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ARTICLE

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Outcomes of second-line axicabtagene ciloleucel for large B-cell lymphoma in the UK

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Abstract

Following approval of axicabtagene ciloleucel (axi-cel) as second-line (2 L) treatment for large B-cell lymphoma (LBCL), results from real-world CAR T cohorts will be key to confirm safety and efficacy in standard practice. We present comprehensive clinical outcomes of LBCL patients intended to be treated with 2 L axi-cel through the UK National CAR T service. Of 345 patients approved for 2 L axi-cel, 302 (87.5%) were infused. The median age was 62 years (range 22–78); 21% were over 70 years. 75% of patients were approved for CAR T within 3 months from end of first-line (1 L) therapy. 42% of patients required pre-apheresis holding therapy, and 97% received bridging therapy. The best overall response rate was 86% (64% complete response). The 12-month OS was 73.9% (95% CI: 68.3–78.7) for infused patients and 1.5 months (0.9–3.0) for patients not proceeding to CAR T. The 12-month PFS was 52.4% (46.3–58.0). In multivariable analysis, advanced stage, male sex, no response to 1 L therapy, high LDH, and high CRP pre-infusion were independently associated with PFS. Grade ≥3 CRS and ICANS rates were 5% and 18%, respectively. Outcomes in patients aged ≥70 years were similar to the younger population. In this large UK real-world cohort of 2 L axi-cel in LBCL, we demonstrate efficacy and toxicity outcomes comparable to the pivotal ZUMA-7 trial, despite 42% patients requiring urgent holding therapy. Outcomes were favorable in patients aged ≥70 years, supporting the use of 2 L CAR T in older fit patients.

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INTRODUCTION

CD19 CAR T-cell therapy has been licensed for patients with large B-cell lymphoma (LBCL) relapsed or refractory (r/r) within 12 months of first-line (1 L) therapy, after the pivotal ZUMA-7 and TRANSFORM trials demonstrated superior outcomes of second-line (2 L) CAR T against standard-of-care treatment.[1–3] In ZUMA-7, patients randomized to 2 L axicabtagene ciloleucel (axi-cel) had significantly longer overall survival (OS), despite more than half of patients who progressed on the standard arm receiving axi-cel outside the trial.[2] These results have led to implementation of axi-cel, and more recently, lisocabtagene maraleucel (liso-cel), as new standard-of-care 2 L treatment for LBCL across several countries.

Validation of 2 L CAR T outcomes in the real-world setting is of high significance, to confirm that clinical trial results are generalizable to a more unselected, diverse patient population, and to establish cost-effectiveness in routine practice. Given the rapidly evolving therapeutic landscape in r/r LBCL, contemporary real-world evidence is increasingly important to inform nuanced decision-making for patients who have alternative treatment options available. CD20 × CD3-bispecific antibodies are broadly used for third-line (3 L) treatment of LBCL and approved as 2 L combination therapy (glofitamab plus GemOx) for patients not considered fit for autologous stem-cell transplant (ASCT) in Canada and the European Union. In addition, clinical trials using either bispecific antibodies or CAR T-cell therapy in the 1 L setting are underway. Optimal sequencing of different T-cell engaging therapies will therefore become ever more complex. In the absence of head-to-head comparative data, results from comprehensive real-world and meta-analyses will provide a major source of evidence to guide treatment decisions in daily practice and weigh risks and benefits for individual patients.

After introduction of CD19 CAR T as 3 L treatment for r/r LBCL, results from multi-center real-world cohorts were key to optimize patient selection and clinical management.[4–9] Real-world data have demonstrated the curative potential of CAR T-cell therapy in subgroups that were excluded from the clinical trials, such as rare histological subtypes or less fit/comorbid patients.[5,10–12] Clinical variables, including high total metabolic tumor volume, high LDH, extranodal involvement, and host inflammatory markers, have been associated with inferior CAR T outcomes across different datasets.[4,8,13,14] Detailed analyses on bridging therapy outcomes have shaped clinical practice, moving toward a more pro-active bridging therapy approach with integration of radiotherapy (RT) in many centers.[15–19] In addition, comprehensive short- and long-term toxicity analyses have helped to optimize toxicity management of CAR T patients and improved our understanding of the prolonged risk of severe infections and non-relapse mortality (NRM) after CAR T.[20–24]

As a result of continuous learning from real-world experience, we and others have described improvement in CAR T outcomes over time, with some toxicity and efficacy parameters exceeding results from the pivotal trials.[17] Some findings observed in 3 L CAR T treatment will translate into the 2 L setting, while other risk factors and outcomes might differ in a distinct 2 L patient population of primary refractory LBCL.

First US real-world data on 2 L axi-cel from the CIBMTR registry have been presented in abstract form.[25] In this cohort of 446 patients, efficacy and toxicity outcomes were similar to results from ZUMA-7, with slightly inferior long-term survival in patients who would not have met trial eligibility criteria. To our knowledge, no 2 L CAR T real-world data set has been fully published as yet. Here, we assess outcomes of patients intended to be treated with 2 L axi-cel through the UK National CAR T Program.

METHODS

Patients

Consecutive patients with r/r LBCL approved for funding of 2 L axi-cel at the UK National CAR T Clinical panel (NCCP) between May 2023 and November 2024 across all 18 commissioned CAR T centers were included. NCCP eligibility criteria are provided in the Supplement. Patients had to be deemed fit for ASCT with an ECOG performance status (PS) of 0-1 to be eligible for 2 L CAR T-cell therapy. Data were collected retrospectively from electronic records with ethical approval (REC reference: 24/LO/0527, IRAS project ID: 331212). Holding therapy was defined as any lymphoma-directed therapy administered before leukapheresis, whereas bridging therapy was defined as treatment given between leukapheresis and lymphodepletion chemotherapy (LD). LD with cyclophosphamide and fludarabine was delivered as per SmPC and local guidelines. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) grading was performed as per ASTCT consensus guidelines.[26] The CAR-HEMATOTOX score and immune effector cell-associated hematotoxicity (ICAHT) were assessed as per EHA/EBMT consensus.[22,27] Treatment response was assessed locally using the Lugano 2014 classification.[28] In UK practice, PET-CT scans are planned at 1, 3, and 6 months after infusion; however, some sites may perform the 6-month assessment by contrast-enhanced CT scan or clinical examination if complete metabolic response (CMR) was reported at month 3.

Statistical considerations

Pre-treatment factors, infusion rates, and toxicity were compared using Wilcoxon–Mann–Whitney/Kruskal–Wallis (continuous variables) or Chi-squared/Fisher's exact tests (discrete variables). Progression-free survival (PFS, events: progression and death) and OS (event: death) were analyzed using Kaplan–Meier survival analysis and Cox regression. Competing risk analysis by the method of Fine and Gray was used to analyze progression and NRM cumulative incidence rates, with death in remission and relapse counted as competing risks, respectively. The median follow-up time was calculated using the Kaplan–Meier method, censoring at death. The intent-to-treat (ITT) cohort included all patients approved for 2 L axi-cel at the NCCP. Times were measured from the date of infusion until the date of the first event, with patients who did not experience an event censored at the date last seen, except for the ITT analysis of OS, where time was

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measured from the date of NCCP approval, and analyses for responders, which are measured from the date of response. Multivariable models used stepwise selection techniques.

RESULTS

Patient characteristics

Of 345 patients approved for 2 L axi-cel (ITT cohort), 329 (95%) underwent leukapheresis and 302 (88%) were infused (Figure 1). The main reason for not proceeding to infusion was clinical deterioration from progressive disease (PD; 30 of 43 patients). The median time from approval to infusion was 49 days (IQR: 42–62), with a median vein-to-vein time of 38 days (IQR: 33–46).

Patients' baseline characteristics at the time of approval and pre-infusion are provided in Table 1. In the ITT cohort, the median age was 62 years (range 22–78); 21% were ≥70 years and 13% were from an ethnic minority background. At the time of CAR T approval, 75% of patients had advanced-stage disease, 31% of patients had extranodal involvement of ≥2 sites, and 61% of patients had elevated LDH. The cohort of patients not infused was significantly enriched for patients with bulky disease ($P = 0.010$), advanced stage ($P < 0.001$), extranodal involvement ($P = 0.046$) and elevated LDH ($P < 0.001$), as well as patients with PD at the end of 1 L treatment ($P = 0.015$).

Time from end of 1 L therapy to axi-cel approval was ≤3 months in 75% of patients, between 3 and 6 months in 9% of patients, and 6-12 months in 15% of patients (Table 1). R-CHOP was used as 1 L regimen in 61% of patients and polatuzumab-R-CHP in 30% of patients. 11% of patients had received consolidation RT. The disease status after 1 L therapy was CMR in 25% of patients, partial response (PR) in 29% of patients, stable disease (SD) in 2% of patients, and PD in 44% of patients (21% primary progression, 23% progression in comparison to interim PET scan).

Pre-apheresis holding therapy was required in 42% of patients, with the majority receiving systemic treatment. Post-apheresis bridging therapy was given in 97% of patients (60% systemic therapy, 23% RT, and 12% combined modality treatment [CMT]). Details of systemic holding and bridging regimens are provided in Supporting Information S1: Table S1.

Efficacy

The best overall response rate (ORR) after axi-cel infusion was 86% (64% CMR). With a median follow-up of 15.8 months (IQR: 11.1–20.1) from approval, the median OS was 24.2 months (IQR: 7.8–NR), with a 12-month OS of 73.9% (95% CI: 68.3–78.7) for infused patients (Figure 2A). The median OS of patients not proceeding to axi-cel infusion was 1.5 months (0.9–3.0). The median PFS of infused patients has not been reached, with a 12-months PFS of 52.4% (95% CI: 46.3–58.0; Figure 2B).

Patients aged ≥70 years had comparable outcomes, with a 12-month PFS of 51.2% (37.1–63.7) versus 52.5% (95% CI: 45.7–58.8) in those <70 years (HR 1.02 [95% CI: 0.68–1.54), $P = 0.91$; Figure 2C). Response to 1 L therapy was significantly associated with post-CAR T PFS. Patients with SD/PD at end of 1 L therapy had significantly worse outcome compared to those with PR at end of treatment (EOT) or who relapsed after achieving CMR (HR: 1.64 (95% CI: 1.17–2.29), $P = 0.003$; Figure 2D). Other variables associated with PFS are provided in Table 2. As shown in the 3 L setting, pre-LD LDH levels were strongly associated with outcome after 2 L axi-cel (HR > 1ULN: 1.55 (95% CI: 1.06–2.26), HR > 2ULN: 2.79 (95% CI: 1.75–4.44), $P < 0.0001$; Figure 2E). Higher CAR-HEMATOTOX score was associated with inferior PFS (2+ vs. 0–1 HR: 1.64 (95% CI: 1.15–2.34), $P = 0.007$; Figure 2F); however, the effect was associated with and not independent of pre-infusion CRP levels (data not shown). In multivariable analysis, disease stage, end of 1 L therapy response, patients' sex, and LDH and CRP levels pre-LD were independently significant for PFS (Table 2).

Patients alive and without progression at 1 month ($n = 249$) were assessed for early ICAHT, with worse outcomes seen for patients with grades 3–4 versus 1–2: HR: 1.84 (95% CI: 1.22–2.77),

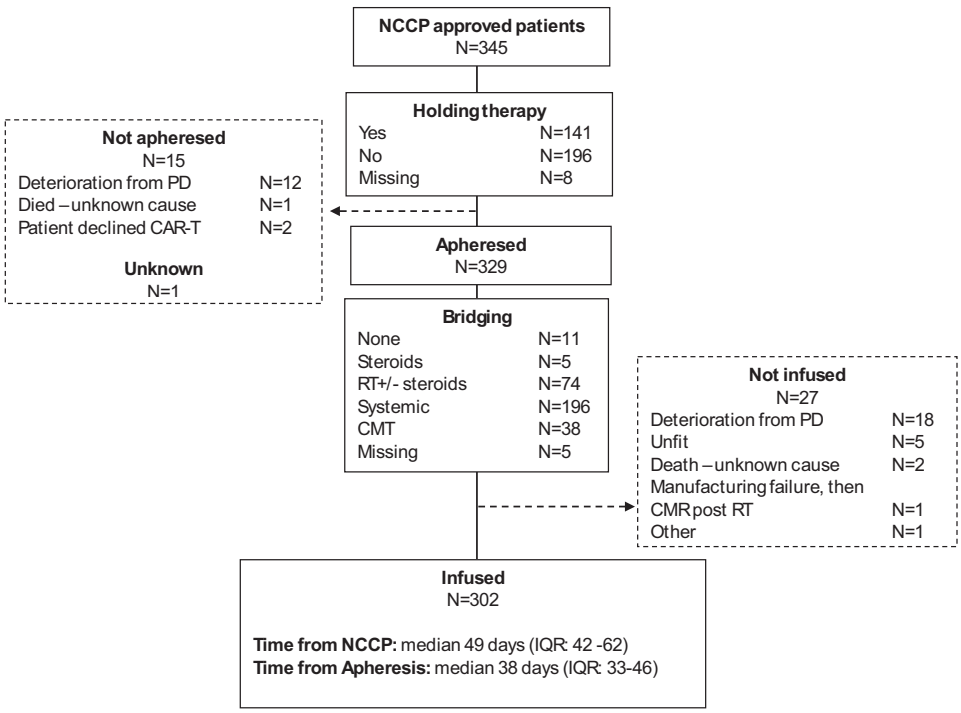

FIGURE 1 Flow chart of patients approved for 2 L axi-cel.

TABLE 1 Baseline characteristics. (continued on next page)

	All patients N = 345[b]	Infused N = 302	Not infused N = 42	P-value[a]
Demographics				
Age, median (IQR) Range	62 (53–68) 22–78	62 (53–68) 22–77	65 (59–70) 46–78	0.12
Age groups, N (%)				
Under 70 y	272 (79.3)	241 (79.8)	30 (75.0)	0.53
≥70 y	71 (20.7)	61 (20.2)	10 (25.0)	
Missing/unknown	2	0	2	
Sex, N (%)				
Male	218 (63.4)	194 (64.2)	24 (58.5)	0.49
Female	126 (36.6)	108 (35.8)	17 (41.5)	
Missing/unknown	1	0	1	
Ethnicity, N (%)				
White	287 (87.2)	255 (87.6)	32 (84.2)	0.43
Asian	27 (8.2)	22 (7.6)	5 (13.2)	
Black	9 (2.7)	8 (2.7)	1 (2.6)	
Other[c]	6 (1.8)	6 (2.1)	0	
Missing/unknown	16	11	4	
Disease subtype, N (%)				
DLBCL NOS	238 (69.4)	208 (68.9)	29 (72.5)	0.79
HGBCL	37 (10.8)	33 (10.9)	4 (10.0)	
T-cell histiocyte-rich LBCL	9 (2.6)	9 (3.0)	0	
t-FL	43 (12.5)	38 (12.6)	5 (12.5)	
t-other[d]	11 (3.2)	9 (3.0)	2 (5.0)	
LBCL other[e]	5 (1.5)	5 (1.7)	0	
Missing/unknown	2	0	2	
Stage at approval, N (%)				
0 (CMR after holding)	1 (0.3)	1 (0.3)	0	<0.001
1	29 (8.5)	29 (9.6)	0	
2	57 (16.7)	56 (18.5)	1 (2.6)	
3	32 (9.4)	30 (9.9)	2 (5.1)	
4	223 (65.2)	186 (61.6)	36 (92.3)	
Missing/unknown	3	0	3	
Bulk (≥7.5 cm) at approval, N (%)				
No	252 (77.1)	230 (79.3)	21 (58.3)	0.010
Yes	75 (22.9)	60 (20.7)	15 (41.7)	
Missing/unknown	18	12	6	
Extranodal sites at approval, N (%)				
No	106 (32.0)	99 (34.1)	7 (17.5)	0.046
Yes	225 (68.0)	191 (65.9)	33 (82.5)	
Missing/unknown	14	12	2	
2 or more extranodal sites, N (%)				
No	227 (68.6)	206 (71.0)	20 (50.0)	0.010
Yes	104 (31.4)	84 (29.0)	20 (50.0)	
Missing/unknown	14	12	2	
LDH elevated at approval, N (%)				
No	130 (39.0)	127 (42.5)	3 (8.8)	<0.001

TABLE 1 (Continued)

	All patients N = 345[b]	Infused N = 302	Not infused N = 42	P-value[a]
Yes	203 (61.0)	172 (57.5)	31 (91.2)	
Missing/unknown	12	3	8	
Secondary IPI,[f] *N* (%)				
0–1	83 (24.6)	83 (27.9)	0	<0.001
2–4	254 (75.4)	215 (72.1)	39 (100.0)	
Missing/unknown	8	4	3	
First-line regimen, *N* (%)				
R-CHOP[g]	207 (60.7)	190 (62.9)	16 (42.1)	0.061
Pola R-CHP	102 (29.9)	83 (27.5)	19 (50.0)	
R-GCVP/CEOP	3 (0.9)	3 (1.0)	0	
R-CODOX-M/R-IVAC	12 (3.5)	11 (3.6)	1 (2.6)	
EPOCH-R	7 (2.1)	6 (2.0)	1 (2.6)	
Other[h]	10 (2.9)	9 (3.0)	1 (2.6)	
Missing/unknown	4	0	4	
Consolidation RT at end of 1 L, *N* (%)				
No	300 (89.0)	266 (89.0)	33 (89.2)	0.61
Yes	37 (11.0)	33 (11.0)	4 (10.8)	
Missing/unknown	8	3	5	
Disease status at approval, *N* (%)				
Relapse after EOT CMR	85 (25.1)	81 (27.1)	4 (10.5)	0.0064
EOT PR	97 (28.7)	87 (29.1)	9 (23.7)	
EOT SD	7 (2.1)	6 (2.0)	1 (2.6)	
EOT PD	149 (44.1)	125 (41.8)	24 (63.2)	
PD (EOT vs. iPET)	*78 (23.1)*	*70 (23.4)*	*8 (21.1)*	
PD (primary progression)	*70 (20.7)*	*54 (18.1)*	*16 (42.1)*	
PD (NOS)	*1 (0.3)*	*1 (0.3)*	*0*	
Missing/unknown	7	3	4	
Time from 1 L to NCCP approval, *N* (%)				
By the EOT	188 (55.1)	155 (51.5)	32 (82.1)	0.0004
Within 3 months	69 (20.2)	64 (21.3)	5 (12.8)	
Within 6 months	32 (9.4)	31 (10.3)	1 (2.6)	
Between 6 and 12 months	52 (15.2)	51 (16.9)	1 (2.6)	
Missing/unknown	4	1	3	
Holding and bridging therapy				
Holding therapy, *N* (%)				
None	196 (58.2)	183 (60.6)	13 (37.1)	0.004
Steroids	36 (10.7)	32 (10.6)	4 (11.4)	
RT ± steroids	16 (4.7)	15 (5.0)	1 (2.9)	
Systemic	86 (25.5)	69 (22.8)	17 (48.6)	
CMT	3 (0.9)	3 (1.0)	0	
Missing/unknown	8	0	7	
Bridging therapy, *N* (%)				
None	11 (3.4)	10 (3.4)	1 (3.8)	0.014
Steroids	5 (1.5)	3 (1.0)	2 (7.7)	
RT ± steroids	74 (22.8)	73 (24.5)	1 (3.8)	
Systemic	196 (60.5)	177 (59.4)	19 (73.1)	

TABLE 1 (Continued)

	All patients N = 345[b]	Infused N = 302	Not infused N = 42	P-value[a]
CMT	38 (11.7)	35 (11.7)	3 (11.5)	
Missing/unknown/no apheresis	21	4	16	
Pre-LD parameters				
Response to bridging, N (%)				
SD/PD	124 (42.5)	108 (39.6)	-	-
CR/PR	168 (57.5)	165 (60.4)	-	
Missing/unknown	53	29	-	
ECOG PS pre-LD, N (%)				
0	130 (42.3)	130 (43.0)	-	-
1	163 (53.1)	160 (53.0)	-	
2	14 (4.6)	12 (4.0)	-	
Missing/unknown	38	0	-	
LDH (grouped) pre-LD, N (%)				
Normal	146 (49.3)	145 (49.8)	-	-
>ULN	110 (37.2)	108 (37.1)	-	
>2ULN	40 (13.5)	38 (13.1)	-	
Missing/unknown	49	11	-	
CRP pre-LD, N (%)				
<10	185 (60.9)	184 (61.5)	-	-
10–20	43 (14.1)	42 (14.0)	-	
20–50	39 (12.8)	38 (12.7)	-	
50+	37 (12.2)	35 (11.7)	-	
Missing/unknown	41	3	-	
CAR-HEMATOTOX score (≥2), N (%)				
No	171 (65.3)	170 (65.4)	-	-
Yes	91 (34.7)	90 (34.6)	-	
Missing/unknown	83	42	-	
CAR-HEMATOTOX score, median (IQR)	1 (0–2)	1 (0–2)	-	-
Range	0–7	0–7		

Abbreviations: EOT, end of treatment; iPET, interim PET scan.

[a]Includes N = 2 patients who were lost to follow-up before infusion, that is, not included in either the infused or not infused columns.

[b]P-values are calculated using Wilcoxon–Mann–Whitney (continuous), Fisher's exact (discrete), and the Chi-square test for trend (ordinal). P-value for stage compares stage 0–2 versus stage 3–4, disease status tests CMR versus PR versus SD/PD (test for trend; P = 0.014 when comparing CR/PR vs. SD/PD); holding considers nonsteroid holding versus no holding/steroids only. "Other" groups are excluded from all comparisons.

[c]Ethnicity other: Russian (N = 1), Chinese (N = 1), Not specified (N = 4).

[d]t-other: NLPHL (N = 4), Waldenström's (N = 1), indeterminate MZL or FL (N = 1).

[e]DLBCL cutaneous leg type (N = 1), DLBCL with 11q aberration (N = 1), EBV + DLBCL (N = 3).

[f]IPI: Only patients with ECOG PS 0/1 were eligible for CAR T, hence maximum IPI = 4.

[g]R-CHOP includes R-CHOP + acalabrutinib (N = 4), CHOP (N = 2), R-CHOP ± tafasitamab lenalidomide (blinded) (N = 1).

[h]Other includes: MATRIx/R-ICE (N = 1), R-CHOP ×2 then R-GCVP ×4 (due to low EF; N = 1), R-GDP (N = 1), Pola-R-CHP ×3 then R-GCVP ×3 (due to previous anthracycline exposure; N = 1), O-CHOP (N = 1), R-CEOP followed by 2 R-CHOP after echo (N = 1), R-CEOP ×2 R-CHOP ×4 (N = 1).

P = 0.004; Table 2). There was no evidence of a differential effect of risk factors across age groups (≥70 years vs. <70 years; data not shown). We did not see differences in PFS or OS according to vein-to-vein time (PFS [HR vs. <28 days]: 28–39 days 0.77 (95% CI: 0.24–2.44), ≥40 days 0.81 (0.58–1.14), P = 0.46). Moreover, there was no association between patients' ethnicity and long-term survival (PFS (HR vs. white): Asian 0.95 (95% CI: 0.50–1.81), Black 1.10 (0.41–2.99), P = 0.97).

Toxicity outcomes

Any grade CRS and ICANS were seen in 98% and 48% of patients, with grade ≥3 in 5% and 18% of patients, respectively (Table 3). 88% of patients received tocilizumab, 61% of patients received corticosteroids, and 19% of patients received anakinra. 23% of patients required ICU admission, but only 8% of patients had organ support. Early ICAHT grade ≥3 was seen in 29% of patients at 1 month. Toxicity outcomes

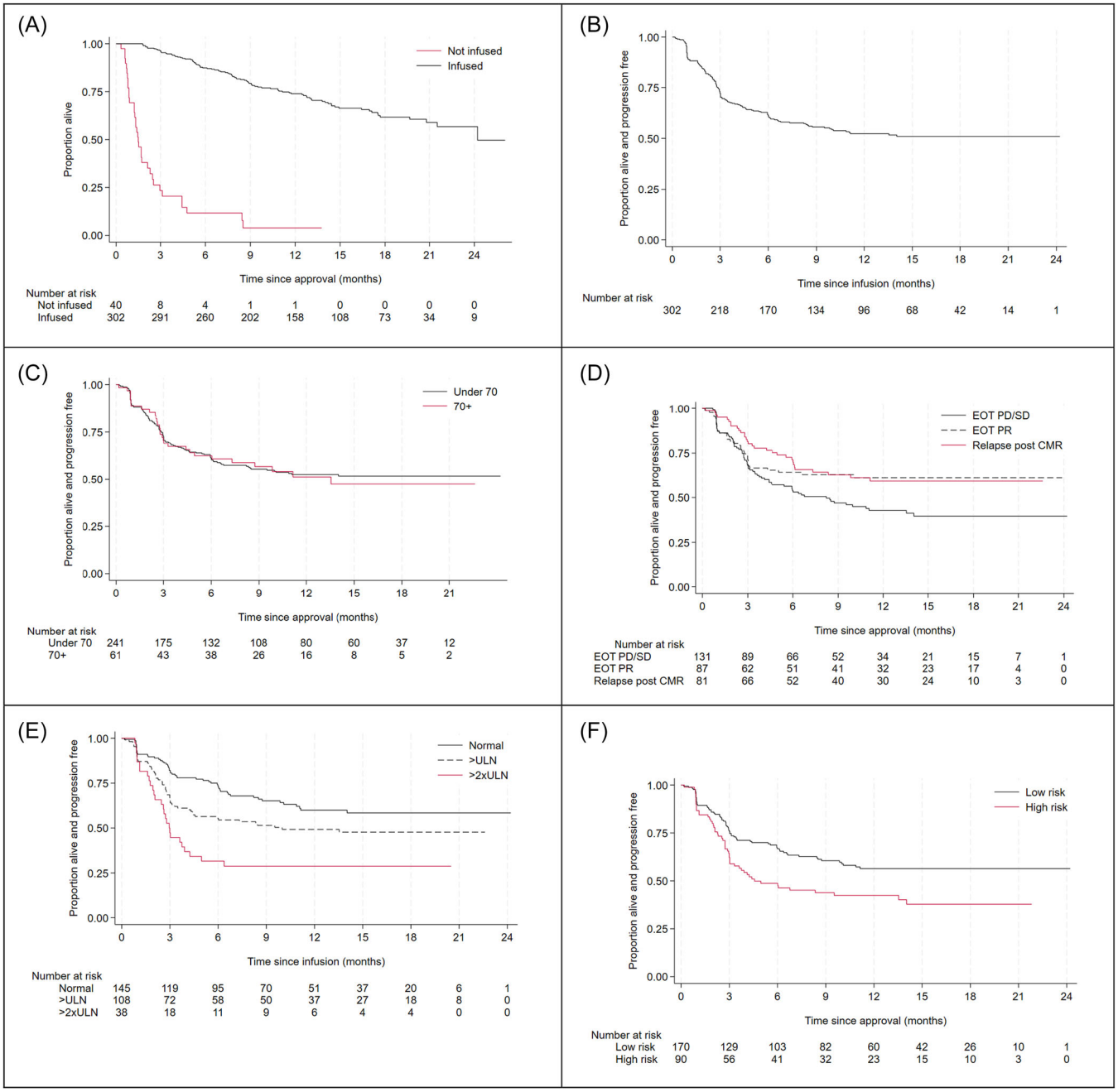

FIGURE 2 **Kaplan–Meier curves of long-term survival. (A)** Overall survival in the intention-to-treat population. **(B)** Progression-free survival (PFS) for the total cohort of infused patients. PFS according to **(C)** age groups, **(D)** end of 1 L therapy response, **(E)** pre-LD LDH levels, and **(F)** HEMATOTOX score.

were similar between age groups (Table 3). The cumulative incidence of NRM at 12 months was 6.9% (95% CI: 4.5–10.5), with no significant difference between age groups (8.6% vs. 6.5% at 12 months; HR: 1.51 (0.59–3.87), $P = 0.39$; Supporting Information S1: Figure S1 and Supporting Information S1: Table S2). Infections were the main cause of NRM (Supporting Information S1: Table S2).

The CAR-HEMATOTOX score (as continuous variable or 0–1 vs. ≥2) was significantly associated with grade ≥3 cytopenias at 1 month and 3 months (data not shown). Patients with high CAR-HEMATOTOX score ≥2 had a significantly higher incidence of early ICAHT grade ≥3 (OR: 3.88 (2.34–6.43), $P < 0.0001$). No association between the CAR-HEMATOTOX score and NRM was observed (6.9% 2+ vs. 7.4% 0–1; HR: 1.24 (95% CI: 0.51–3.04), $P = 0.63$).

DISCUSSION

In this consecutive, national cohort of patients approved for 2 L axicel in the United Kingdom, we provide detailed efficacy and toxicity outcomes in an intent-to-CAR T real-world population.

Our efficacy outcomes are remarkably similar to results from the pivotal ZUMA-7 trial, with near identical response rates of 86% (83% in ZUMA-7) and 12-month PFS of 52% (52% in ZUMA-7).[1,2] These favorable results were achieved despite the majority of patients in our cohort undergoing holding and/or bridging therapy, which was an exclusion criterion for ZUMA-7. However, we did not prospectively assess eligibility for ZUMA-7. While most patients who require urgent pre-apheresis holding therapy would unlikely be considered suitable

TABLE 2 Variables associated with PFS.

Factor	Events/*N*	HR (95% CI)	*P*-value
Univariable			
Age (for an increase of 10 years)	140/302	0.91 (0.79–1.05)	0.20
Sex			
Male	95/194	1.00	0.25
Female	45/108	0.81 (0.57–1.16)	
Subtype			
De novo DLBCL	116/255	1.00	0.30
t-FL	21/38	1.37 (0.86–2.18)	
t-other	3/9	0.67 (0.21–2.09)	
Disease status at approval, *N* (%)			
PD/SD at EOT	64/168	1.00	0.0030
PR/CMR EOT	74/131	1.64 (1.17–2.29)	
Stage at approval[a]			
0–2	30/86	1.00	0.010
3–4	110/216	1.69 (1.13–2.53)	
Extranodal sites at approval[a]			
0–1	95/206	1.00	0.53
2+	43/84	1.12 (0.78–1.61)	
For an increase of 1 site	138/290	1.17 (1.02–1.33)	0.023
Bulk at approval[a]			
No	102/230	1.00	0.23
Yes	32/60	1.28 (0.86–1.90)	
LDH pre-LD[b]			
Normal	54/145	1.00	<0.000 1[c]
>ULN	55/108	1.55 (1.06–2.26)	
>2ULN	27/38	2.79 (1.75–4.44)	
CRP pre-LD			
<10	69/184	1.00	<0.000 1[c]
10-20	23/42	1.65 (1.03–2.65)	
20-50	22/38	1.82 (1.12–2.94)	
50+	25/35	2.72 (1.72–4.30)	
CAR-HEMATOTOX score (for an increase of 1 point)	112/239	1.22 (1.09–1.37)	0.004
Holding therapy			
None/steroids alone	96/230	1.00	0.004
Systemic/CMT	44/72	1.68 (1.17–2.40)	
Early ICAHT grade 3–4[d]			
No	61/179	1.00	0.004
Yes	36/70	1.84 (1.22–2.77)	
Multivariable[e]			
Stage at approval			
0–2	27/77	1.00	0.011
3–4	100/189	1.76 (1.14–2.71)	
Sex			
Male	88/171	1.00	0.040
Female	39/95	0.67 (0.45–0.98)	
SD/PD at EOT			
No	62/156	1.00	0.013
Yes	65/110	1.56 (1.10–2.23)	
LDH pre-LD			
≤2ULN	102/231	1.00	0.010
>2ULN	25/35	1.89 (0.17–3.06)	
CRP pre-LD			
<50	103/234	1.00	0.010
≥50	24/32	1.87 (1.16–3.00)	

[a]Stage, bulk, and extranodal sites were included at NCCP approval rather than baseline; models with both were considered; stage and extranodal sites at NCCP approval appeared to be more important (HRs for diagnostic reduced to <1); and neither bulk at diagnosis nor NCCP approval appeared to be predictive or significantly associated with PFS.

[b]LDH pre-LD used over LDH at NCCP approval. This parameter had greater granularity available, and when both variables were included, only pre-LD LDH remained significant.

[c]Log-rank test for trend.

[d]Early ICAHT was only assessed for patients who were alive and without PD at 1 month post CAR T infusion.

[e]All variables except holding therapy, CAR-HEMATOTOX score, and early ICAHT were included in the MVA with stepwise selection used ($P = 0.05$ for exclusion) to come to the final MVA model. Due to the violation in proportional hazards and the similar long-term outcomes for patients who were PR at EOT or relapsed post CMR (see Figure 2D), refractoriness was included as PD/SD at EOT versus response at EOT.

trial candidates, the use of bridging therapy does not necessarily reflect a "requirement" of treatment, but rather the pro-active bridging therapy approach that has evolved over time.[17]

Results from this real-world cohort re-affirm the importance of ITT outcomes in the context of CAR T-cell therapy. Patients who did not proceed to infusion had a dismal outcome, with a median survival of only 1.5 months. This appears similar to the median OS of 2.1 months for non-infused patients that we have described in the 3 L setting, despite the availability of post-CAR T bispecific antibodies in the current cohort.[8]

Due to the prospective nature of our cohort, with centralized registration of all CAR T-approved patients through the NCCP, we provide a fully representative national real-world data set. In contrast, most registry data are collected in a nonconsecutive, retrospective manner. When presenting real-world outcomes of 2 L axi-cel from the CIBMTR registry, the authors acknowledged that some patients who received bridging therapy may have been mis-registered as 3 L LBCL and not included in their analysis, highlighting these limitations.

Patients' disposition was similar to ZUMA-7 regarding risk factors such as advanced stage (75% vs. 77%), primary refractory disease (defined as no CMR at EOT; 75% vs. 74%), or elevated LDH (61% vs. 56%). Details on extranodal involvement and bulk are not available for ZUMA-7. Only 13% of UK patients came from ethnic minority backgrounds, similar to our previous results in 3 L CAR T, which was representative of the LBCL background population.[29]

Interestingly, within the group of primary refractory patients, only 28% had primary progression to 1 L therapy. The remaining patients had either progression at EOT compared to interim PET response, or PR with repeat biopsy and/or follow-up scan demonstrating active disease. These findings indicate that patients are identified early for 2 L CAR T in standard practice. Only 11% of patients had received 1 L consolidation radiotherapy, potentially indicating that some patients with residual disease at EOT who would historically have been

TABLE 3 Toxicity.

	All patients N = 302	Age < 70 y N = 241	Age ≥ 70 y N = 61	P-value[a]
Any CRS, *N* (%)				
No	7 (2.3)	5 (2.1)	2 (3.3)	0.63[a]
Yes	295 (97.7)	236 (97.9)	59 (96.7)	
Grade 3 + CRS, *N* (%)				
No	286 (94.7)	228 (94.6)	58 (95.1)	>0.99
Yes	16 (5.3)	13 (5.4)	3 (4.9)	
Any ICANS, *N* (%)				
No	157 (52.2)	132 (55.0)	25 (41.0)	0.062
Yes	144 (47.8)	108 (45.0)	36 (59.0)	
Missing/unknown	1	1	0	
Grade 3 + ICANS, *N* (%)				
No	247 (82.1)	195 (81.2)	52 (85.2)	0.58
Yes	54 (17.9)	45 (18.8)	9 (14.8)	
Missing/unknown	1	1	0	
Anakinra given, *N* (%)				
No	241 (81.4)	193 (81.1)	48 (82.8)	0.85
Yes	55 (18.6)	45 (18.9)	10 (17.2)	
Missing/unknown	6	3	3	
Steroids given, *N* (%)				
No	118 (39.2)	97 (40.4)	21 (34.4)	0.46
Yes	183 (60.8)	143 (59.6)	40 (65.6)	
Missing/unknown	1	1	0	
Tocilizumab given, *N* (%)				
0	35 (11.6)	30 (12.4)	5 (8.2)	0.50
1	267 (88.4)	211 (87.6)	56 (91.8)	
Tocilizumab doses, median (IQR) Range	2 (1–3) 0–4	2 (1–4) 0–4	2 (1–3) 0–4	0.82
ICU support, *N* (%)				
No	230 (76.9)	184 (77.0)	46 (76.7)	0.47[c]
Observation	27 (9.0)	23 (9.6)	4 (6.7)	
Inotropes	17 (5.7)	15 (6.3)	2 (3.3)	
Organ support	25 (8.4)	17 (7.1)	8 (13.3)	
Missing/unknown	3	2	1	
Early ICAHT grade, *N* (%)				
1 (ANC < = 0.5 less than 7 d)	88 (32.0)	68 (31.3)	20 (34.5)	0.97[c]
2 (ANC < = 0.5 7–13 d)	107 (38.9)	88 (40.6)	19 (32.8)	
3 (ANC < = 0.5 14+d or <=0.1 for 7–13 d)	47 (17.1)	34 (15.7)	13 (22.4)	
4 (ANC never 0.5 or <0.1 for <14 d)	33 (12.0)	27 (12.4)	6 (10.3)	
Missing/unknown	27	24	3	
Cytopenias[d]				
Grade 3+ cytopenia at 1 month, *N* (%)				
No	105 (39.8)	90 (42.9)	15 (27.8)	0.061
Yes	159 (60.2)	120 (57.1)	39 (72.2)	
Missing/unknown/PD or death by this point	38	31	7	
Grade 3+ cytopenia at 3 months, *N* (%)				
No	143 (81.7)	113 (83.1)	30 (76.9)	0.48
Yes	32 (18.3)	23 (16.9)	9 (23.1)	
Missing/unknown/PD or death by this point	127	105	22	
Grade 3+ neutropenia at 1 month, *N* (%)				
No	131 (49.8)	109 (52.2)	22 (40.7)	0.17
Yes	132 (50.2)	100 (47.8)	32 (59.3)	
Missing/unknown/PD or death by this point	39	32	7	
Grade 3+ thrombocytopenia at 1 month, *N* (%)				
No	137 (51.7)	110 (52.1)	27 (50.0)	0.88
Yes	128 (48.3)	101 (47.9)	27 (50.0)	
Missing/unknown/PD or death by this point	37	30	7	
Grade 3+ neutropenia at 3 months, *N* (%)				
No	154 (89.0)	121 (90.3)	33 (84.6)	0.38
Yes	19 (11.0)	13 (9.7)	6 (15.4)	
Missing/unknown/PD or death by this point	129	107	22	
Grade 3+ thrombocytopenia at 3 months, *N* (%)				
No	150 (85.7)	117 (86.0)	33 (84.6)	0.80
Yes	25 (14.3)	19 (14.0)	6 (15.4)	
Missing/unknown/PD or death by this point	127	105	22	

[a]Fisher's exact test unless otherwise specified.
[b]Wilcoxon–Mann–Whitney test.
[c]Chi-squared test for trend.
[d]Cytopenia grading as per CTCAEv5.0.

considered for radiotherapy are now referred for 2 L CAR T. In our study, we were able to categorize primary refractory patients into those with PD, SD, or PR at EOT and show variability in outcomes between these groups. Details on the time and type of refractoriness are not available for the ZUMA-7 or CIBMTR cohorts for comparison.

The median vein-to-vein time of 38 days in our cohort was significantly longer than that in ZUMA-7 (13 days) or the CIBMTR registry (29 days), in line with the generally longer CAR T turnaround times seen in Europe.[30] We did not observe differences in outcome according to time from approval-to-infusion or vein-to-vein time. In a systematic literature review and meta-analysis by Locke et al, longer vein-to-vein times were associated with inferior outcome in axi-cel-treated patients.[30] However, the reason for prolonged vein-to-vein times may significantly differ between centers and health care systems. The axi-cel manufacturing time has been reduced to 21 days in the United Kingdom, but product delivery within 3 weeks is often not

requested by the treating center, in order to complete bridging therapy and leave a treatment-free window before LD in patients who are clinically stable. It will be interesting to see at which point of shortened turnaround times a change in management will take effect, that is, broad omission of bridging therapy, with potentially further improvement in the drop-out rate between leukapheresis and infusion (currently 8%) and long-term survival.

Toxicity outcomes were comparable to results from ZUMA-7.[1] We confirm reduction of high-grade CRS rates with pro-active toxicity management, as shown before in 3 L CAR T.[17,31] A rate of 5% high-grade CRS is similar to the incidence seen with bispecific antibodies, without routine use of prophylactic corticosteroids.[32] ICANS rates did not change over time and will remain a significant barrier for outpatient delivery of axi-cel. Severe early ICAHT ≥ 3 was found in 29% of our patients, slightly higher than previously reported in 3 L CAR T (23%),[33] despite 2 L patients being less heavily pre-treated. The pre-infusion CAR-HEMATOTOX score was associated with post-CAR T cytopenias and ICAHT, which, to our knowledge, is the first validation of the score in a 2 L axi-cel cohort. Although CAR-HEMATOTOX was associated with PFS in univariable analysis, we found that it was not independent of pre-infusion CRP levels; larger cohorts are needed to assess whether both factors can improve predictive models. The 12-month NRM rate observed in our cohort (6.9%) was consistent with previous results in 3 L axi-cel-treated patients (7.4%).[34]

The median age in our cohort was slightly older, 62 years compared to 58 years in ZUMA-7, with 21% of patients aged ≥70. We demonstrate similar ITT outcomes in patients ≥70 years compared to younger patients, confirming the curative potential of CAR T-cell therapy in an age group historically not often considered for intense treatment. A pre-planned subgroup analysis from ZUMA-7 demonstrated superior efficacy and quality of life outcomes for 2 L axi-cel over standard of care in patients aged ≥65.[35] In the same analysis, a numerically higher incidence of CRS and ICANS was seen in older patients, with 33% high-grade neurological events in patients aged ≥70.[35] In our cohort, no significant increase in CRS, ICANS, or NRM events was seen in patients ≥70 years, which, similar to ZUMA-7, was restricted to patients deemed fit for ASCT. In the United States and many European countries, 2 L CAR T is used irrespective of ASCT fitness, based on favorable results from the ALYCANTE and PILOT trials.[36,37] In ALYCANTE, most patients were deemed unfit for ASCT based on age ≥65, with 53% of recruited patients being ≥70 years. Outcomes of patients aged ≥70 in our cohort are very similar to ALYCANTE (12-month PFS 51.2% vs 48.4%), questioning the historic categorization of ASCT fitness in an era where ASCT is increasingly being replaced by other curative treatments like CAR T. Patients considered for CAR T-cell therapy should ideally be assessed according to their fitness for CAR T and their anticipated clinical benefit.

Interestingly, response to 1 L therapy was found to be an independent prognostic factor for PFS. Depth of initial 1 L response (CMR vs. PR) made no difference in the long term, with earlier events in PR patients, but with the curves meeting at 6 months. The effect remained when adjusting for measures of tumor burden such as LDH and CRP, indicating that "response to 1 L" is largely a surrogate for aggressive disease biology rather than a mere reflection of tumor burden. It is noteworthy that transformed follicular lymphoma histology was not associated with post-CAR T outcome, which is different to findings in the 3 L axi-cel setting.[10]

Limitations of our analysis include the retrospective data collection (albeit prospective case registration) and the relatively short follow-up (less than the median survival), although if following the relapse pattern seen in ZUMA-7, we do cover the period with the majority of events and 12-month rates should be robust. In addition, data on infectious complications were not captured.

With a fast-moving field of novel treatments for LBCL, and availability of different T-cell engaging therapies, optimal sequencing of treatments for individual patients will require detailed knowledge of clinical outcomes in specific subgroups and implications of each treatment pathway. We demonstrate that results from the pivotal ZUMA-7 trial can be translated into standard practice, setting a new benchmark for 2 L treatment of refractory LBCL patients.

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AUTHOR CONTRIBUTIONS

Andrea Kuhnl: Conceptualization; investigation; writing—original draft; methodology; visualization; data curation; supervision. **Amy A. Kirkwood**: Methodology; investigation; writing—original draft; data curation; formal analysis; software; validation; visualization; conceptualization. **Michael Northend**: Data curation; writing—review and editing. **Caroline Besley**: Data curation; writing—review and editing. **Ben Uttenthal**: Data curation; writing—review and editing. **Jane Norman**: Data curation; writing—review and editing. **Hwai Hiew**: Data curation; writing—review and editing. **Frances Seymour**: Data curation; writing—review and editing. **Bernard Maybury**: Data curation; writing—review and editing. **Wendy Osborne**: Data curation; writing—review and editing. **Francesca Sillito**: Data curation; writing—review and editing. **Ahmed Abdulgawad**: Writing—review and editing; data curation. **Ceri Jones**: Data curation; writing—review and editing. **Pierre McCarthy**: Data curation; writing—review and editing. **Aikaterini Panopoulou**: Data curation; writing—review and editing. **John G. Gribben**: Data curation; writing—review and editing. **Edward Bataillard**: Data curation; writing—review and editing. **Nicolas Martinez-Calle**: Data curation; writing—review and editing. **Lavanya Gajendran**: Data curation. **Maeve O'Reilly**: Data curation. **Emil Kumar**: Writing—review and editing. **Robert P. Wilson**: Data curation. **Shenbagaram Kasivisvanathan**: Data curation. **Nada Fadlelmula**: Data curation. **Angharad Pryce**: Data curation; writing—review and editing. **Olateni Awofisayo**: Data curation. **Adrian Maraj**: Data curation. **William Townsend**: Writing—review and editing. **Kate Cwynarski**: Writing—review and editing. **Shankara Paneesha**: Writing—review and editing. **Amrith Mathew**: Data curation. **Vaishali Dulobdas**: Writing—review and editing. **Dima El-Sharkawi**: Writing—review and editing. **Thomas Creasey**: Data curation; writing—review and editing. **Mary Warren**: Writing—review and editing. **Ram Malladi**: Writing—review and editing. **Mary Owen**: Writing—review and editing. **Muddeha Waraich**: Data curation. **Kushani Ediriwickrema**: Data curation; writing—review and editing. **Joseph Froggatt**: Data curation. **Alison Delaney**: Writing—review and editing. **Andrew J. Davies**: Writing—review and editing. **Rajesh Alajangi**: Writing—review and editing; data curation. **Graham P. Collins**: Writing—review and editing. **Robin Sanderson**: Writing—review and editing. **Claire Roddie**: Writing—review and editing. **Tobias Menne**: Data curation; writing—review and editing; methodology; conceptualization; investigation. **Sridhar Chaganti**: Data curation; writing—review and editing; conceptualization; investigation; writing—original draft; methodology.

CONFLICT OF INTEREST STATEMENT

A.K.: advisory boards and honoraria from Kite/Gilead, Novartis, AbbVie, Roche, BMS. A.A.K.: consultancy for BeOne Medicines and Kite/Gilead. M.N.: honoraria from Kite/Gilead. C.B.: honoraria from Novartis and Kite/Gilead. J.N.: advisory board and honoraria from Kite/Gilead. R.S.: advisory boards for Kite/Gilead. W.O.: advisory

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Deidentified clinical data can be made available upon request to the corresponding author.

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Additional supporting information can be found in the online version of this article.

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