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Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma

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Abstract:
The impact of bridging therapy (BT) on CD19-directed chimeric antigen receptor T-cell (CD19CAR-T) outcomes in large B-cell lymphoma (LBCL) is poorly characterised. Current practice is guided by physician preference rather than established evidence. Identification of effective BT modalities and factors predictive of response could improve CAR-T intention to treat and clinical outcomes. We assessed BT modality and response in 375 adult LBCL patients in relation to outcomes following axicabtagene ciloleucel (Axi-cel) or tisagenlecleucel (Tisa-cel). The majority of patients received BT with chemotherapy (57%) or radiotherapy (17%). We observed that BT was safe for patients, with minimal morbidity/mortality. We showed that complete or partial response to BT conferred a 42% reduction in disease progression and death following CD19CAR-T therapy. Multivariate analysis identified several factors associated with likelihood of response to BT, including response to last line therapy, the absence of bulky disease, and the use of Polatuzumab-containing chemotherapy regimens. Our data suggested that complete/partial response to BT may be more important for Tisa-cel than Axi-cel, as all Tisa-cel patients with less than partial response to BT experienced frank relapse within 12 months of CD19CAR-T infusion. In summary, BT in LBCL should be carefully planned towards optimal response and disease debulking, to improve CD19CAR-T patient outcomes. Polatuzumab-containing regimens should be strongly considered for all suitable patients, and failure to achieve complete/partial response to BT pre-Tisa-cel may prompt consideration of further lines of BT where possible.

Conflict of interest: COI declared - see note

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ABSTRACT:

The impact of bridging therapy (BT) on CD19-directed chimeric antigen receptor T-cell (CD19CAR-T) outcomes in large B-cell lymphoma (LBCL) is poorly characterised. Current practice is guided by physician preference rather than established evidence. Identification of effective BT modalities and factors predictive of response could improve CAR-T intention to treat and clinical outcomes. We assessed BT modality and response in 375 adult LBCL patients in relation to outcomes following axicabtagene ciloleucel (Axi-cel) or tisagenlecleucel (Tisa-cel). The majority of patients received BT with chemotherapy (57%) or radiotherapy (17%). We observed that BT was safe for patients, with minimal morbidity/mortality. We showed that complete or partial response to BT conferred a 42% reduction in disease progression and death following CD19CAR-T therapy. Multivariate analysis identified several factors associated with likelihood of response to BT, including response to last line therapy, the absence of bulky disease, and the use of Polatuzumab-containing chemotherapy regimens. Our data suggested that complete/partial response to BT may be more important for Tisa-cel than Axi-cel, as all Tisa-cel patients with less than partial response to BT experienced frank relapse within 12 months of CD19CAR-T infusion. In summary, BT in LBCL should be carefully planned towards optimal response and disease debulking, to improve CD19CAR-T patient outcomes. Polatuzumab-containing regimens should be strongly considered for all suitable patients, and failure to achieve complete/partial response to BT pre-Tisa-cel may prompt consideration of further lines of BT where possible.

KEY POINTS:

- Bridging therapy (BT) is safe, and complete/partial response to BT confers a 42% reduction in risk of progression/death post–CD19CAR-T.
- Good response to BT is twice as likely with polatuzumab than with other modalities and is particularly important for Tisa-cel outcomes.

KEYWORDS:

CAR T cells, large B cell lymphoma, bridging, Polatuzumab

For data sharing, contact the corresponding author: c.roddie@ucl.ac.uk.

INTRODUCTION:

Chimeric Antigen Receptor T-cell (CAR-T) therapy confers durable responses in 30-40% of patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL)[1,2,3,4,5], leading to FDA approval of Tisagenlecleucel (Tisa-cel), Axicabtagene ciloleucel (Axi-cel), and Lisocabtagene Maraleucel.

Bridging Therapy (BT) is the anti-cancer therapy administered to patients during the CAR-T manufacture period. Intention to treat with CAR-T is compromised by poor disease control during this period, and dismal prognosis is reported for patients failing to reach CAR-T infusion[1]. 92% of patients on the Juliet study[2] and approximately 80% of real-world cohorts received BT[6–9], but current practice is guided by patient and physician preferences rather than published evidence[2,10,11]. Algorithms to identify which patients are likely to benefit from BT and which strategies[12,13,14] confer best CAR-T outcomes would be clinically valuable.

Retrospective analyses suggesting worse CAR-T outcomes in bridged patients[15–18] also found an association between BT and high-risk baseline disease factors, indicating a selection bias towards more intensive BT for patients with aggressive disease. More recently, several groups have described the deleterious impact of high tumour burden pre-CAR-T infusion[19–21] with the result that many clinicians are moving towards more intensive BT practices for tumour debulking purposes pre-CAR-T.

In some patients, BT unexpectedly leads to complete response (CR)[22]. Limited published data on CAR-T efficacy and toxicity in the absence of measurable disease, and a lack of clarity around minimum tumour burden/antigen threshold requirements for effective CAR-T therapy means that physicians frequently defer CAR-T infusion in this setting. However, emerging evidence suggests good outcomes in patients proceeding to CAR-T in CR[23].

Here we report outcomes of BT in 375 adult r/r LBCL patients undergoing leukapheresis for Axi-cel or Tisa-cel. The objectives of the study were to identify which patients respond to BT (including those who achieve CR to BT and proceed to CAR-T infusion), and a comparison of the impact of BT on CAR-T safety and efficacy outcomes between Axi-cel and Tisa-cel treated patient groups.

METHODS:

Patients

As part of a National Service Evaluation, data were collected retrospectively from electronic medical records for consecutive patients with r/r LBCL submitted to the UK National CAR Clinical Panel (NCCP) for approval of treatment with licenced CD19CAR-T at commissioned CAR-T centres. An

additional 12 patients approved by the NCCP equivalent Scottish CAR-T centre using similar eligibility criteria were included[1]

Bridging therapy (BT)

BT was defined as lymphoma-directed therapy administered between leukapheresis and lymphodepletion (LD). BT was subdivided into none (no BT), corticosteroids alone, chemotherapy (CT); radiotherapy (RT), and combined-modality therapy (CMT) i.e. CT + RT. CT was further categorised into high-dose chemotherapy (HDT), low-dose chemotherapy (LDT) and Rituxamab-Bendamustine-Polatuzumab (RBP)[14,]. HDT is defined as regimens that are delivered intravenously, many of which are conventionally used in LBCL patients fit for autologous stem cell transplant and are associated with periods of neutropenia and in some cases a requirement for hospital admission. HDT was subdivided into gemcitabine-based (HDT-Gem), ifosphamide-based (HDT-Ifos), and other (HDT-Other).

LDT bridging was defined as either oral treatments or intravenous regimens not considered to be conventional LBCL salvage e.g. single agent Rituximab, Rituximab-Bendamustine. Definitions and details of BT modalities are listed in Supplementary Table 1 . If patients received≥1 line of BT (N=9), the final regimen was used for this analysis. Patients achieving CR to BT could proceed to CAR-T infusion at the discretion of the CAR-T centre.

Statistics

Pre-treatment factors were compared using Wilcoxon Mann-Whitney/Kruskal Wallis (non-normally distributed continuous variables) or Chi-squared/Fisher's exact tests (discreate variables). Progression-free survival (PFS) and overall survival (OS) were analysed using Kaplan-Meier survival analysis, Cox regression and the log rank test. Time was measured from the date of infusion until the first event. Non-relapse mortality was analysed using the method of Fine and Grey with relapse treated as a competing event. Logistic regression was used to compare baseline characteristics and response to bridging. All analyses were performed using STATA version 16.1 (STATACORP, Texas)**.**

RESULTS:

Demographics and BT for all leukapheresed patients

Between December 2018 and November 2020, 375 UK patients with r/r LBCL underwent leukapheresis for CD19CAR-T, and 87% (326/375) received BT (Figure 1). The majority received CT bridging and of these, most received a single cycle (148/194; 76.3%) (Sup. Table 1).

Baseline demographics for all leukapheresed and infused patients according to BT modality are illustrated in Table 1 and Sup. Table 2. CT-bridged patients were significantly more likely than non-BT patients to have stage III/IV disease (84.4% vs 69.9%, p=0.033), more extranodal disease (≥1 site: 72.3% vs 41%, p<0.001), and have an ECOG of 1 rather than 0 (62.4% vs 36.7%, p=0.001). RT-bridged patients had significantly less stage III/IV disease (p=0.024), lower LDH (p=0.039), and less extranodal disease (p=0.041) than CT patients. Only 16 patients received CMT bridging, but baseline characteristics were similar to the CT group.

HDT (compared with LDT) was delivered to younger patients (median 53y vs 65y, p=0.0016), to those with advanced stage (Stage III/IV, 91.7% vs 78.4%, p=0.029) and to 'rapid progressors' i.e. patients in whom life expectancy without response to BT was predicted to be <3 months by clinicians (74.5% vs 41.7%, p<0.001). RBP patients were also older and had higher HCT-CI scores (15.8% vs 4.8% ≥3 p=0.015) compared to the HDT group (Sup. Table 3).

BT selection evolved towards more intensive approaches in 2019/2020 compared with 2018/2019. CT (64.0% vs 51.2%) and RT (19.9% vs 14.7%) were increasingly used, with a concomitant reduction in corticosteroids alone (1.8% vs 15.2%) and no BT (10.4% vs 15.2%) (Sup. Table 4). RBP became the CT regimen of choice (68.1% vs 6.1%) through the Early Access to Medicines Scheme (EAMS) from June 2019 onwards. Patient selection also evolved in 2019/2020 to increasingly include older patients (median 62.5y vs 58y, p=0.011), those unfit for auto-SCT (23.8% vs 15.6%, p=0.047), and patients with primary refractory disease (i.e. refractory to R-CHOP)/ 'never responders'(i.e. refractory to all lines of therapy pre-CAR-T) (49.7% vs 38.6%, p=0.036), likely reflecting access to RBP as a tolerable and effective BT, and clinicians growing confidence and familiarity with delivery of CAR-T.

Response to BT and impact on CAR-T infusion rates

Overall response rates (ORR) to BT were higher with RT and RBP (65% and 42% respectively), compared with LDT (18%), HDT (29%) and CMT (33%) (Table 2). Overall, 23 patients achieved CR to BT: 4 following RT and 19 following CT (RBP in 11/19 cases), and 13 and 8 were infused with Axi-cel and Tisa-cel respectively. Failure to reach CAR-T infusion was higher in HDT patients than in other cohorts (30% vs 13-18%), largely due to progressive disease (PD), central nervous system relapse or death. Only 6 patients in total (RT, N=1; CT, N=4; CMT, N=1) died of non-PD causes, mostly infection (5/6 cases). The interval between leukapheresis and infusion was not significantly different between BT cohorts, but significant delays of 8/more weeks were most commonly ascribed to AEs (N=11) and COVID-19 (N=10) and were more frequent in BT patients (Table 2).

CAR-T toxicity according to BT and response to BT

No difference in cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), use of Tocilizumab/corticosteroids or ICU admission was observed across BT cohorts (Table 3; Sup. Table 5). Rates of ≥G3 thrombocytopenia at 1-month post-CAR-T differed by BT type (p<0.001), with the highest incidence observed in CT-bridged patients (56.0%) compared to no BT (20.6%) and other BT groups (10-31.9%). There was a higher incidence of ≥G3 neutropenia at month 1 in BT vs no BT groups (40-45% vs 27.3%; p=0.051), and within the CT-bridged group, rates of both were highest in HDT-bridged patients compared with LDT and RBP-bridged patients (p=0.012 and p=0.002). There were no significant differences by month 3.

BT was not associated with increased non-relapse mortality (NRM) (Sup. Figures 1a-b; Table 3). In particular, CT-bridged patients had similar NRM rates at 1 year to those who did not receive BT (9.4% vs 8.0%). Landmark analyses showed a significant association between thrombocytopenia at 1 month and higher NRM, but not inferior progression-free survival (PFS) (Sup. Figures 1c-d). No significant difference in NRM was observed for neutropenia at 1 or 3 months.

Despite a reduction in tumour burden, there was no significant difference in the incidence of ≥G3 CRS, the use of Tocilizumab or ICU admission in patients with CR/PR post-BT compared with non-responders. In contrast, the incidence of ≥G3 ICANS was significantly higher in BT-non-responders than in patients achieving CR/PR (21.7% vs 9.5%/6%, p=0.005), but corticosteroid use was similar between these groups (CR=45.2%; non-responder=42.9%) (Sup. Table 6).

CAR-T efficacy according to BT and response to BT

ORR to CAR-T at 3 months according to BT modality appears to show differences: RT, 64.8%; no BT, 55%; CMT, 45.5%; CT, 44.6%, and corticosteroids-alone, 27.6% The same pattern was also observed in PFS and overall survival (OS) (Figures 2ab and Sup Figures 2a-b).

Amongst BT patients (excluding corticosteroids-only) post-BT CR/PR vs non-response was associated with a 1-year PFS of 50.1% vs 29.7% (HR: 0.55 (95% CI: 0.39 – 0.79, p=0.001), and a 1-year OS of 63.2% c.f. 45.9% (HR: 0.51 (95% CI: 0.33 0 0.77), p=0.001) (Figures 2c-d). PFS and OS benefit were similar between patients achieving CR and PR (data not shown).

Response to bridging was included in a multivariable analysis along with other pre-treatment factors to investigate its association with post CAR-T PFS. This identified a 42% reduction in the risk of progression or death for patients with CR/PR to BT compared with non-responders (Table 4). Whilst response to BT was prognostic, BT modality was not, as responders did well regardless of how the response was achieved (interaction p=0.44 for RT/CT/CMT; p = 0.70 for CT type). Although a

reasonable effect size was still seen in MVA for OS (0.61 vs 0.51 in univariate analysis (UVA)), this did not reach significance.

Impact of response to BT on Axi-cel vs Tisa-cel outcomes

Of the CAR-T infused patients, 224/300 (74.7%) received Axi-cel and 76/300 (25.3%) received Tisa-cel. Tisa-cel patients were significantly older and were significantly less likely to have bulky disease and/or low lymphocytes[1]. Evaluation of PFS in Axi-cel vs Tisa-cel treated patients shows a significant interaction (p=0.006) between product and response to BT Figures 3a-b). For Axi-cel, the effect was smaller, and did not reach significance (HR: 0.68 (0.45 – 1.03), p=0.071), but for Tisa-cel, non-response to BT (N=23) was associated with disease relapse within 12 months in all patients (HR: 0.22 (0.11 – 0.44), p<0.001). Analysis of BT non-responders showed that Tisa-cel patients were significantly less likely than Axi-cel patients to achieve a response to CAR-T at 1, 3 and 6 months post-infusion (Sup. Table 7). A comparison of baseline patient and disease characteristics of CAR-T-infused BT non-responders shows a trend towards Tisa-cel patients being older and less likely to have bulky disease, but without clear identifiers for heightened risk of relapse (Sup. Table 8).

Factors association with response to BT

Factors that were independently associated with higher likelihood of response to BT in MVA were RBP-bridging, where patients were twice as likely to achieve a response (OR compared to LDT/HDT: 2.21 (1.21 – 4.05), p = 0.010); response to last line of therapy (OR: 2.17 (1.11 – 4.22, p = 0.023), and the absence of bulky disease (>7.5cm diameter, OR: 0.49 (0.25 - 0.98, p = 0.045).) (Table 4).

DISCUSSION:

The development of novel bridging approaches for r/r LBCL patients referred for CAR-T therapy is a clinical research priority. Data from trials and real-world analyses show that the majority of CAR-T patients currently receive conventional BT, but in chemo-refractory patients, conventional BT approaches are often ineffective and a significant proportion of bridged patients fail to reach CAR-T infusion[1,2,18]. Some studies also show that there is heightened CAR-T toxicity[16] and inferior CAR-T outcomes[16,17] for bridged patients, but this may be confounded by the limited use of BT in some centres, where only patients with high-risk disease features (i.e. those who are already at risk of worse toxicity and outcomes post-CAR-T) receive BT.

In this analysis, the majority (87%) of patients (not just those with high-risk features), received BT after leukapheresis. BT selection by clinicians was based on perception of patient fitness and pace of disease progression. As expected, clinicians elected for CT-based bridging in patients with high-risk disease features (more extra nodal sites, advanced stage, higher LDH, ECOG 1, and risk of "rapid

progression"), hence comparison of outcomes to CT may be skewed and should be interpreted with caution.

BT was broadly safe. There was no specific association between BT modality and delayed CAR-T infusion. There was no excess toxicity observed between BT vs no-BT patients, and specifically no difference between BT modalities. Very few patients died pre-CAR-T from adverse events associated with BT. Rather, patients were more likely to die from PD following failure of BT to control disease.

BT modality did not impact on the incidence of CAR-T toxicity, excepting an increased rate of G3-4 thrombocytopenia at 1 month in patients bridged with CT (highest in HDT). Protracted cytopenias are associated with increased morbidity and mortality post-CAR-T[24,25] and caution should be exercised in the use of BT which confers a heightened risk of haematotoxicity, albeit no evidence of a difference in NRM was seen in our cohort.

Here we describe the largest cohort of patients treated with CAR-T in CR in the literature[22]. In line with Bishop et al. who reported outcomes from 7 patients treated with Tisa-cel in CR post-BT in the Juliet study[26], we conclude that this approach is both safe and effective. We observed similar CRS rates between CR patients and BT-non-responders, implying CAR-T expansion in the absence of measurable disease. Further, durable remissions were observed in the majority of post-BT CR patients. This would be unexpected following a single cycle of BT in multiply-relapsed, chemorefractory LBCL, and implies that CAR-T as 'consolidation' post-BT may be an effective strategy, providing evidence to clinicians that this is a valid approach.

We provide evidence for the selection of more intensive BT modalities for patients. Our data clearly show that response to BT significantly increases the likelihood of durable remission post-CAR-T, regardless of the bridging modality used, with a substantial 42% reduction in the risk of progression/death in those with CR/PR post-BT compared to non-responders. These data do not allow us to definitively state that disease reduction pre-CAR-T, irrespective of biology, is what confers durable remissions post-CAR-T, or whether response to BT is simply a marker of "better disease" which may in and of itself be more CAR-T responsive.

We observed that RT or RBP was associated with the highest rates of CR/PR pre-CAR-T and an MVA for systemically bridged patients, also suggested that RBP bridging, absence of bulky disease, and response to last line therapy were associated with higher rates of response.
Although this gives clinicians a suggestion of which patients are most likely to respond to BT, the only modifiable risk factor identified is choice of bridging modality. With the caveat that this is not a randomised comparison, we show here in this exploratory analysis what we have observed in practice,

that RBP is a safe and potent bridging option, and is twice as likely to deliver a response compared to LDT/HDT so should be strongly considered in all suitable patients.

Why RBP appeared to be more effective in delivering CR/PR than other modalities is likely due to the immunotherapeutic targeting of CD79b in patients with no prior Polatuzumab exposure, whose disease was to that point 'naïve' to this mode of targeting. In contrast, all patients were multiply chemotherapy-exposed and chemo-relapsed/refractory, likely increasing the futility of conventional chemotherapy-based salvage/HDT. For RBP non-responders, alternative BT approaches are urgently required, and agents such as lenalidomide, BTKi[30] and bispecific antibodies targeting B-cell antigens[31,32] hold significant promise in this space.

Interestingly, our data suggested that BT non-response may have a larger prognostic impact in patients scheduled for Tisa-cel vs Axi-cel therapy. All Tisa-cel infused patients with non-response to BT relapsed within 12 months of infusion. This has potentially important clinical management implications and physicians may want to carefully consider CAR-T infusion (and/or consider alternative lines of BT) in this scenario. Whilst there were no overt differences in baseline demographics for BT non-responders receiving Tisa-cel vs Axi-cel therapy, we recognise that this is a subgroup analysis with relatively small patient numbers, and the potential for unmeasured confounding variables, and therefore this finding needs to be confirmed in other datasets.

We acknowledge several limitations of this retrospective data analysis. We performed multiple comparisons, had small numbers in some treatment groups, and analysed the impact of non-randomised treatment modalities and regimens where there was clearly a treatment selection bias, which may not be overcome with the use of multivariable analyses. However, despite these caveats, this data suggests that BT is safe, and that a reduction in disease burden pre-CAR-T can lead to better outcomes.

The median time from apheresis to infusion in the UK was 42 days (IQR 37–53) [1]. Whilst this interval between apheresis and infusion may appear long, we found no association between PFS post CAR-T and time to infusion[1], and the interval is in keeping with other real world datasets[8,27]. In the US, this interval can be shorter and may deter physicians from giving BT[28] due to time constraints. However, it is becoming increasingly apparent that BT may be more than just a 'holding measure' during the manufacture period. We and others have shown that CR/PR following effective BT is associated with lower rates of immunotoxicity and better PFS post CAR-T[29].

As we begin to treat older, frailer patients in whom the minimisation of immunotoxicity is paramount, the role of BT in disease burden reduction pre-CAR-T becomes increasingly important. Further, the clear association of BT response and improved PFS illustrates that better BT approaches may help to

improve CAR-T outcomes, independently of advances in CAR-T design or targeting. Optimised BT towards increased CR/PR and improved CAR-T ITT may also impact upon health economics and QoL measures.

Here we identify pre-treatment factors predictive of response to BT and highlight the transformative impact of RBP-bridging as a safe and effective strategy to improve CAR-T delivery and ITT.

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AUTHOR CONTRIBUTIONS:

CR, AK, AAK and LN conceived of the project, collected the data, and wrote the manuscript. All of the remaining authors collected data and wrote/reviewed the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST:

A.K., S.C., C.B, S.I., and C.R. have served on advisory boards and received honoraria from Kite/Gilead,
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on advisory boards and received honoraria from Kite/Gilead, Novartis, BMS, Janssen, Roche, Servier, Pfizer. W.T. has received honoraria and consultancy fees from Kite, BMS, and Roche.

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TABLES:

Table 1: Demographics for all leukapheresed patients at submission. *Compares RT/CT/CMT. p-values are chi squared or Fisher's exact test (discreate variables) or Kruskal Wallis (continuous).*

	No bridging	Bridging therapy				p-value none vs RT	p-value none vs CT	p-value steroids vs none	p-value steroids vs RT	p-value steroids vs CT	p-value CT vs RT
	N=49	Steroids N=35	RT N=62	CT N=213	CMT N=16						
Age	63.0(58 - 68)	58.0(51 - 65)	57.0(49 - 66)	60.0(51 - 68)	63.0(47.5 - 66.5)	0.0082	0.080	0.069	0.54	0.78	0.20
Sex, N (%)											
Male	30 (61.2)	21 (60.0)	37 (59.7)	134 (62.9)	8 (50.0)	>0.99	0.87	>0.99	>0.99	0.85	0.66
Female	19 (38.8)	14 (40.0)	25 (40.3)	79 (37.1)	8 (50.0)						
Disease type, N (%)											
De novo DLBCL	31 (63.3)	24 (68.6)	40 (64.5)	148 (69.5)	9 (56.3)	0.95	0.72	0.53	0.58	0.30	0.44
PMBL	3 (6.1)	0	4 (6.5)	11 (5.2)	2 (12.5)						
tFL	12 (24.5)	10 (28.6)	16 (25.8)	39 (18.3)	4 (25.0)						
t-Other	3 (6.1)	1 (2.9)	2 (3.2)	15 (7.0)	1 (6.3)						
DHL/THL, N (%)											
No	28 (75.7)	24 (75.0)	38 (69.1)	128 (68.8)	8 (61.5)	0.84	0.78	>0.99	0.88	0.87	0.84
Yes	4 (10.8)	3 (9.4)	8 (14.5)	23 (12.4)	2 (15.4)						
DE/TE	5 (13.5)	5 (15.6)	9 (16.4)	35 (18.8)	3 (23.1)						
Missing/unknown	12	3	7	27	3						
Stage, N (%)											
Stage 1-2	14 (30.4)	9 (25.7)	18 (29.5)	33 (15.6)	2 (13.3)	>0.99	0.033	0.80	0.82	0.15	0.024
Stage 3-4	32 (69.6)	26 (74.3)	43 (70.5)	179 (84.4)	13 (86.7)						
Missing/unknown	3	0	1	1	1						
ECOG, N (%)											
0	31 (63.3)	18 (51.4)	32 (51.6)	80 (37.6)	3 (18.8)	0.25	0.001	0.37	>0.99	0.14	0.056
1	18 (36.7)	17 (48.6)	30 (48.4)	133 (62.4)	13 (81.3)						
Bulk>7.5cm, N (%)											
No	39 (79.6)	26 (74.3)	41 (66.1)	149 (70.0)	8 (53.3)	0.14	0.22	0.61	0.50	0.69	0.64
Yes	10 (20.4)	9 (25.7)	21 (33.9)	64 (30.0)	7 (46.7)						
Missing/unknown	0	0	0	0	1						
No. of extra nodal sites, N (%)											
None	29 (59.2)	15 (44.1)	25 (40.3)	59 (27.7)	4 (25.0)	0.039	<0.001	0.083	0.90	0.19	0.041
1-2	19 (38.8)	14 (41.2)	33 (53.2)	129 (60.6)	9 (56.3)						
3+	1 (2.0)	5 (14.7)	4 (6.5)	25 (11.7)	3 (18.8)						
Missing/unknown	0	1	0	0	0						
LDH, N (%)											
<ULN	12 (25.0)	10 (28.6)	19 (33.3)	40 (19.6)	0	0.83	0.062	0.79	0.67	0.23	0.039
>ULN	29 (60.4)	17 (48.6)	26 (45.6)	104 (51.0)	10 (71.4)						
>2ULN	7 (14.6)	8 (22.9)	12 (21.1)	60 (29.4)	4 (28.6)						
Missing/unknown	1	0	5	9	2						

	No bridging	Bridging therapy				p-value none vs RT	p-value none vs CT	p-value steroids vs none	p-value steroids vs RT	p-value steroids vs CT	p-value CT vs RT
	N=49	Steroids N=35	RT N=62	CT N=213	CMT N=16						
IPI , N (%)											
0-2	26 (60.5)	20 (57.1)	32 (56.1)	93 (45.1)	8 (57.1)	0.69	0.093	0.82	>0.99	0.20	0.18
3+	17 (39.5)	15 (42.9)	25 (43.9)	113 (54.9)	6 (42.9)						
Missing/unknown	6	0	5	7	2						
Fit for SCT?, N (%)											
No	11 (22.4)	7 (20.0)	6 (9.7)	43 (20.2)	5 (31.3)	0.11	0.70	>0.99	0.21	>0.99	0.061
Yes	38 (77.6)	28 (80.0)	56 (90.3)	170 (79.8)	11 (68.8)						
HCT-CI score, N (%)											
<3	47 (95.9)	30 (85.7)	59 (96.7)	194 (91.9)	13 (81.3)	>0.99	0.54	0.12	0.22	0.22	0.26
≥3	2 (4.1)	5 (14.3)	2 (3.3)	17 (8.1)	3 (18.8)						
Missing/unknown	0	0	1	2	0						
Life expectancy of less than 3 months if no response to bridging, N (%)											
No	42 (85.7)	20 (58.8)	42 (67.7)	120 (56.3)	11 (68.8)	0.044	<0.001	0.009	0.50	0.85	0.14
Yes	7 (14.3)	14 (41.2)	20 (32.3)	93 (43.7)	5 (31.3)						
Missing/unknown	0	1	0	0	0						
>2 previous lines, N (%)											
No	29 (59.2)	19 (54.3)	43 (69.4)	123 (57.7)	12 (75.0)	0.32	0.87	0.66	0.19	0.72	0.11
Yes	20 (40.8)	16 (45.7)	19 (30.6)	90 (42.3)	4 (25.0)						
Previous transplant, N (%)											
No	41 (83.7)	30 (85.7)	51 (82.3)	173 (81.2)	13 (81.3)	0.60	0.93	>0.99	0.36	0.70	0.69
Auto	7 (14.3)	4 (11.4)	11 (17.7)	35 (16.4)	3 (18.8)						
Allo	1 (2.0)	1 (2.9)	0	5 (2.3)	0						
Refractory, N (%)											
No	24 (50.0)	21 (60.0)	34 (55.7)	117 (57.6)	9 (60.0)	0.57	0.42	0.38	0.83	0.85	0.88
Yes	24 (50.0)	14 (40.0)	27 (44.3)	86 (42.4)	6 (40.0)						
Missing/unknown	1	0	1	10	1						
Response to last line, N (%)											
CMR/PR	18 (36.7)	13 (37.1)	15 (24.2)	50 (23.5)	5 (31.3)	0.21	0.070	>0.99	0.24	0.096	>0.99
SD/PD	31 (63.3)	22 (62.9)	47 (75.8)	163 (76.5)	11 (68.8)						

Table 2: Response to bridging and feasibility of CAR-T infusion. **p-values are chi squared or Fisher's exact test (discreate variables) or Kruskal Wallis (continuous) and compare all 5 groups (except response which compares RT/CT/CMT only). [1] RT (pneumonia), CT (Covid 19, neutropenic sepsis/PCP, sepsis, sudden death/PE), CMT (neutropenic sepsis/ischaemic bowel), [2]RT(Clinical deterioration due to LRTI/Flu requiring intubation), CT(clinical deterioration – perforation, Inflammatory pneumonitis, MI), [3] No bridging (patient was in CMR, decided not to proceed, MDS diagnosis), RT(patient was in CMR, decided not to proceed), CT (Patient choice), [4]ORR/CR rate by HDT group: All patients: HDT-Ifos: 8(26.7%)/1(3.3%), HDT-Gem: 9(25.0%)/2(5.6%), HDT-other: 9(39.1%)/4(17.4%), Infused patients: HDT-Ifos: 7(33.3%)/1(44.8%), HDT-Gem: 8(30.8%)/2(7.7%), HDT-other: 9(60.0%)/4(26.7%)*

		Bridging Therapy					CT bridging		
	No bridging N=49	Steroids N=35	RT N=62	CT N=213	CMT N=16	p-value*	Low Dose N=51	High Dose[4] N=84	RBP N=77
Response to bridging, N(%)									
CR/PR	-	-	40 (67.8)	64 (31.4)	5 (33.3)	<0.001	8 (15.7)	23 (27.4)	33 (42.9)
SD/PD/death before infusion	-	-	19 (32.2)	140 (68.6)	10 (66.7)		35 (68.3)	60 (71.4)	43 (57.1)
Unknown	-	-	3	9	1		8	1	0
CR	-	-	4 (6.8)	19 (9.3)	0	<0.001	1 (2.0)	7 (8.3)	11 (14.3)
Infused, N(%)									
Infused	40 (81.6)	29 (82.9)	54 (87.1)	166 (77.9)	11 (68.8)	0.39	42 (82.4)	58 (69.1)	66 (85.7)
Not infused	9 (18.4)	6 (17.1)	8 (12.9)	47 (22.1)	5 (31.3)		9 (17.7)	26 (31.0)	11 (14.3)
PD/CNS relapse/death due to PD	*7*	*6*	*5*	*34*	*4*		*7*	*21*	*5*
Death (not PD)[1]	*0*	*0*	*1*	*4*	*1*		*0*	*2*	*2*
Patient fitness/AE[2]	*0*	*0*	*1*	*3*	*0*		*0*	*1*	*2*
Manufacturing failure	*0*	*0*	*0*	*5*	*0*		*2*	*2*	*1*
Other[3]	*2*	*0*	*1*	*1*	*0*		*0*	*0*	*1*
Infused patients	**No bridging N=40**	**Bridging Therapy**				**p-value**	**CT bridging**		
		Steroids N=29	**RT N=54**	**CT N=166**	**CMT N=11**		**Low Dose N=43**	**High Dose N=64**	**RBP N=70**
Response, N(%)									
CR/PR	-	-	37 (72.6)	63 (39.9)	4 (40.0)	<0.001	8 (18.6)	24 (37.5)	35 (50.0)
SD/PD/death before infusion	-	-	14 (27.5)	95 (60.1)	6 (60.0)		28 (65.1)	38 (59.4)	35 (50.0)
Unknown			3	8	1		7	1	0
CR	-	-	2 (3.9)	19 (12.0)	0	<0.001	1 (2.4)	7 (12.1)	11 (16.7)
Time to infusion (days), median (IQR)	45 (37.5 – 49)	42 (35 – 47.5)	42 (36 – 55)	42 (37 – 54)	54 (48 – 62)	0.17	40 (34 – 48)	43 (39-53)	41.5 (37-57)
range	33 - 189	35 - 105	32 - 118	12 - 264	34-74		12-116	32-159	16 - 264
Number delayed >8 weeks	5 (12.5)	2 (6.9)	13 (24.1)	33 (19.9)	5 (45.5)	0.049	7 (16.7)	9 (15.5)	17 (25.8)
Delay reasons (patients could have multiple reasons)									
AE	*2*	*0*	*4*	*5*	*0*		1	3	10
PD/disease requiring further bridging	*2*	*0*	*0*	*1*	*1*		0	1	0
Apheresis/manufacturing capacity	*1*	*1*	*3*	*0*	*0*		1	1	1
Bridging	*0*	*0*	*2*	*1*	*0*		0	1	0
CMR	*1*	*0*	*2*	*0*	*0*		0	0	0
COVID	*0*	*0*	*2*	*8*	*0*		1	2	5
Patient choice	*0*	*0*	*0*	*2*	*0*		1	0	1
Awaiting biopsy results	*0*	*0*	*0*	*1*	*0*		1	0	0
Unknown	*1*	*1*	*4*	*14*	*4*		1	3	10

Pre-infusion characteristics									
Low platelets (<50)	1 (2.5)	4 (13.8)	1 (1.9)	18 (10.8)	0	0.075	3 (7.1)	10 (17.2)	5 (7.6)
Low lymphocytes (<0.5)	7 (17.5)	12 (41.4)	26 (48.2)	76 (46.6)	6 (54.6)	0.008	23 (57.5)	20 (34.5)	33 (50.8)
LDH									
Normal	12 (30.8)	9 (31/90)	15 (30.6)	32 (20.0)	0	0.057	8 (19.1)	8 (13.8)	16 (24.2)
>ULN	24 (61.5)	16 (55.2)	23 (46.9)	85 (53.1)	8 (80.0)		244 (57.1)	27 (46.6)	24 (51.5)
>2ULN	3 (7.7)	4 (13.8)	11 (22.5)	43 (26.9)	2 (20.0)		8 (19.1)	19 (32.8)	16 (24.2)
Missing	1	0	5	6	1		2	4	0

Table 3: Toxicity from CAR-T according to bridging strategy. *[1]Patients with PD are excluded, [2]Infection details: None; Covid-19, steroids; RSV pneumonia, RT; Sepsis (NOS), Systemic; Covid-19 (N=5), Fungal chest infection/HLH (N=1), Necrotizing fasciitis(N=1), sepsis (NOS) (N=3), fungal sepsis (N=1) Notes: one ITU level missing (CT bridging).*

	No Bridging	**Bridging therapy**				**p-value**
		Steroids	**RT**	**CT**	**CMT**	
	N=40	**N=29**	**N=54**	**N=166**	**N=11**	
CAR-T toxicities						
CRS (grade 3+), N(%)	1 (2.5)	4 (13.8)	5 (9.3)	11 (6.6)	2 (18.2)	0.19
ICANS (grade 3+), N(%)	7 (17.5)	6 (20.7)	8 (14.8)	26 (15.7)	0	0.64
Grade 3+ Neutropenia (1 month)[1]	9/33 (27.3)	9/20 (45.0)	20/45 (44.4)	64/114 (44.4)	4/10 (40.0)	0.051
Grade 3+ Neutropenia (3 months)[1]	3/20 (15.0)	2/8 (25.0)	7/31 (22.6)	13/67 (19.4)	1/5 (20.0)	0.94
Grade 3+ Thrombocytopenia (1 month)[1]	7/34 (20.6)	6/30 (30.0)	15/47 (31.9)	65/116 (56.0)	1/10 (10.0)	<0.001
Grade 3+ Thrombocytopenia (3 months)[1]	1/20 (5.0)	0/8 (0)	2/31 (6.5)	15/67 (22.4)	1/5 (20)	0.11
Toxicity therapies						
Steroids given, N(%)	15 (37.5)	13 (44.8)	23 (45.6)	61 (36.8)	4 (36.4)	0.88
Tocilizumab used, N(%)	22 (55.0)	30 (69.0)	39 (72.2)	114 (68.7)	5 (45.5)	0.22
ITU required, N(%)	9 (22.5)	11 (37.9)	14 (25.9)	46 (27.7)	3 (27.3)	0.72
Observation only	*1 (2.5)*	*3 (10.3)*	*6 (11.1)*	*15 (9.1)*	*0*	
Inotropes	*4 (10.0)*	*5 (17.2)*	*5 (9.3)*	*16 (9.7)*	*3 (26.3)*	
Organ support/Intubation	*4 (10.0)*	*3 (10.3)*	*3 (5.6)*	*14 (8.5)*	*0*	
Cumulative incidence of NRM at 1 year	8.0% (2.6 – 23.0)	3.5% (0.5 – 22.1)	3.7% (0.9 – 14.0)	9.4% (5.6 -15.5)	0%	
NRM events	**3**	**1**	**2**	**15**	**0**	
Infection[2]	*2*	*1*	*1*	*11*	*0*	
Cardiac	*1*	*0*	*0*	*0*	*0*	
Haematemesis	*0*	*0*	*1*	*0*	*0*	
Second malignancy	*0*	*0*	*0*	*1*	*0*	
HLH	*0*	*0*	*0*	*1*	*0*	
Bowel perforation	*0*	*0*	*0*	*2*	*0*	

Table 4: Multivariable analysis of baseline factors (at submission) influencing outcome to systemic BT and factors associated with PFS post-CAR-T infusion. *MVA baseline factors associated with response BT: (responder vs non-responder; CR/PR vs SD/PD). *logistic regression, using backwards selection (p = 0.05 inclusion) incorporating the following variables all measured at submission: bridging chemotherapy type, age, sex, ECOG, stage, bulky disease, extra nodal sites, LDH, lymphoma subtype, DHL, refractoriness to previous therapies, response to last line, and ≥3 lines of previous therapy. MVA factors associated with PFS post-infusion including BT response (RT/CT/CMT patients only). Variables that remain significant in MVA (backwards selection, p = 0.05 for rejection). Variables included in the MVA: age, sex, ECOG, stage (submission), bulky disease, extra nodal sites (submission), LDH (pre-LD), CRP, low platelets, low lymphocytes, lymphoma subtype, DHL, refractory to previous therapies, response last line, >2 lines previous therapy and response to bridging.*

Factors affecting response to BT		Responder/N	OR (95% CI)	p-value
RBP bridging				
	No	34/134	1.00	0.010
	Yes	35/83	2.21 (1.21 – 4.05)	
Response last line				
	SD/PD	45/165	1.00	0.023
	CR/PR	24/52	2.16 (1.11 – 4.22)	
Bulky disease				
	No	55/149	1.00	0.045
	Yes	14/68	0.49 (0.25 – 0.98)	

Factors affecting response to CAR-T		Events/N	HR (95% CI)	p-value
LDH at LD				
	≤2ULN	74/141	1.00	0.001
	>2ULN	34/41	2.06 (1.34 – 3.16)	
Extra nodal sites				
	<3	91.160	1.00	0.001
	≥3	17/22	2.51 (1.46 – 4.32)	
BT Response				
	SD/PD	68/100	1.00	0.012
	CR/PR	40/82	0.58 (0.38 – 0.89)	

FIGURE LEGENDS:

Figure 1:

Consort diagram of all approved patients.

Figure 2:

Figure 2a: PFS: comparing BT groups 1-year rates; no BT 46.0% (29.7 – 60.9), steroids 23.7% (10.2 – 40.2), RT 59.1% (44.8 – 70.9), CT 31.3% (23.9 – 38.9), CMT 45.5% (16.7 – 70.7)

Figure 2b: OS: comparing BT groups 1-year rates; no BT 69.7% (51.4 – 82.2), steroids 37.4% (20.2 – 54.5), RT 70.3% (55.4 – 81.0), CT 46.9% (38.1 – 55.2), CMT 62.3% (27.8 – 84.0)

Figure 2c: PFS: comparing BT responder vs non-responder: HR 0.55 (0.39 – 0.79), p=0.001. 1-year rates: Responder: 50.1% (39.6 – 59.7); Non-Responder: 29.7% (21.3 – 38.6)

Figure 2d: OS: comparing BT responder vs non-responder: HR 0.51 (0.33 – 0.77), p=0.001. 1-year rates: Responder: 63.2% (51.5 – 72.8); Non-Responder: 45.9% (35.9 - 55.3)

Figure 3:

Figure 3a: PFS post-Axi-Cel: comparing BT responders vs non-responders: HR (response vs no response): 0.68 0.45 – 1.03), p = 0.071

Figure 3b: PFS post-Tisa-Cel: comparing BT responders vs non-responders: HR (response vs no response): 0.22 (0.11 – 0.44), p = <0.001

Figure 1

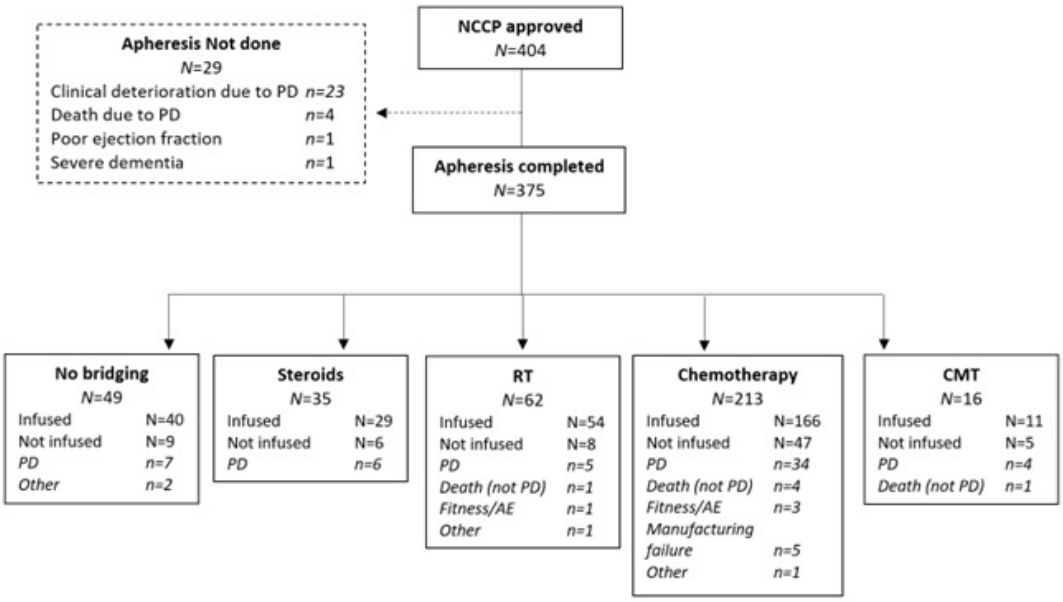

Figure 2 **Figure 2**

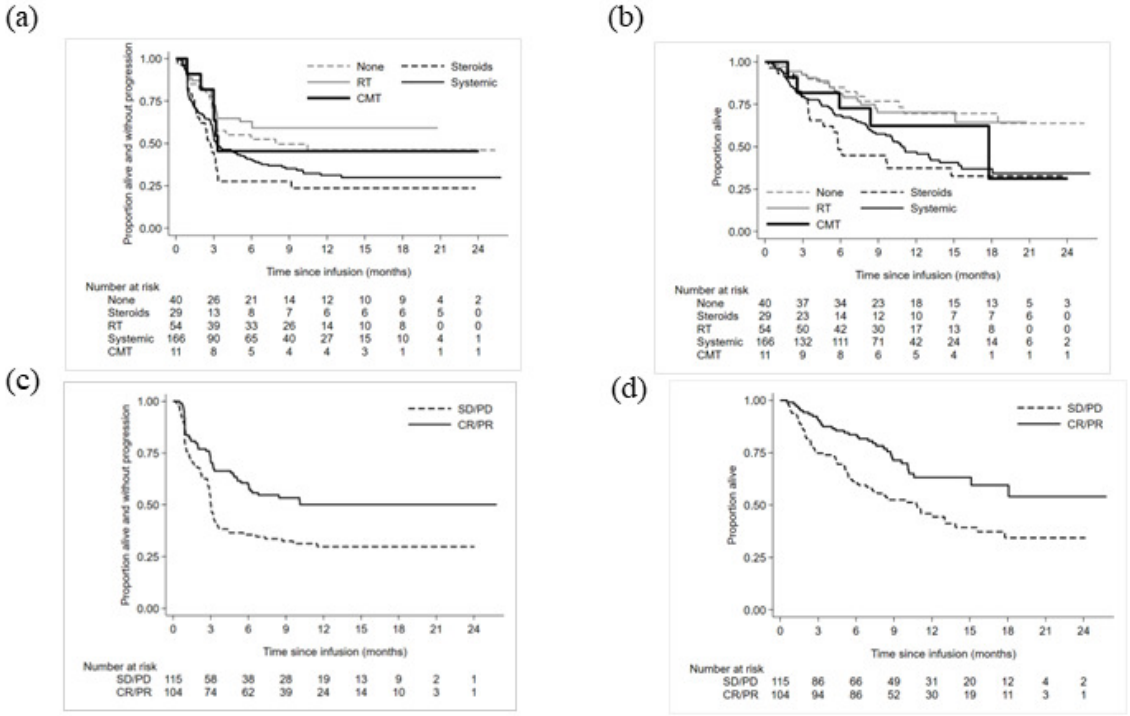

Figure 3 **Figure 3**