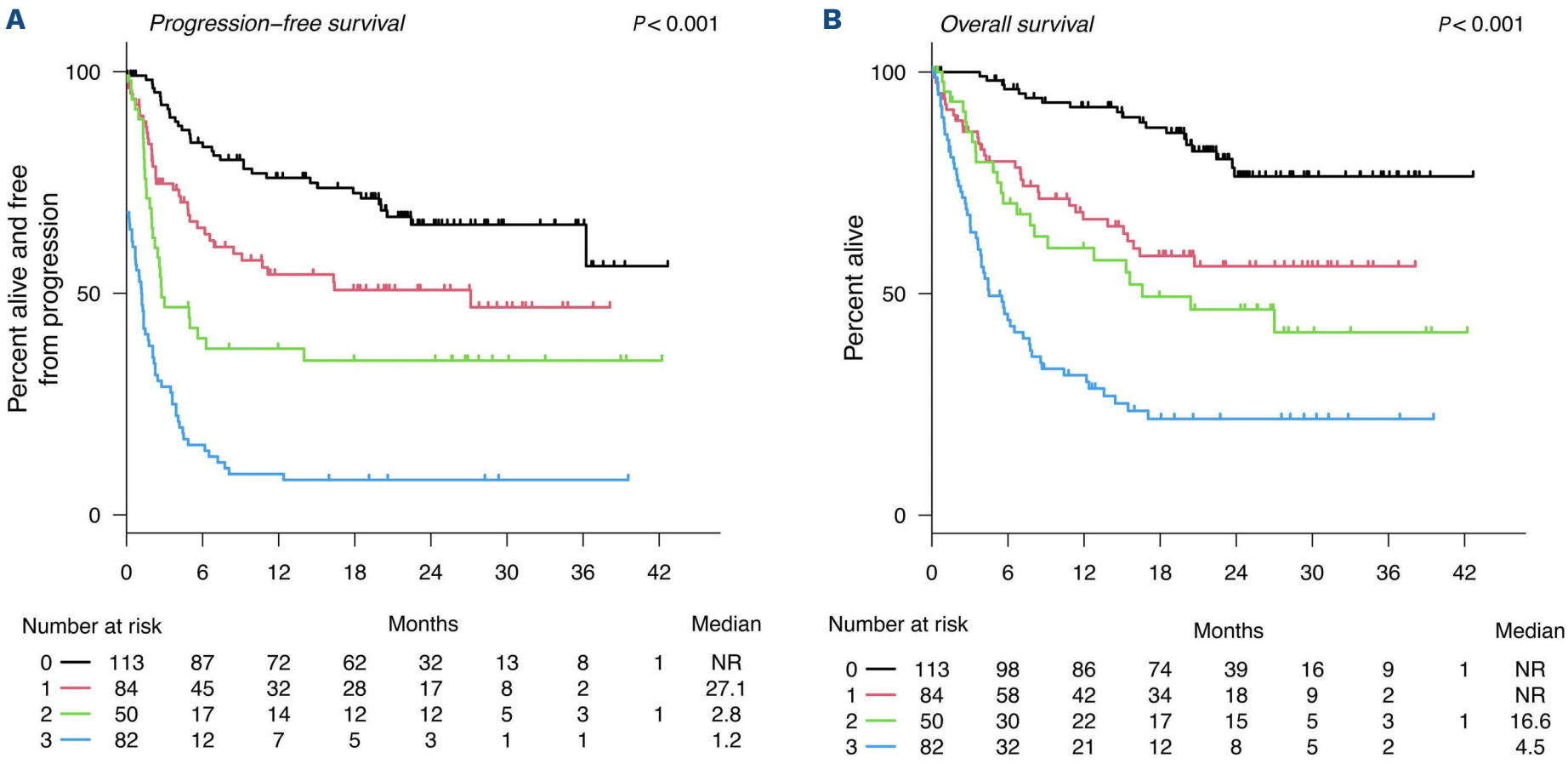

Figure 2. Progression-free survival and overall survival based on risk score. (A) Progression-free survival among patients with a risk score of 0-3. (B) Overall survival among patients with a risk score of 0-3. NR: not reached.

we did not have uniform data on tumor volume or SUV_{max}, metrics which have demonstrated prognostic value after CAR T-cell therapy.[2,9] However, this study, which is the largest retrospective study performed to date and of multicenter nature, should allow robust estimates of long-term outcomes for patients who reach the 1-month restaging timepoint. In the future, we also expect that other novel biomarkers, such as minimal residual disease, may further aid in prognostication in the CAR T-cell setting.[10,11] Further research into the application of this risk score as well as novel biomarkers in treatment strategies are warranted in patients with large B-cell lymphoma receiving CAR T-cell therapy.

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Contributions

JLC, CAJ, PA, and BH developed the research idea, performed research, and wrote the manuscript. RR performed the statistical analysis and reviewed the manuscript. GS, AH, VAC, JG, EM, KC, JK, JR, JC, and AS performed research and reviewed the manuscript. RH developed the research idea and reviewed the manuscript.

Data-sharing statement

The data that support the findings of this study are available on request from the corresponding author.

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