






ORIGINAL PAPER

Haematological Malignancy – Clinical

Bridging practices prior to brexucabtagene autoleucel for mantle cell lymphoma in the United Kingdom: An analysis of modality, response, toxicity and survival

Maeve A. O'Reilly^{1,2}  | William Wilson³ | Bernard Maybury⁴ | Andrea Kuhn⁵  |
Claire Roddie^{1,2} | Ben Uttenthal⁶ | Rod Johnson⁷ | Rajesh Alajangi⁸ | Thomas Creasey⁹ |
Ahmed Abdulgawad¹⁰ | Carlos Gonzalez Arias¹¹  | Sunil Iyengar¹¹  |
Graeme Ferguson¹² | Katerina Panopoulou¹³ | Alison Delaney¹⁴ | Angharad Pryce¹⁵ |
Lourdes Rubio¹⁶ | Ceri Jones¹⁷ | Jonathan Lambert¹ | Shweta Gupta¹ | Amrith Mathew⁴ |
Shenbagaram Kasivisvanathan⁶ | Olateni Awofisayo⁷ | Shreyas Hanmantgad⁵ |
Graham P. Collins¹³ | Caroline Besley⁸ | Frances Seymour⁷  | Robin Sanderson⁵  |
Sridhar Chaganti⁴

Correspondence

Maeve A. O'Reilly, Department of
Haematology, University College London
Hospital, London, UK.
Email: maeve.o'reilly@ucl.ac.uk

Summary

Bridging therapy (BT) prior to brexucabtagene autoleucel (brexu-cel) in mantle cell lymphoma (MCL) is supported by limited evidence. Here, we report BT modality and outcome in 176 patients at 15 centres in the United Kingdom. BT was delivered to 90% (158/176), the majority receiving standard chemotherapy +/- radiotherapy (53%) (SD chemo +/- RT) or targeted therapy (TT) alone (23%). Clinicians favoured SD chemo +/- RT in those with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1, blastoid disease, bulk >5 cm and elevated lactate dehydrogenase. Overall response rate (ORR) was 46%. Higher ORR was observed with SD chemo +/- RT (58%), particularly R-BAC (64%). Progressive disease despite BT was associated with a lower ORR to brexu-cel (77% vs. 91%, $p=0.03$) and a higher risk of \geq grade 3 ICANS (OR 3.43, 95% CI 1.44–8.10, $p=0.01$). SD chemo +/- RT was associated with a higher incidence of \geq grade 3 neutropenia (Month 1), \geq grade 3 thrombocytopenia (Month 1, Month 3) and early non-relapse mortality (<90 days, 13% vs. 0%) compared to TT alone. Neither BT modality nor response impacted progression-free or overall survival post-infusion. Review of haematopoietic reserve prior to the selection of BT regimen, rigorous management of delayed cytopenia post-infusion and more effective and tolerable BT should be prioritised.

KEY WORDS

brexucabtagene autoleucel, bridging therapy, mantle cell lymphoma

For affiliations refer to page 10.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2026 The Author(s). *British Journal of Haematology* published by British Society for Haematology and John Wiley & Sons Ltd.

INTRODUCTION

Brexucabtagene autoleucel (brexu-cel) was granted conditional marketing authorisation by the European Medicines Agency (EMA) for mantle cell lymphoma (MCL) after ≥ 2 lines, including a Bruton's tyrosine kinase inhibitor (BTKi) (2020). ZUMA-2 reported overall response (ORR) and complete response (CR) rates of 93% and 67%, respectively, with 37% in ongoing response at median follow-up of 35.6 months.^{1,2} In the real world, progressive disease (PD) is the primary reason for drop out between approval and infusion,^{3–5} compromising intention-to-treat (ITT) outcomes. Those who fail to reach chimeric antigen receptor T-cell therapy (CAR T) infusion have a dismal overall survival (OS).^{3,4}

In ZUMA-2, bridging therapy (BT) was limited to a BTKi and/or steroids¹ and delivered to 37% of patients. In TRANSCEND NHL 001 (lisocabtagene maraleucel, liso-cel), BT was delivered to 66% of patients, the majority receiving systemic therapy (71%) or combined systemic and radiotherapy (RT) (24%).⁶ In contrast, 68%–90% of real-world patients receive BT prior to brexu-cel.^{3,4,7–9} BT strategies are at the discretion of the treating physician, tailored to individual circumstances and supported by limited evidence. An understanding of which patients may benefit and which strategies confer superior outcomes would be valuable.

Akin to large B-cell lymphoma (LBCL) where BT has been associated with adverse prognostic risk,^{10,11} BT in MCL has been associated with higher risk features such as high Ki-67, blastoid/pleomorphic variants and *TP53* aberrations.⁸ BT has also been associated with a higher incidence of \geq grade 3 ICANS⁸ and inferior expansion,⁹ potentially reflective of use in poorer risk candidates. Superior UK outcomes have been noted in LBCL patients achieving a CR or partial response (PR) to BT¹² with a 42% reduction in PD and death post-infusion. However, there are conflicting reports on the impact of BT in MCL.^{3,4,8}

With an ORR to BT ranging from 22% to 41%^{3,7,8} and compromised ITT outcomes, key components of the success of CAR T in MCL include (a) identification of the most effective BT strategies and patients most likely to benefit (b) an understanding of the impact of BT on outcome and (c) access to more effective BT. Here, we report BT outcomes for 176 patients harvested for third-line brexu-cel in the United Kingdom.

METHODS

Patients

Consecutive patients approved by the National CAR T Clinical Panel (NCCP) (or Scottish equivalent) from 15 UK centres (Table S1) between February 2021 and July 2024 were included (ITT cohort). Data were collected retrospectively (REC reference: 24/EM/0221, IRAS project ID: 336254). Treatment eligibility has been described.³

Definitions

BT included lymphoma-directed therapy between harvest and lymphodepletion with the intention of stabilising disease. Use and choice of BT was at the discretion of the treating physician. BT was categorised into (a) no bridging or steroids only, (b) targeted therapy (TT) (BTKi, BCL2 inhibitor), (c) RT +/- TT, (d) rituximab +/- low-dose chemotherapy and (e) standard chemotherapy +/- RT (SD chemo +/- RT). Low-dose chemo included gentle oral regimens, delivered in an outpatient setting. Standard chemo included intravenous (IV) treatment, often associated with neutropenia and/or hospital admission. Patients who received any SD chemo +/- RT after harvest were included the SD chemo +/- RT group regardless of sequencing. Fludarabine and cyclophosphamide lymphodepletion (LD) was administered as per manufacturer's instructions. American Society for Transplantation and Cellular Therapy consensus guidelines¹³ graded cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Severe and life-threatening infections were defined as requiring IV therapy or organ support/with symptoms of haemodynamic instability respectively.^{14–16} Organ function requirements, toxicity management and response assessments (Lugano 2014¹⁷) were determined locally.

Statistical analyses

Associations between pretreatment factors and choice of BT were assessed using Fisher's exact and Wilcoxon rank-sum tests for categorical and continuous variables respectively. Using univariate and multivariable logistic regression, associations were further examined for (a) SD chemo +/- RT and (b) TT alone. Response rates to BT and toxicity by type and response were compared using logistic regression. Kaplan–Meier and Cox regression assessed PFS and OS. Non-relapse mortality (NRM) was analysed using Fine and Gray (relapse a competing risk).

RESULTS

Patient characteristics

One hundred and seventy-six patients were harvested for brexu-cel and BT was delivered to 90% ($n = 158$) (Figure 1, Table 1). 53% and 23% received a standard chemotherapy regimen and TT alone respectively. >1 chemotherapy regimen and/or BT modality were administered to 10% with the remaining 90% receiving one cycle and/or modality. R-Bendamustine-containing regimens were the most common (70/176, 40%) (Table S2).

Compared to TT alone, patients who received SD chemo +/- RT were more likely to have ECOG PS of 1 (73% vs.

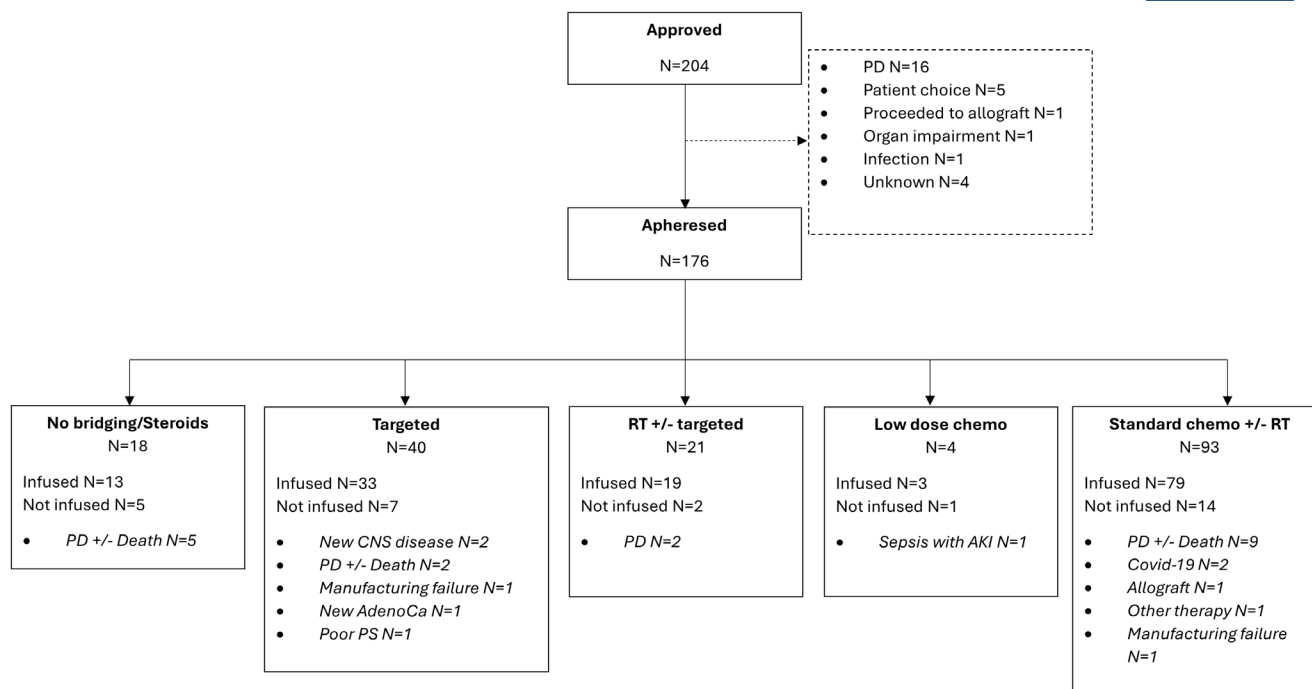


FIGURE 1 Intention-to-treat outcomes by type of bridging therapy.

45%, $p=0.003$), blastoid MCL (49% vs. 17%, $p=0.01$), bulk >5 cm (43% vs. 23%, $p=0.05$) and an elevated lactate dehydrogenase (LDH) (60% vs. 40%, $p=0.04$) (Table 1). In multivariable analysis (MVA), only ECOG PS 1 remained significantly associated with choice of SD chemo +/- RT over TT alone (OR=2.96, 95% CI 1.06–8.22, $p=0.04$) (Table S3).

BT response and CAR T infusion rates

BT response assessment was available in 97% ($n=154$). The ORR was 46% (71/154) with a CR rate of 12% (19/154). ORR was highest among those receiving SD chemo +/- RT (58%) compared to other modalities (OR=3.24, 95% CI 1.64–6.40, $p=0.001$) and lowest in TT alone (23%) (OR=0.25, 95% CI 0.11–0.59, $p=0.001$). Adjustment in MVA for ECOG PS, LDH, extra-nodal (EN) sites and bulk did not alter these findings (Table 2) with patients receiving SD chemo +/- RT almost four times more likely to respond [OR=3.79 (1.76–8.16), $p=0.001$].

When compared with other BT modalities, the use of rituximab, bendamustine and cytarabine (R-BAC) chemotherapy¹⁸ alone was associated with a significantly higher ORR (64%, CR 16%). Those receiving R-BAC were three times more likely to respond to BT (relative to other BT options) (OR=3.06, 95% CI 1.54–6.08, $p=0.001$). When compared with other SD chemo (excluding concomitant or sequential RT), the superior efficacy of R-BAC trended towards significance (OR=2.33, 95% CI 0.92–5.90, $p=0.07$). Although the ORR with TT alone was only 23%, more favourable ORRs

were noted in those who switched TT after approval ($n=13$) with an ORR of 58% (7/12 with response data). Other TT included venetoclax ($n=9$), venetoclax + ibrutinib ($n=2$) and pirtobrutinib ($n=2$).

No specific disease features such as BTKi refractoriness, subtype, progression of disease within 24 months of front-line therapy (POD24), bulk, TP53 mutation status or LDH were associated with response to BT. The only significant predictor of response was use of SD chemo +/- RT, with the strongest signal for R-BAC chemotherapy.

Of 176 apheresed patients, 147 (84%) received their infusion. Infusion rates did not differ by BT modality (Fisher's exact $p=0.5$) (Figure 1). Likewise, BT choice had no impact on time from harvest to cell infusion (Kruskal–Wallis $p=0.7$) (Figure S1). Median time from harvest to infusion for all was 38 days (range 26–271).

Best overall response to CAR T and survival by type and response to BT

The best ORR to CAR T was 87% (81% CR, 6% PR) with no demonstrable impact by BT modality. However, PD despite BT was associated with a lower ORR to CAR T compared with stable disease (SD), PR or CR to bridging (77% vs. 91%, $p=0.03$) (Table S4). Twelve-month PFS and OS rate for infused patients was 68% (95% CI 59–75) and 75% (95% CI 67–82) respectively. There were no significant differences between PFS and OS by type of BT (Figure 2A,B). Similarly, PFS and OS outcomes were unaffected by BT response (Figure 3A,B). Despite a significantly higher ORR to

TABLE 1 Patient demographics by modality of BT.

Characteristics	Bridging therapy				p value ^a					
	No bridging/ steroids only, N=18	Targeted, N=40	RT +/- targeted, N=21	Low-dose chemo, N=4	SD chemo +/- RT, N=93	None vs. targeted	None vs. RT +/- targeted	None vs. SD chemo +/- RT	Targeted vs. SD chemo +/- RT	RT +/- targeted vs. SD chemo +/- RT
Age, median (range)	66 (56-74)	67 (46-78)	69 (49-77)	69.5 (58-74)	68 (41-81)	0.980	0.413	0.334	0.416	0.843
Sex										
Female	3 (17%)	10 (25%)	7 (33%)	1 (25%)	19 (20%)	0.735	0.290	1	0.555	0.250
Male	15 (83%)	30 (75%)	14 (67%)	3 (75%)	74 (80%)					
ECOG at submission										
0	8 (44%)	22 (55%)	9 (43%)	1 (25%)	25 (27%)	0.573	1	0.169	0.426	0.193
1	10 (56%)	18 (45%)	12 (57%)	3 (75%)	66 (73%)					
Unknown	0	0	0	0	2					
sMPI at submission										
Low	3 (23%)	12 (32%)	4 (21%)	0	13 (16%)	0.783	0.658	0.849	0.605	0.383
Intermediate	4 (31%)	13 (34%)	9 (47%)	3 (75%)	27 (34%)					
High	6 (46%)	13 (34%)	6 (32%)	1 (25%)	40 (50%)					
Unknown	5	2	2	0	13					
HCT-CI at submission										
0	6 (43%)	19 (51%)	7 (44%)	4 (100%)	46 (52%)	0.700	1	0.739	0.922	0.768
1 or 2	6 (43%)	11 (30%)	6 (38%)	0	27 (30%)					
≥3	2 (14%)	7 (19%)	3 (19%)	0	16 (18%)					
Unknown	4	3	5	0	4					
Ki-67 at submission										
<30%	1 (10%)	5 (25%)	4 (24%)	0	9 (17%)	0.700	1	0.739	0.922	0.768
≥30%	9 (90%)	15 (75%)	13 (76%)	2 (100%)	45 (83%)					
Unknown	8	20	4	2	39					
Subtype at submission										
Blastoid	2 (15%)	4 (17%)	9 (50%)	0	35 (49%)	0.441	0.004	0.058	0.001	0.147
Classical	11 (85%)	15 (65%)	5 (28%)	2 (67%)	27 (38%)					
Leukaemic non-nodal	0	2 (9%)	0	0	4 (6%)					
Pleomorphic	0	2 (9%)	4 (22%)	1 (33%)	6 (8%)					
Unknown	5	17	3	1	21					

TABLE 1 (Continued)

		Bridging therapy					p value ^a					
		No bridging/ steroids only, N=18	Targeted, N=40	RT +/- targeted, N=21	Low-dose chemo, N=4	SD chemo +/- RT, N=93	None vs. targeted	None vs. RT +/- targeted	None vs. SD chemo +/- RT	Targeted vs. RT +/- targeted	Targeted vs. SD chemo +/- RT	RT +/- targeted vs. SD chemo +/- RT
Characteristics												
<i>TP53</i> mutation												
No <i>TP53</i> mutation	6 (67%)	7 (35%)	9 (75%)	1 (100%)	21 (60%)	0.226	1	1	0.066	0.097	0.492	
<i>TP53</i> mutation	3 (33%)	13 (65%)	3 (25%)	0	14 (40%)							
Unknown	9	20	9	3	58							
Stage at submission												
I-II	1 (6%)	4 (11%)	4 (20%)	1 (25%)	6 (7%)	0.685	0.055	0.208	0.198	0.435	0.107	
III	0	3 (8%)	4 (20%)	0	14 (15%)							
IV	16 (94%)	31 (82%)	12 (60%)	3 (75%)	71 (78%)							
Unknown	1	2	1	0	2							
History of CNS disease												
No	18 (100%)	40 (100%)	21 (100%)	4 (100%)	87 (95%)	N/A	N/A	0.589	N/A	0.322	0.582	
Yes	0	0	0	0	5 (5%)							
Unknown	0	0	0	0	1							
Bulk (>5 cm) at submission												
No	15 (88%)	30 (77%)	11 (58%)	4 (100%)	52 (57%)	0.473	0.065	0.015	0.218	0.047	1	
Yes	2 (12%)	9 (23%)	8 (42%)	0	39 (43%)							
Unknown	1	1	2	0	2							
LDH at submission, median (range)	238.5 (161-694)	227 (105-2233)	242 (149-393)	207.5 (150-251)	262.5 (120-3313)	0.293	0.939	0.403	0.326	0.012	0.398	
LDH at submission												
Normal	9 (50%)	24 (60%)	7 (39%)	2 (50%)	36 (40%)	0.571	0.738	0.442	0.163	0.037	1	
Elevated	9 (50%)	16 (40%)	11 (61%)	2 (50%)	55 (60%)							
Unknown	0	0	3	0	2							
EN sites at submission												
0	1 (6%)	10 (26%)	8 (42%)	1 (25%)	30 (33%)	0.156	0.060	0.070	0.499	0.871	0.799	
1	12 (71%)	15 (39%)	8 (42%)	2 (50%)	34 (37%)							
2	3 (18%)	8 (21%)	2 (11%)	1 (25%)	19 (21%)							

(Continues)

TABLE 1 (Continued)

Characteristics	Bridging therapy				p value ^a					
	No bridging/ steroids only, N=18	Targed, N=40	RT +/- targeted, N=21	Low-dose chemo, N=4	SD chemo +/- RT, N=93	None vs. targeted	None vs. RT +/- targeted	None vs. SD chemo +/- RT	Targeted vs. SD chemo +/- RT	RT +/- targeted vs. SD chemo +/- RT
3	1 (6%)	5 (13%)	1 (5%)	0	8 (9%)					
4	0	0	0	0	1 (1%)					
Unknown	1	2	2	0	1					
Prior lines, median (range)	2.5 (2-6)	2 (2-7)	2 (2-5)	3 (2-4)	2 (2-5)	0.121	0.305	0.146	0.684	0.670
Time to 1st line progression (POD24)										
>24 months	10 (59%)	12 (32%)	5 (28%)	2 (50%)	38 (42%)	0.081	0.092	0.288	1	0.326
≤24 months	7 (41%)	25 (68%)	13 (72%)	2 (50%)	52 (58%)					
Unknown	1	3	3	0	3					
Primary refractory (to all lines)										
No	17 (94%)	33 (85%)	17 (85%)	4 (100%)	87 (94%)	0.413	0.606	1	1	0.180
Yes	1 (6%)	6 (15%)	3 (15%)	0	6 (6%)					
Unknown	0	1	1	0	0					
Ibrutinib refractory										
No	14 (82%)	26 (65%)	14 (70%)	3 (75%)	63 (69%)	0.224	0.462	0.385	0.777	0.686
Yes	3 (18%)	14 (35%)	6 (30%)	1 (25%)	28 (31%)					1
Unknown	1	0	1	0	2					
Previous ASCT										
No	8 (44%)	26 (65%)	15 (75%)	2 (50%)	63 (68%)	0.162	0.096	0.067	0.560	0.841
Yes	10 (56%)	14 (35%)	5 (25%)	2 (50%)	30 (32%)					
Unknown	0	0	1	0	0					
Previous Allo-SCT										
No	15 (83%)	34 (85%)	18 (86%)	3 (75%)	87 (94%)	0.162	0.096	0.067	0.560	0.841
Yes	3 (17%)	6 (15%)	3 (14%)	1 (25%)	6 (6%)					

Abbreviations: Allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EN, extra-nodal; HCT-CI, Haematopoietic Cell Transplantation-specific Comorbidity Index; LDH, lactate dehydrogenase; SD, Standard; sMIP1, simplified MCL international prognostic index.

^aCalculated using Fisher's exact test and Wilcoxon rank-sum test.

TABLE 2 Response to BT by modality.

Response	Targeted, N=40	RT +/- targeted, N=21	Low-dose chemo, N=4	Standard chemo +/- RT, N=93
CR	3 (8%)	1 (5%)	0	15 (16%)
PR	6 (15%)	8 (38%)	1 (25%)	37 (40%)
SD	13 (33%)	4 (19%)	1 (25%)	14 (15%)
PD	17 (44%)	8 (38%)	2 (50%)	24 (26%)
Unknown (excluded)	1	0	0	3
ORR (95% CI)	23% (11–39)	43% (22–66)	25% (1–81)	58% (47–68)
Unadjusted	0.25 (0.11–0.59)	0.86 (0.34–2.17)	0.38 (0.04–3.75)	3.24 (1.64–6.40)
OR ^a (95% CI), <i>p</i> -value	<i>p</i> =0.001	<i>p</i> =0.7	<i>p</i> =0.4	<i>p</i> =0.001
Adjusted ^b OR ^a (95% CI), <i>p</i> -value	0.26 (0.11–0.65) <i>p</i> =0.004	0.62 (0.21–1.81) <i>p</i> =0.4	N/A	3.79 (1.76–8.16), <i>p</i> =0.001

Abbreviations: BT, Bridging therapy; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, Standard.

^aOdds ratios calculated using logistic regression comparing response (CR or PR) in each modality to all other modalities combined.

^bAdjusted for ECOG PS, elevated LDH, ≥ 3 EN sites and bulk >5 cm (at submission).

BT with SD chemo +/- RT compared to TT alone, no significant difference in survival post-infusion was observed (PFS HR = 1.78, 95% CI 0.85–3.71, *p* = 0.1; OS HR = 1.86, 95% CI 0.89–3.89, *p* = 0.1) (Figure S2a,b). On MVA, factors associated with inferior PFS post-infusion included history of CNS disease, POD24, elevated LDH and platelets $<75 \times 10^9/L$ (Table S5).

No difference in ORR to CAR T was observed in recipients nor responders to R-BAC alone (*n* = 58). PFS and OS post R-BAC BT were not significant on univariate analysis (UVA) nor MVA when adjusted for factors which likely influenced BT choice at submission (ECOG PS, bulk and LDH) (Figure 2C,D).

Toxicity by type and response to BT

Of 147 infused, 94% (*n* = 138) developed CRS with \geq grade 3 in 13% (*n* = 18, grade 5 *n* = 1). Factors associated with \geq grade 3 CRS on UVA included ECOG PS of 1 (17% vs. 5%, *p* = 0.04), ≥ 3 EN sites (42% vs. 10%, *p* = 0.01) and 2 (vs. 3) prior lines (17% vs. 4%, *p* = 0.03). Modality and response to BT had no impact on maximum grade (Figure S3a). However, those with PD despite BT (vs. SD/PR/CR) were more likely to require tocilizumab for CRS (30% vs. 9%, *p* = 0.04). ICANS occurred in 61% (*n* = 89) with \geq grade 3 in 24% (*n* = 35). While BT choice had no impact on maximum grade, patients with PD despite BT were over three times more likely to develop \geq grade 3 ICANS (OR 3.43 (95% CI 1.44–8.10), *p* = 0.01), occurring in 40% of those who progressed prior to infusion (Figure S3b). No other factors associated with \geq grade 3 ICANS were identified. BT choice and response had no impact on requirement for steroids or intensive care. 31% had a severe or life-threatening infection within 30 days. Neither BT modality nor response impacted this risk (Table S6).

\geq Grade 3 thrombocytopenia and neutropenia

Patients who received SD chemo +/- RT were more likely to experience \geq grade 3 thrombocytopenia at Month 1 (OR = 3.80, 95% CI 1.80–8.01, *p* < 0.001) and Month 3 (OR = 3.46, 95% CI 1.52–7.89, *p* = 0.003) versus other modalities combined. Those who received TT alone were less likely to have \geq grade 3 thrombocytopenia at Month 1 (OR = 0.17, 95% CI 0.07–0.40, *p* < 0.001) and Month 3 (OR = 0.25, 95% CI 0.08–0.80, *p* = 0.02) (Table S7a,b) versus other modalities combined.

Those who received SD chemo +/- RT were also more likely to experience \geq grade 3 neutropenia at Month 1 (OR = 2.22, 95% CI 1.09–4.55, *p* = 0.03) (vs. other modalities combined) but not at Month 3 (1.79, 95% CI 0.77–4.17, *p* = 0.2). Patients who received TT alone were less likely to experience \geq grade 3 neutropenia in Month 1 (OR = 0.41, 95% CI 0.18–0.93, *p* = 0.03) but no significant difference is seen at Month 3 (OR = 0.55, 95% CI 0.19–1.62, *p* = 0.3) (Table S7a,b). BT response had no impact on the incidence of \geq grade 3 neutropenia or thrombocytopenia.

Non-relapse mortality (NRM)

With median follow-up from infusion of 16 months (interquartile range (IQR) 9.2–25.8), TT had a lower cumulative NRM risk relative to no bridging (subhazard ratio (SHR) = 0.07, 95% CI 0.01–0.51, *p* = 0.009), rituximab +/- low dose chemo (SHR = 0.07, 95% CI 0.01–0.98, *p* = 0.05) and SD chemo +/- RT (SHR = 0.11, 95% CI 0.01–0.82, *p* = 0.03) (Figure S4a, Table S8a). Notably, patients bridged with TT and SD chemo +/- RT were more likely to be ECOG PS 0 and 1 at submission respectively (Table 1). Adjusted for ECOG PS, the lower cumulative NRM risk of TT versus SD chemo +/- RT still trended towards significance [SHR 0.13 (95% CI 0.02–1.07), *p* = 0.06]. NRM risk with R-BAC (vs. all other BT) did not reach significance (Figure S4b).

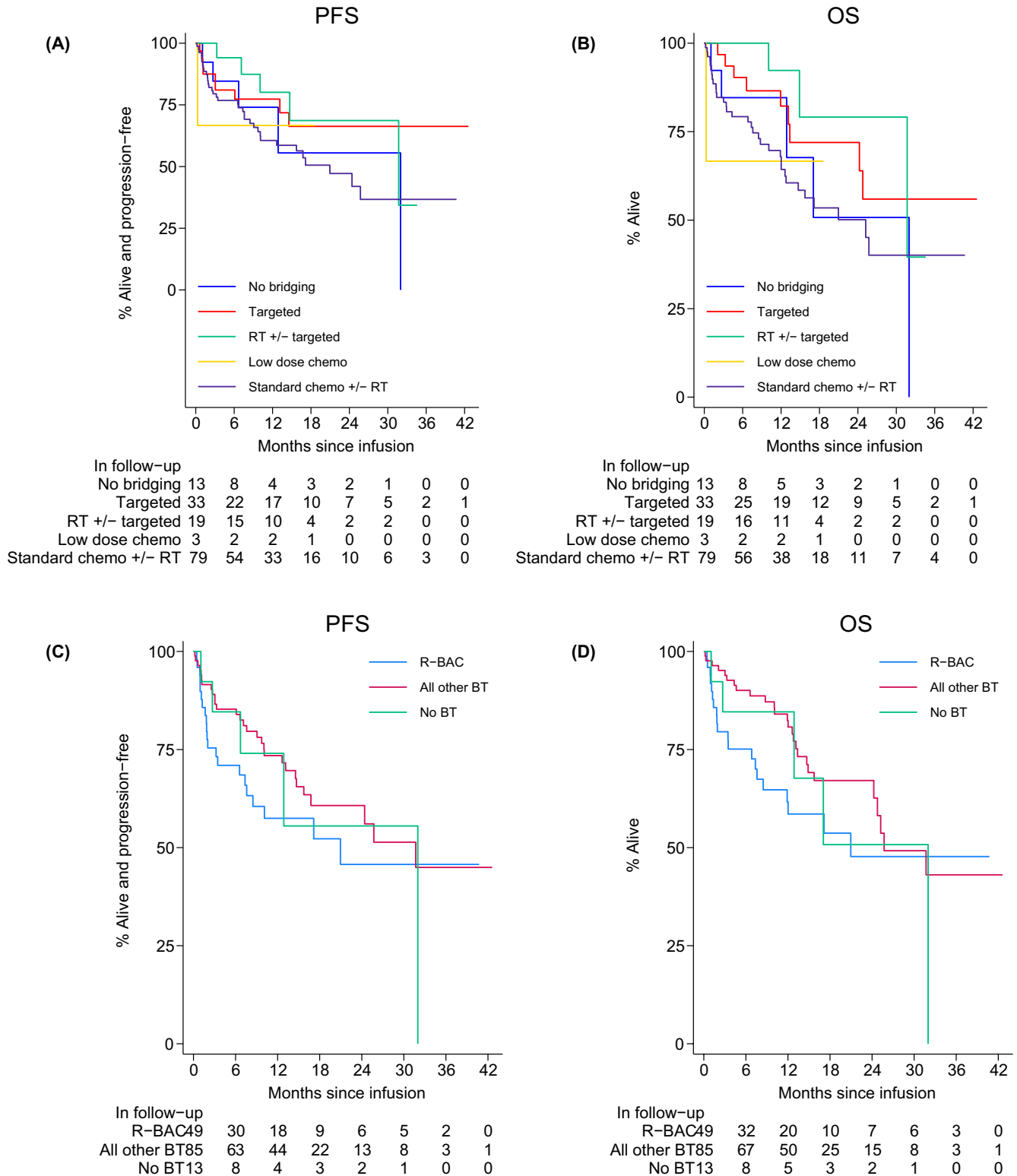


FIGURE 2 (A) Progression-free survival (PFS) by type of BT; (B) overall survival (OS) by type of BT. (C) Progression-free survival (PFS) post R-BAC BT and (D) overall survival (OS) post R-BAC BT. PFS (R-BAC vs. all other BT): UVA: Hazard ratio (HR) = 1.47 (95% CI 0.84–2.58), $p=0.2$; MVA: HR = 0.94 (0.51–1.71), $p=0.8$. OS (R-BAC vs. all other BT): UVA: HR = 1.60 (0.89–2.87), $p=0.1$; MVA: HR = 1.01 (0.54–1.89), $p>0.9$.

Patients receiving TT were also less likely to have an early NRM event (<90 days) (0%) relative to patients receiving more intensive regimens (13%) (Figure S4c, Table S8b). There was no difference in cumulative NRM (SHR = 1.10, 95% CI 0.48–2.50,

$p=0.8$) nor early NRM rates (10% [6/61] vs. 4% [4/63], $p=0.5$) between bridging responders and non-responders (Figure S5).

Other factors associated with early NRM included ECOG PS >1, elevated LDH, \geq grade 3 neutropenia at

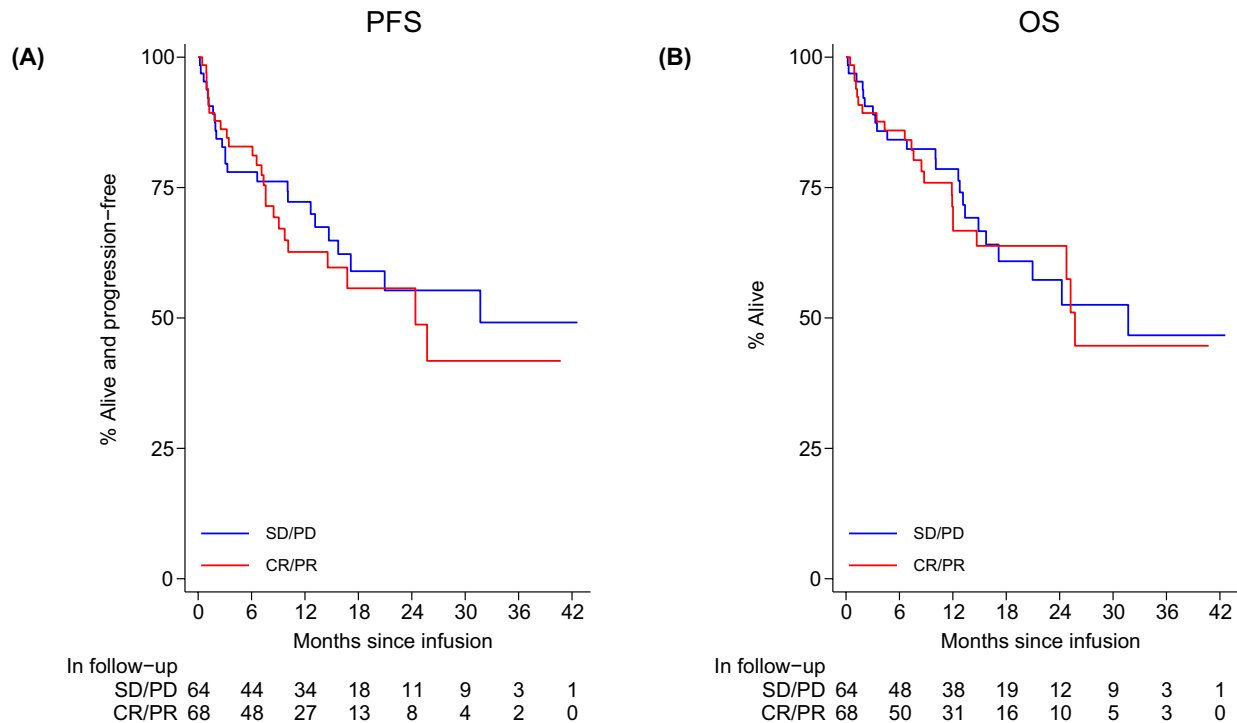


FIGURE 3 (A) Progression-free survival* (PFS) by response to BT and (B) overall survival* (OS) by response to BT. *Includes those who received BT with available response data. PFS CR/PR versus SD/PD HR = 1.14 (95% CI 0.65–2.01), $p = 0.6$, OS CR/PR versus SD/PD HR = 1.07 (95% CI 0.59–1.92), $p = 0.8$.

Month 1, severe or life-threatening infection and \geq grade 3 ICANS (Table S9). Of note, 10/13 early NRM events were recipients of SD chemo +/- RT and the majority (8/10, 80%) had not recovered their neutrophils to $>0.5 \times 10^9/L$ at death. Sepsis contributed to death in 63% (5/8) of cases (Table S10).

DISCUSSION

Aside from symptom control and patient stabilisation, rationale for BT in MCL has been extrapolated from LBCL where markers of burden and inflammation (LDH, bulk, metabolic tumour volume) appear to correlate with inferior efficacy and/or toxicity outcomes.^{12,19–23} Emerging data suggest that such variables may also compromise survival and/or safety in MCL.^{3,8,9,24} However, the evidence underpinning BT, knowledge of the relative efficacy of modalities and impact on outcome is limited. Although the French ($n = 152$) reported a superior 12-month OS for responders versus non-responders to BT (79.9% vs. 58%),⁴ United States ($n = 168$) and United Kingdom ($n = 83$), authors reported no impact of BT or BT response on survival.^{3,8}

90% of UK harvested patients received BT. With this majority, it was not possible to determine which factors influenced the decision to administer BT (vs. watch and wait). BT was highly heterogeneous and likely guided by disease burden and pace, prior therapy/sensitivity, physician

preference, patient fitness, haematopoietic reserve and access to novel therapies. Clinicians favoured SD chemo +/- RT in higher risk cases, with ECOG PS 1 the apparent main driver. The decision to deliver BT and/or more intensive BT in poorer risk candidates has been demonstrated in MCL⁸ and LBCL^{11,12} and may confound assessment of outcomes. Therefore, comparisons of SD chemo +/- RT versus other modalities in our analysis should be interpreted with caution.

PD constituted the primary reason for drop out between apheresis and infusion (20/29, 69%). 84% of harvested patients received their infusion and BT modality had no clear impact on the risk of drop out nor time to infusion. Median time from harvest to infusion was 38 days (range 26–271), longer than ZUMA-2 but comparable to US⁸ and European⁷ experiences. Reassuringly, there is no suggestion that adverse events secondary to BT increased morbidity or mortality pre-LD. Nevertheless, BT response rates remained suboptimal at 46%. Those receiving SD chemo +/- RT were almost four times more likely to respond with the strongest signal for R-BAC. The only clear predictor of response to BT was the use of SD chemo +/- RT. However, missing data on high-risk features such as subtype, *TP53* mutation status and Ki-67% may have limited this analysis. An alternative BTKi or a BCL-2 inhibitor may deliver more favourable responses but small numbers precluded further analysis.

PD despite BT was associated with a lower ORR to CAR T (91% vs. 77%, $p = 0.03$). This lower ORR may be the

consequence of higher burden at infusion or may reflect resistant disease biology. Regardless, our work supports the conclusion that neither use of nor response to BT impacts survival post brexu-cel. This is despite our observation that disease burden variables (bulk >5 cm, LDH, ECOG PS > 1 and ≥ 3 EN sites) were associated with PFS. Notably, 61% of patients with a radiological CR after BT had a persistently elevated LDH, potentially accounting for the lack of a survival benefit in BT-responders (Table S11). BT response was determined locally, primarily using PET-CT. Bone marrows were not routinely performed to confirm CRs. Therefore, rates of CR (albeit low at 12%) may have been overestimated. However, response to BT was defined as achievement of CR/PR, and hence, it is unlikely that many BT responders were misclassified.

PD despite BT was associated with more frequent use of tocilizumab and higher risk of \geq grade 3 ICANS. High-grade ICANS is of concern given the older median age in MCL, the higher incidence in elderly cohorts²⁵⁻²⁸ and the NRM signal.^{14,29} Risk of \geq grade 3 ICANS in BT non-responders has been reported and validated externally in LBCL.^{12,30} BT response had no impact on cumulative or early NRM risk. However, intensive regimens were associated with higher risk of early NRM (13%) versus TT (0%). The physician decision to administer an intensive regimen over TT is likely reflective of an adverse risk group. ECOG PS of 1 was significantly associated with choice of SD chemo +/- RT over TT. Although NRM risk for a more intensive regimen appeared to persist when adjusted for PS, there may be other factors contributing to higher NRM in such candidates. It should be acknowledged that intensive regimens were associated with a greater incidence of \geq grade 3 neutropenia at Month 1 and that this variable was also significant for early NRM. Vigilance and rigorous supportive care are required in the post-infusion period to reduce the risk of early mortality. Severe immune effector cell-associated haematotoxicity (ICAHT) is associated with higher incidence of severe infections, NRM and inferior survival outcomes.³¹ Rajeski et al. reported the increased incidence of severe ICAHT in MCL (brexu-cel, 28%) relative to other B-cell malignancies (LBCL 23%, myeloma 15%) and products. With adjusted analysis, marrow infiltration, ferritin and baseline cytopenia were associated with the severe phenotype of ICAHT.³¹ Clinicians should therefore be mindful that the selection of a BT regimen for MCL patients warrants careful consideration of haematopoietic reserve and inflammatory markers. If concern persists that a regimen may adversely affect the haematopoietic progenitor compartment but a response to BT is highly desirable, attenuated drug dosing can be considered. In the post-infusion period, early GCSF, anti-microbial prophylaxis and timely stem cell top up should be employed in select candidates. European Hematology Association/European Society for Blood and Marrow Transplantation consensus guidelines propose a treatment algorithm for ICAHT post CAR T.³²

Our work is limited by retrospective data and local review of response. Data on hematotox scores and ICAHT grading

were not collated. BT practices for brexu-cel in the United States may differ, influenced by turnaround times, FDA label for brexu-cel with no prerequisite for ≥ 2 lines and/or BTKi and approval of liso-cel. A differential survival outcome between products and BT response has been noted in LBCL.¹² Therefore, studies are needed to elucidate the impact of BT on safety and efficacy outcomes post liso-cel.

With CAR T preferred for eligible MCL patients at ≥ 3 rd line, new BT strategies are needed to minimise drop-out. Pirtobrutinib, with an ORR of 57% in covalent BTKi-exposed, may be a well-tolerated and attractive option.³³ Likewise, T-cell engagers represent another emerging agent but are not yet accessible outside of clinical trials.³⁴ The incorporation of BTKi's into front-line therapy may modify future treatment pathways.³⁵

In summary, standard chemotherapy regimens (particularly R-BAC) are more likely to deliver a response prior to brexu-cel. Those who responded to BT had a higher ORR to CAR T and lower risk of high-grade ICANS, but no survival benefit was observed. Controlling disease with the least toxic regimen should be the goal of BT. Careful review of haematopoietic reserve prior to the selection of a BT regimen, rigorous supportive care for those with delayed cytopenia post-infusion and more effective and tolerable BT strategies should be prioritised.

AUTHOR CONTRIBUTIONS

Maeve A. O'Reilly: Conceptualisation, supervision, data curation and writing the original draft. William Wilson: Conceptualisation, formal analysis, data curation and writing the original draft. Bernard Maybury, Andrea Kuhn, Claire Roddie, Ben Uttenthal, Rod Johnson, Rajesh Alajangi, Thomas Creasey, Ahmed Abdulgawad, Carlos Gonzalez Arias, Sunil Iyengar, Graeme Ferguson, Katerina Panopoulou, Alison Delaney, Angharad Pryce, Lourdes Rubio, Ceri Jones, Jonathan Lambert, Shweta Gupta, Amrith Mathew, Shenbagaram Kasivisvanathan, Olateni Awofisayo, Shreyas Hanmantgad, Graham P. Collins, Caroline Besley, Frances Seymour, Robin Sanderson, Sridhar Chaganti: Data curation, writing, review and editing.

AFFILIATIONS

¹Department of Haematology, University College London Hospital, London, UK

²Department of Haematology, University College London Cancer Institute, London, UK

³Cancer Research UK and University College London Cancer Trials Centre, London, UK

⁴Department of Haematology, University Hospital Birmingham, Birmingham, UK

⁵Department of Haematology, Kings College Hospital, London, UK

⁶Department of Haematology, Cambridge University Hospital, Cambridge, UK

⁷Department of Haematology, Leeds Teaching Hospital, Leeds, UK

⁸Department of Haematology, University Hospital Bristol, Bristol, UK

⁹Department of Haematology, Newcastle upon Tyne Hospitals, Newcastle, UK

¹⁰Department of Haematology, The Christie NHS Foundation Trust, Manchester, UK

¹¹Department of Haematology, The Royal Marsden Hospital, London, UK

¹²Department of Haematology, Queen Elizabeth University Hospital, Glasgow, Scotland, UK

¹³Department of Haematology, Oxford University Hospital, Oxford, UK

¹⁴Department of Haematology, Sheffield Teaching Hospital, Sheffield, UK

¹⁵Department of Haematology, University Hospital Southampton, Southampton, UK

¹⁶Department of Haematology, Manchester Royal Infirmary, Manchester, UK

¹⁷Department of Haematology, Cardiff and Vale University Health Board, Cardiff, UK

ACKNOWLEDGEMENTS

MOR and CR acknowledge support of the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre.

FUNDING INFORMATION

No funding received.

CONFLICT OF INTEREST STATEMENT

MOR: honoraria from Kite Gilead, Novartis and Janssen. Advisory boards Kite Gilead and Autolus. Conference/travel support Kite Gilead. WW: No COI. BM: Conference support Kite Gilead. AK: Advisory boards and honoraria from Kite/Gilead, Novartis, Abbvie, Roche and BMS. CR: Advisory boards and speakers fees Novartis, Kite Gilead, BMS, Amgen, Autolus. BU: No COI. RJ: No COI. RA: No COI. TC: No COI. AA: No COI. CA: No COI. SI: conference support Beigene, BMS, Takeda. Speaker fees Kite Gilead, Takeda. Advisory boards Kite, MSD. GF: Course funding Abbvie. KP: No COI. AD: Advisory board and sponsorship for conference (Kite Gilead) and speaker fees (Roche and Abbvie). AP: No COI. LR: No COI. CJ: No COI. JL: No COI. SG: No COI. AM: No COI. SK: No COI. OA: No COI. SH: No COI. GC: Kite Gilead speaker fees, advisory board. CB: Honoraria Kite, Janssen, Novartis and Takeda. FS: No COI. RS: Kite Gilead speakers bureau, honoraria, conference travel, Novartis speakers bureau, honoraria, conference travel. SC: honoraria from Takeda, Kite/Gilead, Incyte, AbbVie, Pierre Fabre: F. Hoffmann-La Roche Ltd., Atara Bio, Orion Pharma, Adicet Bio, Incyte, Novartis, Amgen, Sobi, Pierre Fabre, BMS-Celgene and Miltenyi Biotec and meeting attendance support from Takeda, Kite-Gilead, Abbvie and Pierre Fabre.

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.

ETHICS STATEMENT

REC reference: 24/EM/0221, IRAS project ID: 336254.

PATIENT CONSENT

Consent acquired for use of data.

ORCID

Maeve A. O'Reilly  <https://orcid.org/0000-0002-2702-397X>

Andrea Kuhn  <https://orcid.org/0000-0002-4952-2550>

Carlos Gonzalez Arias  <https://orcid.org/0000-0002-4988-309X>

[org/0000-0002-4988-309X](https://orcid.org/0000-0002-4988-309X)

Sunil Iyengar  <https://orcid.org/0000-0003-4863-4160>

Frances Seymour  <https://orcid.org/0000-0002-0887-7195>

Robin Sanderson  <https://orcid.org/0000-0003-4915-2833>

REFERENCES

- Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331–42.
- Wang M, Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. *J Clin Oncol*. 2022;41:555–67.
- O'Reilly MA, Wilson W, Burns D, Kuhn A, Seymour F, Uttenthal B, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: a real-world intention-to-treat analysis. *HemaSphere*. 2024;8:e87.
- Herbaux C, Bret C, Bachy E, Bories P, Di Blasi R, Cuffel A, et al. Brexucabtagene autoleucel in relapsed or refractory mantle cell lymphoma, intention-to-treat use in the DESCAR-T registry. *Haematologica*. 2024;109:3745.
- Battiwalla M, Tees M, Flinn I, Pantin J, Berdeja J, Gregory T, et al. Access barriers to anti-CD19+ CART therapy for NHL across a community transplant and cellular therapy network. *Blood Adv*. 2025;9:429–35.
- Wang M, Siddiqi T, Gordon LI, Kamdar M, Lunning M, Hirayama AV, et al. Lisocabtagene maraleucel in relapsed/refractory mantle cell lymphoma: primary analysis of the mantle cell lymphoma cohort from TRANSCEND NHL 001, a phase I multicenter seamless design study. *J Clin Oncol*. 2024;42:1146–57.
- Iacoboni G, Rejeski K, Villacampa G, van Doesum J, Chiappella A, Bonifazi F, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. 2022;6:3606–10.
- Wang Y, Jain P, Locke FL, Maurer MJ, Frank MJ, Munoz JL, et al. Brexucabtagene Autoleucel for relapsed or refractory mantle cell lymphoma in standard-of-care practice: results from the US lymphoma CAR T consortium. *J Clin Oncol*. 2023;41:2594–606.
- Stella F, Chiappella A, Magni M, Bonifazi F, de Philippis C, Musso M, et al. Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: results from CART-SIE study. *Br J Haematol*. 2025;206:644–51.
- Pinnix C, Gunther JR, Dabaja BS, Strati P, Fang P, Hawkins MC, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood Adv*. 2020;4(13):2871–83.
- Jain MD, Jacobs MT, Gao F, Nastoupil LJ, Spiegel JY, Lin Y, et al. Bridging therapy with axicabtagene ciloleucel for large B-cell lymphoma: results from the US lymphoma CAR-T consortium. *Blood Adv*. 2024;8(4):1042–50.
- Roddie C, Neill L, Osborne W, Iyengar S, Tholouli E, Irvine D, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. *Blood Adv*. 2023;7(12):2872–83.
- Lee DW, Santomaso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2018;25:625–38.
- O'Reilly MA, Neill L, Collin SM, Stone N, Springell D, Mensah J, et al. High pretreatment disease burden as a risk factor for infectious complications following CD19 chimeric antigen receptor T-cell therapy for large B-cell lymphoma. *Hema*. 2024;8:e29.
- Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor–modified T-cell immunotherapy. *Blood*. 2018;131:121–30.
- Young J-AH, Logan BR, Wu J, Wingard JR, Weisdorf DJ, Mudrick C, et al. Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. *Biol Blood Marrow Transplant*. 2016;22:359–70.
- Cheson BD, Richard F I, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–67.
- McCulloch R, Visco C, Eyre TA, Frewin R, Phillips N, Tucker DL, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *Br J Haematol*. 2020;189:684–8.
- Vercellino L, di Blasi R, Kanoun S, Tessoulin B, Rossi C, D'Aveni-Piney M, et al. Predictive factors of early progression after CAR T-cell

- therapy in relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv.* 2020;4:5607–15.
20. Kuhn A, Roddie C, Kirkwood AA, Tholouli E, Menne T, Patel A, et al. A national service for delivering CD19 CAR-T in large B-cell lymphoma—the UK real-world experience. *Br J Haematol.* 2022;198:492–502.
 21. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US lymphoma CAR T consortium. *J Clin Oncol.* 2020;38:3119.
 22. Locke FL, Oluwale OO, Kuruvilla J, Thieblemont C, Morschhauser F, Salles G, et al. Axicabtagene ciloleucel vs standard of care in second-line large B-cell lymphoma: outcomes by metabolic tumor volume. *Blood.* 2024;143:2464–73.
 23. Keijzer K, de Boer JW, van Doesum JA, Noordzij W, Huls GA, van Dijk LV, et al. Reducing and controlling metabolic active tumor volume prior to CAR T-cell infusion can improve survival outcomes in patients with large B-cell lymphoma. *Blood Cancer J.* 2024;14:41.
 24. Rejeski K, Wang Y, Albanyan O, Munoz J, Sesques P, Iacoboni G, et al. The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene autoleucel for relapsed or refractory MCL. *Am J Hematol.* 2023;98:1699–710.
 25. Jacobson CA, Locke FL, Ma L, Asubonteng J, Hu Z-H, Siddiqi T, et al. Real-world evidence of Axicabtagene Ciloleucel for the treatment of large B-cell lymphoma in the United States. *Transplant Cell Ther.* 2022;28:581.e1–581.e8.
 26. Rubin DB, Al Jarrah A, Li K, LaRose S, Monk AD, Ali AB, et al. Clinical predictors of neurotoxicity after chimeric antigen receptor T-cell therapy. *JAMA Neurol.* 2020;77:1536–42.
 27. Mirza A-S, Hosing C, Foss FM, Kim S, Moskop A, Oloyede T, et al. Impact of age on outcomes after CD19 directed CAR T cell therapy for large B cell lymphomas: real world experience from the Center for International Blood & Marrow Transplant Research (CIBMTR). *Blood.* 2022;140:4633–5.
 28. Santomaso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov.* 2018;8:958–71.
 29. dos Santos DMC, Tix T, Shouval R, Gafter-Gvili A, Alberge J-B, Cliff ER, et al. Non-relapse mortality after CAR T-cell therapy: a systematic review and meta-analysis of 7,604 lymphoma and myeloma patients. *Nat Med.* 2024;30:2667–78.
 30. Sesques P, Sesques P, Kirkwood AA, Kwon M, Rejeski K, Jain MD, et al. Novel prognostic scoring systems for severe CRS and ICANS after anti-CD19 CAR T cells in large B-cell lymphoma. *J Hematol Oncol.* 2024;17:61.
 31. Rejeski K, Wang Y, Hansen DK, Iacoboni G, Bachy E, Bansal R, et al. Applying the EHA/EBMT grading for ICAHT after CAR-T: comparative incidence and association with infections and mortality. *Blood Adv.* 2024;8:1857–68.
 32. Rejeski K, Subklewe M, Aljurf M, Bachy E, Balduzzi A, Barba P, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. *Blood.* 2023;142:865–77.
 33. Wang ML, Jurczak W, Zinzani PL, Eyre TA, Cheah CY, Ujjani CS, et al. Pirtobrutinib in covalent Bruton tyrosine kinase inhibitor pre-treated mantle-cell lymphoma. *J Clin Oncol.* 2023;41:3988–97.
 34. Phillips TJ, Carlo-Stella C, Morschhauser F, Bachy E, Crump M, Trněný M, et al. Glofitamab in relapsed/refractory mantle cell lymphoma: results from a phase I/II study. *J Clin Oncol.* 2025;43:318–28.
 35. Dreyling M, Doorduijn J, Giné E, Jerkeman M, Walewski J, Hutchings M, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European mantle cell lymphoma network. *Lancet.* 2024;403:2293–306.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: O'Reilly MA, Wilson W, Maybury B, Kuhn A, Roddie C, Uttenthal B, et al. Bridging practices prior to brexucabtagene autoleucel for mantle cell lymphoma in the United Kingdom: An analysis of modality, response, toxicity and survival. *Br J Haematol.* 2026;00:1–12. <https://doi.org/10.1111/bjh.70357>