CAR T in patients with large B-cell lymphoma not fit for autologous transplant

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

CAR T in patients with large B-cell lymphoma not fit for autologous transplant

A Kuhnl,[1] AA Kirkwood,[2] C Roddie,[3,4] T Menne,[5] E Tholouli,[6] A Bloor,[7] C Besley,[8] S Chaganti,[9] W Osborne,[5] J Norman,[6] A Gibb,[7] K Sharplin,[8] M Cuadrado,[1] M Correia de Farias,[1] K Cheok,[3] L Neill,[3] AL Latif,[10] C Arias,[11] B Uttenthal,[12] C Jones,[13] R Johnson,[14] A McMillan,[15] R Sanderson,[1] W Townsend[3]

1 Department of Haematology, King's College Hospital, London, UK

2 Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, University College London, London, UK

3 Department of Haematology, University College London Hospitals, London, UK

4 UCL Cancer Institute, University College London, London, UK

5 Department of Haematology, Freeman Hospital, Newcastle, UK

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

7 Department of Haematology, The Christie Hospital, Manchester, UK

8 Department of Haematology, University Hospitals Bristol and Weston, Bristol, UK

9 Department of Haematology, Queen Elizabeth Hospital, Birmingham, UK

10 Department of Haematology, Queen Elizabeth II Hospital, Glasgow, UK

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

12 Department of Haematology, Addenbrooke's Hospital, Cambridge, UK

13 Department of Haematology. University Hospital of Wales, Cardiff, UK

14 Department of Haematology, St. James's Hospital, Leeds, UK

15 Department of Haematology, Nottingham University Hospitals, Nottingham, UK

Correspondence:

Andrea Kuhnl
Department of Haematology
King's College Hospital
Denmark Hill
London
SE5 9RS
United Kingdom
Email: andrea.kuhnl@nhs.net

1

Abstract

Large B-cell lymphoma (LBCL) patients with comorbidities and/or advanced age are increasingly considered for treatment with CD19 CAR T, but data on the clinical benefit of CAR T in the less fit patient population are still limited.

We analysed outcomes of consecutive patients approved for treatment with axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) by the UK National CAR T Clinical Panel, according to fitness for autologous stem cell transplant (ASCT).

81/404 (20%) of approved patients were deemed unfit for ASCT. Unfit patients were more likely to receive tisa-cel vs. axi-cel (52% vs. 48%) compared to 20% vs. 80% in ASCT-fit patients; $p<0.0001$). The drop-out rate from approval to infusion was significantly higher in the ASCT-unfit group (34.6% vs. 23.5%; p=0.042). Among infused patients, response rate, progression-free and overall survival were similar in both cohorts. CAR T was well tolerated in ASCT-unfit patients with an incidence of grade ≥3 cytokine release syndrome and neurotoxicity of 2% and 11%, respectively.

Results from this multi-centre real-world cohort demonstrate that CD19 CAR T can be safely delivered in carefully selected older patients and patients with comorbidities who are not deemed suitable for transplant.

Background

Patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL) not deemed fit for autologous transplant (ASCT) due to comorbidities and/or advanced age have historically poor outcomes. The chances of achieving long-term remission with conventional chemotherapies are low and treatments are usually palliative.[1] Outcome might improve with novel combination therapies like polatuzumab-BR or tafasitamab/lenalidomide,[2,3] but long-term efficacy of these treatments in the real-world (RW) setting has yet to be determined.[4] Some patients unfit for ASCT may be considered for treatment with CD19 CAR T, which has transformed the treatment landscape for r/r LBCL in recent years.[5–8] However, criteria for defining CAR T fitness are not well established and data on the clinical benefit of CAR T in the less fit patient population are limited. The pivotal ZUMA-1 and JULIET trials largely excluded patients with significant comorbidities.[9,10]

Retrospective subgroup analyses published to date have primarily focused on the age group ≥65 years.[11–13] Patients aged ≥65 without significant comorbidities have similar response rates and long-term outcomes after CAR T compared to younger patients. Elderly patients appear to have similar rates of ≥grade 3 cytokine release syndrome (CRS), but potentially higher risk of immune effector cell-associated neurotoxicity syndrome (ICANS).[11,15,16] Patients with high comorbidity burden as assessed by the Cumulative Illness Rating Scale (CIRS) were shown to have inferior progression-free survival (PFS) and overall survival (OS) after CAR T.[17,18] High CIRS was further associated with a higher incidence of CRS and ICANS.[19,18] Long-term treatment-related disabilities and quality of life after CAR T are still understudied in the less fit patient population.

Early identification of less fit LBCL patients as suitable candidates for CAR T will be important to allow timely and appropriate treatment decisions. With elderly and comorbid patients being underrepresented in CAR T clinical trials, RW evidence will be of particular importance for optimizing patient selection, product choice, bridging therapy and toxicity management in this vulnerable patient population. The aim of this study was to assess outcomes of LBCL patients approved for licensed CD19 CAR T in the UK who were deemed unfit for ASCT.

Patients and methods

We analyzed 404 consecutive r/r LBCL patients who have failed 2 or more lines of therapy and were approved for treatment with standard-of-care axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) between December 2018 and November 2020 across 10 UK centers as part of a National Service Evaluation. An additional 25 patients aged ≥75 approved

for treatment in 2021 were also included. Data on patients' fitness and comorbidities were retrospectively collected. Comorbidity burden was assessed using the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI).[20] Treating physicians were asked to define whether patients would have been deemed fit for ASCT at the time of consideration of CAR T based on physical suitability irrespective of disease status. The UK National CAR T Clinical Panel (NCCP) approval process, toxicity grading and response assessment at the centers have been described elsewhere.[21] Patients required to have received full-dose R-CHOP and have a performance status (PS) of 0-1.

Statistical considerations

Pre-treatment factors were compared using Wilcoxon Mann-Whitney (continuous variables) or Chi-squared/Fisher's exact tests (discrete variables). Toxicity endpoints were assessed using logistic regression to allow for adjustment by CAR T product. 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 non-relapse mortality (NRM) cumulative incidence rates, with relapse counted as a competing risk. 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 intention-to-treat (ITT) analysis of OS where time was measured from the date of NCCP approval. The additional cohort of patients aged over 75 treated in 2021 were not included in any age comparisons with patients <75 treated in 2018-2020.

Results

81/404 (20%) of patients approved for CAR T were deemed unfit for ASCT: 40 on the basis of age alone, 11 for frailty (as recorded in local center), and 31 due to comorbidities (Figure 1). 53/81 (65.4%) of patients in the ASCT-unfit cohort underwent CAR T infusion. The drop-out rate from approval to infusion was significantly higher in the ASCT-unfit vs. -fit group (34.6% vs. 23.5%; p=0.042; Figure 1). The main reasons for not proceeding to treatment was clinical deterioration from progressive disease (PD). 28/53 (52.8%) patients received tisa-cel and 25 (47.2%) axi-cel, compared to 19.4% tisa-cel and 80.6% axi-cel in fit patients (p<0.0001).

The median age in the ASCT-unfit cohort was 71 years (range 47-78) vs. 56 years (range 18-72) in the ASCT-fit cohort (p<0.0001). ASCT-unfit patients were more likely to have reduced ECOG performance status (PS; 1 vs 0), higher HCT-CI, lower GFR and lower LVEF (Table 1). No significant differences were seen regarding stage, LDH level, bulky disease, extranodal involvement, response to last treatment line, or the bridging therapy approach (Table 1).

Efficacy

The best overall response rate (ORR) in ASCT-unfit vs. fit patients was 78.4% (56.9% complete remission (CR)) vs. 70.3% (48.1% CR), p=0.24. 39.6% (37.8% CR) of unfit vs. 42.5% (38.5%) of fit patients had ongoing response at 6 months, p=0.70. With a median follow-up from infusion of 21.8 months (IQR: 17.8 – 27.1), the 12-month PFS was 37.7% (24.9 – 50.5) vs. 36.8% (30.9 – 42.8) and 12-month OS 56.6% (42.3 – 68.7) vs. 56.3% (49.9 – 62.2) for infused patients in the ASCT-unfit and fit cohorts, respectively (Figure 2 A/B). There was no evidence of a difference in PFS or OS in ASCT-unfit patients according to CAR T product (Figure 2F). Median OS in the intention-to-treat population was 8.5 months (95%CI 6.8 – 13.4) for unfit and 11.0 months (95%CI: 8.7 – 13.6) for fit patients (p=0.69: Figure 2D). We did not observe significant differences in PFS or OS between groups who were unfit due to age or comorbidities (PFS shown in Figure 2C), nor evidence of worse outcome for patients with impaired kidney- or cardiac function, or according to HCT-CI (data not shown). No significant difference in PFS was seen across age groups (<70 vs. 70-74 vs. ≥75, p=0.81; Figure 2D). We have previously identified risk factors for primary CAR T failure (ECOG PS, LDH >2 ULN, and liver involvement) and for PFS (≥3 extranodal sites, high LDH at lymphodepletion).[21] Significance of these factors did not change when adjusting for ASCT-fitness and effect sizes were similar within the unfit cohort, indicating that the prognostic significance of these factors apply to ASCT-unfit patients. There were insufficient events to perform a separate prognostic model within the ASCT-unfit group. 53.3% and 58.9% of patients who progressed CAR T received further treatment in the unfit and fit cohorts, respectively (p=0.58). In the cohort of

patients over 75 (N=38, median age 76 (IQR 75-77, range 75-85), 24 (63.2%) were infused and 1-year PFS, OS and ITT OS of 33.8% (15.5 – 53.2), 46.2% (23.2 – 66.4) and 35.7% (13.0 – 59.4) were seen.

Toxicity

Among 53 ASCT-unfit patients, there was one case with ≥grade 3 CRS (2%), and 6 patients (11%) with ≥grade 3 ICANS. There were no significant interactions between CAR T product and fitness or age, for any toxicity endpoint, i.e. axi-cel showed a less favourable toxicity profile regardless of fitness.

Details on the incidence and management of CAR T toxicities for each product in ASCT-fit and unfit patients are shown in Table 3. There was no significant difference in the incidence of ≥grade 3 toxicities, the use of tocilizumab/steroids or ICU support in unfit vs fit patients or by age, when adjusting for CAR T product, but ASCT-unfit and older patients had a higher risk of experiencing ICANS, though not at grade≥3 (Table 3).

The 12-month cumulative NRM was similar with 7.6% vs. 6.9% in unfit vs. fit patients, with infections as cause of death in 1/4 and 15/19 cases, respectively (Figure 1). There was some evidence of higher NRM in patients with HCT-CI ≥3 vs. 0-2 (1-year NRM: 17.6% (7.0-40.3) vs. 6.2% (3.9-9.8; log rank p=0.055).

Discussion

Patients with r/r LBCL unfit for ASCT are increasingly considered for CAR T, but criteria for patient selection and details on outcomes are limited. In this national CAR T RW dataset, we provide comprehensive ITT outcomes of ASCT-unfit patients, which constituted 20% of the total UK cohort. ITT outcomes may be particularly relevant in the elderly/comorbid patient population, for informed decision making against alternative off-the-shelf treatments. Despite a higher initial drop-out rate, ITT outcomes in ASCT-unfit patients were comparable to the fit cohort, with a 12-month OS of 38.3%.

Among patients who received treatment, response rates and PFS were similar in unfit vs. fit patients, indicating that CAR T is a potentially curative treatment in both groups. Risk factors for early failure and long-term survival as described before,[21] were applicable to ASCT-unfit patients and might help to guide upfront selection in this patient group. We did not observe an impact of renal and cardiac function and HCT-CI score on CAR T outcomes. There was some evidence that HCT-CI score of ≥3 was associated with increased NRM, but numbers were small. CIRS data were not available for our cohort and might be the more predictive comorbidity scoring system in the context of CAR T.[17]

CAR T treatment was generally well-tolerated in the ASCT-unfit cohort, with low rates of neurotoxicity, different to previous studies.[11] Although this will be partly explained by the higher use of tisa-cel in these patients, analyses adjusted for product showed no difference in high grade events. No difference in PFS and OS was observed in ASCT-unfit patients according to CAR T product, indicating that both licensed product are suitable choices in this patient group. Although the use of tocilizumab and corticosteroids for each product was similar by fitness, we cannot exclude differences in toxicity management, i.e. differences in cumulative steroid doses or supportive medication in less fit patients.

Our original cohort contained only 14 patients over 75 (N=7 infused), so data on an additional 24 treated in 2021 were collected. Although not comparable to the younger patient within original dataset, and with limited follow-up, the 1-year PFS of 33.8% and ITT OS of 35.7% provides reassurance that CAR T is worth exploring in this older age group.

Limitations of our analysis include the retrospective nature of the data collection (albeit from a consecutive ITT cohort) and the non-standardized definition of ASCT-fitness according to each CAR T centre's local practice. However, in the absence of internationally accepted thresholds for age or organ function to define ASCT-fitness, patient selection for transplant in daily practice is always based on local criteria, hence why this definition is clinically meaningful and describes a subgroup of patients who would not have been considered for ASCT as alternative to CAR T.

Our data indicate that carefully selected patients with r/r LBCL who are not fit for ASCT have favourable outcomes with CD19 CAR T, which provides a potentially curative treatment option for this difficult-to-treat patient group. CAR T fitness in elderly and comorbid patients should be assessed early on the treatment pathway to ensure that all treatment options are considered.

Acknowledgements

Authorship Contributions

A.K., A.A.K., W.T.: designed the research, collected the data, analyzed the data, and wrote the manuscript; C.R., T.M., E.T., A.B., C.B., S.C., W.O., J.N., A.G., K.S., M.C., M.C.D.F., K.C., L.N., A.L.L., C.G.A., B.U., C.J., R.S.: contributed to collecting the data and reviewed the manuscript; R.J., A.M.: contributed to recruiting patients and reviewed the manuscript.

Conflict of interest disclosures: A.K. and C.R. have served on advisory boards and received honoraria from Kite/Gilead, Novartis and BMS. A.A.K. received honoraria from Kite/Gilead. R.S. has served on advisory boards and received honoraria from Kite/Gilead and Novartis. T.M has served on advisory boards and received honoraria from Kite/Gilead, Novartis, BMS, Janssen, Roche, Servier, Pfizer, Amgen. E.T. served on advisory boards and received honoraria from Kite/Gilead, Novartis, BMS/Celgene, Janssen. A.G. has served on advisory boards for Takeda and received honoraria from Kite/Gilead and Takeda. W.O. has received honoraria from Roche, Takeda, Pfizer, Servier, Kite/Gilead, MSD, Novartis, Beigene, Astra Zeneca, Syneos, Autolus, Kyowa Kirin, Abbvie, Incyte, BMS, Janssen. K.C. received honoraria from Kite/Gilead. C.G.A has served on advisory boards and received honoraria from Kite/Gilead, Novartis and received research funding from Kite/Gilead. B.U. has served on advisory boards for Kite/Gilead, Novartis and Atara and received conference sponsorship from Kite/Gilead, Novartis and BMS. R.J has served on advisory boards and received honoraria from Kite/Gilead and Takeda. W.T. has received honoraria and consultancy fees from Celgene BMS, Incyte, and Roche.

References

1. Salles, G. A. *et al.* Treatment of aggressive B-cell non-Hodgkin lymphoma beyond frontline therapy in patients not eligible for stem cell transplantation: a structured review. *Leukemia and Lymphoma* vol. 60 (2019).

2. Sehn, L. H. *et al.* Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. in *Journal of Clinical Oncology* vol. 38 (2020).

3. Salles, G. *et al.* Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol.* **21**, (2020).

4. Northend, M. *et al.* Results of a UK real world study of polatuzumab vedotin, bendamustine, and rituximab for relapsed/refractory large B-cell lymphoma. *Blood Adv.* (2022) doi:10.1182/bloodadvances.2021005953.

5. Frederick L. Locke, MD1; Armin Ghobadi, MD2; Caron A. Jacobson, M. D. B. *et al.* Long-term safety and efficacy of axicabtagene ciloleucel (anti-CD19 CAR T) in refractory large B-cell lymphoma: a multicenter, single arm, phase 1-2 trial. *Lancet Oncol.* (2018) doi:10.1016/S1470-2045(18)30864-7.

6. Schuster, S. J. *et al.* Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* **22**, (2021).

7. Nastoupil, L. J. *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.* **38**, (2020).

8. Jacobson, C. A. *et al.* Axicabtagene ciloleucel in the non-trial setting: Outcomes and correlates of response, resistance, and toxicity. *J. Clin. Oncol.* **38**, 3095–3106 (2020).

9. Neelapu, S. S. *et al.* Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. *N. Engl. J. Med.* **377**, 2531–2544 (2017).

10. Schuster, S. J. *et al.* Tisagenlecleucel in Adult Relapsed or Refractory DLBCL. *N. Engl. J. Med.* **380**, 45–56 (2019).

11. Neelapu, S. S. *et al.* Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood* vol. 135 (2020).

12. Vercellino, L. *et al.* Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv.* **4**, (2020).

13. Iacoboni, G. *et al.* Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. *Cancer Med.* **10**, (2021).

14. Sano, D. *et al.* Safety of Axicabtagene Ciloleucel CD19 CAR T-Cell Therapy in Elderly Patients with Relapsed or Refractory Large B-Cell Lymphoma. *Blood* **132**, (2018).

15. Zettler, M. E. *et al.* Real-world adverse events associated with CAR T-cell therapy among adults age ≥ 65 years. *J. Geriatr. Oncol.* **12**, (2021).

16. Locke, F. L. *et al.* Real-World Outcomes of Axicabtagene Ciloleucel (Axi-cel) for the Treatment of Large B-Cell Lymphoma (LBCL): Impact of Age and Specific Organ Dysfunction. *Blood* **138**, (2021).

17. Kittai, A. S. *et al.* Comorbidities Predict Inferior Survival in Patients Receiving Chimeric Antigen Receptor T Cell Therapy for Diffuse Large B Cell Lymphoma: A Multicenter Analysis. *Biol. Blood Marrow Transplant.* (2020) doi:10.1016/j.bbmt.2020.09.028.

18. Shouse, G. *et al.* Impact of Comorbidities on Outcomes and Toxicity in Patients Treated with CAR T-Cell Therapy for Diffuse Large B Cell Lymphoma (DLBCL): A Multicenter Rwe Study. *Blood* **138**, (2021).

19. Fitzgerald, L. *et al.* Real-world outcomes of elderly patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) treated with chimeric antigen receptor T-cell (CAR-T) therapy. *J. Clin. Oncol.* **38**,

(2020).

20. Sorror, M. L. *et al.* Hematopoietic cell transplantation (HCT)-specific comorbidity index: A new tool for risk assessment before allogeneic HCT. *Blood* **106**, (2005).

21. Kuhnl, A. *et al.* A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience. *Br. J. Haematol.* (2022) doi:10.1111/bjh.18209.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables and Figures

Figure 1: Flow chart of CAR T approved patients.

Reason deemed unfit (n=81)
- Age alone (n=40)
- Frailty (n=11)
- Cardiac comorbidities (n=11)
- Renal comorbidities (n=8)
- Other comorbidities (n=6)
- Multiple comorbidities (n=5)
- Unknown (n=1)

CAR-T approved
N=404

ASCT-unfit
N=81

ASCT-fit
N=323

Drop-out (n=28)
- Clinical deterioration due to PD (n=21)
- Deaths (n=2)
- CNS relapse (n=1)
- Manufacturing failure (n=1)
- Patient fitness/AE (n=2)
- Diagnosis of MDS (n=1)

Apheresis completed
N=70

Apheresis completed
N=303

Drop-out (n=76)
- Clinical deterioration due to PD (n=44)
- Deaths (n=13)
- CNS relapse (n=8)
- Manufacturing failure (n=4)
- Patient fitness/AE (n=4)
- Other (n=3)

25 Axi-cel
28 Tisa-cel

CAR-T infused
N=53

CAR-T infused
N=247

199 Axi-cel
48 Tisa-cel

Non-relapse deaths (n=4)
- Infection (n=1)
- Bowel perforation (n=1)
- Heart failure (n=1)
- GI haemorrhage (n=1)

Median follow-up
19.3 months

Median follow-up
22.7 months

Non-relapse deaths (n=18)
- Infection (n=15; 6/15 COVID19)
- Bowel perforation (n=1)
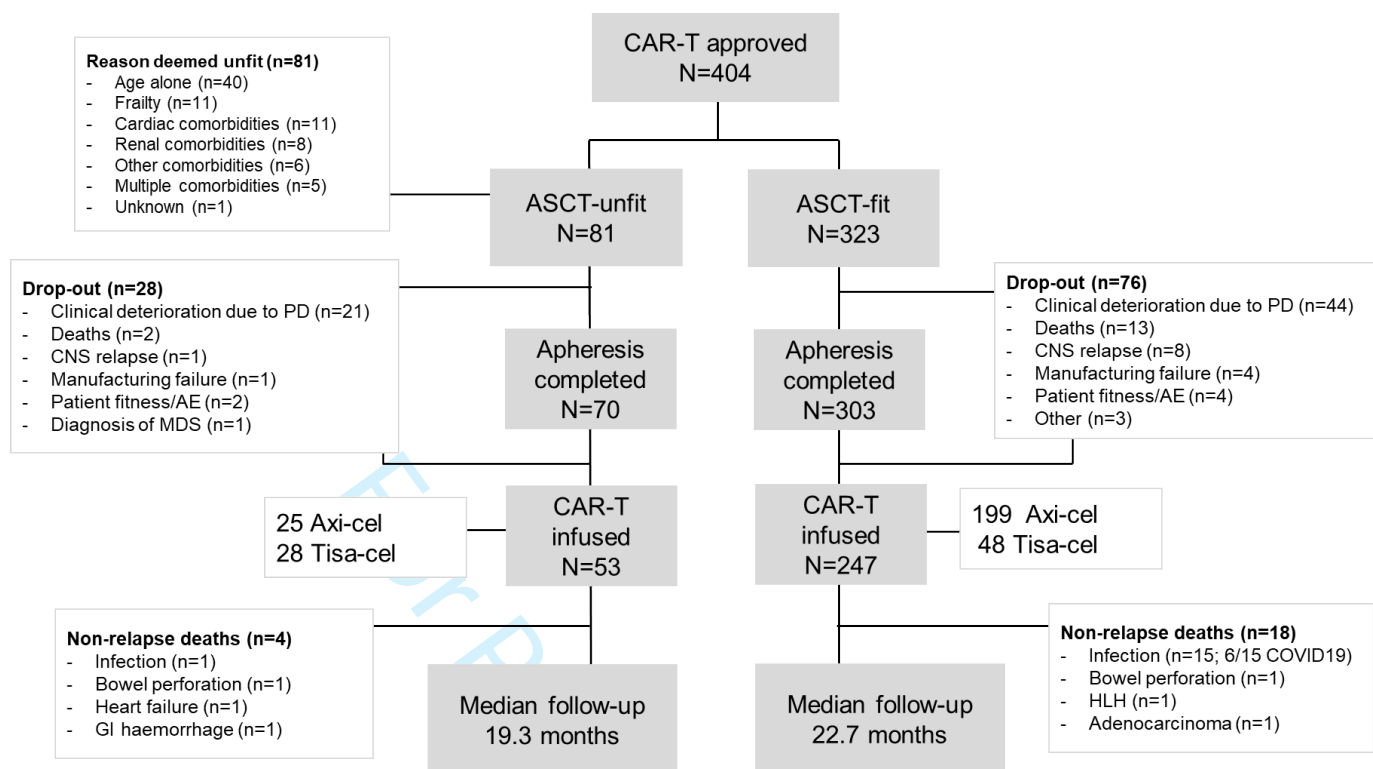- HLH (n=1)
- Adenocarcinoma (n=1)

Table 1: Baseline characteristics and bridging therapy by ASCT-fitness (all approved patients)

	All N=404	Unfit N=81	Fit N=323	*P*
Age, median (range)	60 (18 - 78)	71 (46 - 78)	57 (18 - 74)	<0.0001
Sex, N (%)				
Male	246 (60.9)	52 (64.2)	194 (60.1)	0.50
Female	158 (39.1)	29 (35.8)	129 (39.9)	
Stage at approval, N (%)				
Stage 1-2	77 (19.4)	14 (17.7)	63 (19.9)	0.67
Stage 3-4	319 (80.6)	65 (82.3)	254 (80.1)	
Missing/unknown	8	2	6	
ECOG PS at approval, N (%)				
0	170 (42.1)	22 (27.2)	148 (45.8)	0.0024
1	234 (57.9)	59 (72.8)	175 (54.2)	
HCTCI-score at approval, median (range)	0.0(0 - 6)	0.0(0 - 5)	0.0(0 - 6)	0.00042
HCTCI-score at approval, N(%)				
<3	368 (91.8)	65 (80.2)	303 (94.7)	0.00013*
≥3	33 (8.2)	16 (19.8)	17 (5.3)	
Unknown	3	0	3	
IPI group at approval, N (%)				
0-2	186 (49.1)	22 (29.7)	164 (53.8)	0.00021
3-4	193 (50.9)	52 (70.3)	141 (46.2)	
Missing/unknown	25	7	18	
Bulk>7.5cm, N (%)				
No	276 (69.0)	59 (73.8)	217 (67.8)	0.30
Yes	124 (31.0)	21 (26.3)	103 (32.2)	
Number of extranodal sites, N (%)				
0	142 (35.3)	26 (32.1)	116 (36.1)	0.56**
1	150 (37.3)	32 (39.5)	118 (36.8)	
2	69 (17.2)	14 (17.3)	55 (17.1)	
3+	41 (10.2)	9 (11.1)	32 (10.0)	
Missing/unknown	2	0	2	
Subtype, N (%)				
De novo LBCL	278 (68.8)	54 (66.7)	224 (69.3)	0.0028*
PMBL	20 (5.0)	0	20 (6.2)	
tFL	84 (20.8)	23 (28.4)	61 (18.9)	
t-Other	22 (5.4)	4 (4.9)	18 (5.6)	
Cell-of-origin, N (%)				
GCB	195 (59.5)	46 (66.7)	149 (57.5)	0.17
non-GCB	133 (40.5)	23 (33.3)	110 (42.5)	
Missing/unknown	76	12	64	
Double hit/expressor, N (%)				
No	240 (70.2)	56 (80.0)	184 (67.6)	0.065
Double/Tripe hit	41 (12.0)	8 (11.4)	33 (12.1)	
Double/Triple expressor	61 (17.8)	6 (8.6)	55 (20.2)	
Missing/unknown	62	11	51	
LDH at approval, N (%)				
<ULN	82 (21.6)	16 (20.8)	66 (21.9)	0.44**
>ULN	190 (50.1)	44 (57.1)	146 (48.3)	
>2ULN	107 (28.2)	17 (22.1)	90 (29.8)	
Missing/unknown	25	4	21	
LVEF ≥50%, N (%)				
Yes	254 (91.7)	42 (80.8)	212 (94.2)	0.0015

	All N=404	Unfit N=81	Fit N=323	P
No	23 (8.3)	10 (19.2)	13 (5.8)	
Missing/unknown	127	29	98	
GFR ≥50ml/min, N (%)				
Yes	282 (91.0)	41 (71.9)	241 (95.3)	<0.0001
No	28 (9.0)	16 (28.1)	12 (4.7)	
Missing/unknown	94	24	70	
Previous treatment lines >2, N (%)				
No	245 (60.6)	46 (56.8)	199 (61.6)	0.43
Yes	159 (39.4)	35 (43.2)	124 (38.4)	
Response to last treatment), N (%)				
CR/PR	221 (56.7)	36 (46.8)	185 (59.1)	0.32
SD/PD	169 (43.3)	41 (53.2)	128 (40.9)	
Bridging (apheresed only), N (%)				
None	48 (12.8)	11 (15.3)	37 (12.3)	0.18*
Corticosteroids only	35 (9.4)	7 (9.7)	28 (9.3)	
Systemic treatment	213 (57.0)	43 (59.7)	170 (56.3)	
Radiotherapy	62 (16.6)	6 (8.3)	56 (18.5)	
Combined modality	16 (4.3)	5 (6.9)	11 (3.6)	
Unknown	1	0	1	

P-values are chi-squared for discreate variables, Wilcoxon Mann Whitney for continuous except * which are Fisher's exact and ** which test for trend.

Table 2: Response to CAR T

	Age <70 N=252	Age 70-74 N=41	Age 75+ N=7	P
3 months				
CR	**99 (39.4)**	**19 (46.3)**	**2 (28.6)**	
PR	21 (8.4)	3 (7.3)	0	
PD (inc. PD before assessment)	121 (48.0)	17 ()	5 (71.4)	
Died before assessment	10 (4.0)	2 (4.9)	0	
Not done	1	0	0	
ORR	**120 (47.8)**	**22 (53.7)**	**2 (28.6)**	**0.89**
6 months				
CR	**98 (38.9)**	**15 (36.6)**	**2 (28.6)**	
PR	11 (4.4)	1 (2.4)	0	
PD (inc. PD before assessment)	132 (52.4)	21 (51.2)	5 (71.4)	
Died before assessment	11 (4.4)	4 (9.8)	0	
ORR	**109 (43.3)**	**16 (39.0)**	**2 (28.6)**	**0.66**
Best response				
ORR	**71.0%**	**78.1%**	**85.7%**	**0.37**
CR	**49.6%**	**53.7%**	**57.1%**	

PR, partial response

13

Table 3. CAR T toxicity

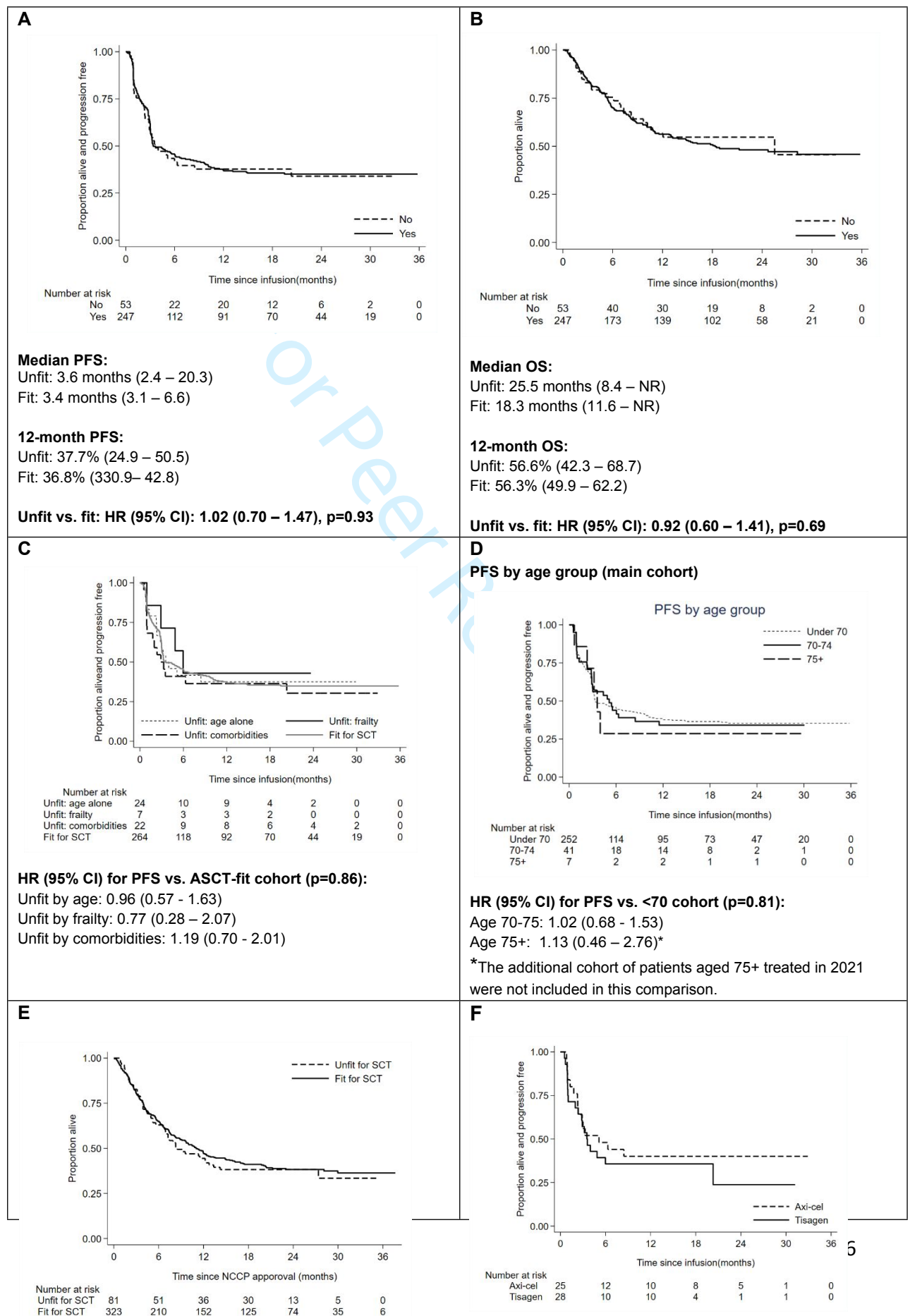|	Axi-cel		Tisa-cel			
	Unfit **N=25**	**Fit** **N=199**	**Unfit** **N=28**	**Fit** **N=48**	*OR unfit vs fit (95% CI)**	*p-value*
Tocilizumab used, N (%)						
No	4 (16.0)	56 (28.1)	12 (42.9)	28 (58.3)	1.94 (0.95 – 3.98)	0.069
Yes	21 (84.0)	143 (71.9)	16 (57.1)	20 (41.7)		
Steroid used, N (%)						
No	4 (16.0)	56 (28.1)	21 (75.0)	36 (75.0)	1.28 (0.66 – 2.46)	0.46
Yes	21 (84.0)	143 (71.9)	7 (25.0)	12 (25.0)		
ICU, N (%)						
No	4 (16.0)	56 (28.1)	25 (89.3)	38 (79.2)	0.80 (0.38 to 1.69)	0.55
Yes	21 (84.0)	143 (71.9)	3 (10.7)	10 (20.8)		
Any CRS, N (%)						
No	3 (12.0)	13 (6.5)	5 (17.9)	15 (31.3)	1.28 (0.51 – 3.20)	0.60
Yes	22 (88.0)	186 (93.5)	23 (82.1)	33 (68.8)		
Grade ≥3 CRS, N (%)						
No	25 (100.0)	182 (91.5)	27 (96.4)	43 (89.6)	0.18 (0.02 – 1.37)	0.097
Yes	0	17 (8.5)	1 (3.6)	5 (10.4)		
Any ICANS grade, N (%)[#]						
No	10 (40.0)	115 (57.8)	22 (78.6)	43 (89.6)	2.14 (1.05 - 4.36)	0.036
Yes	15 (60.0)	84 (42.2)	6 (21.4)	5 (10.4)		
Grade ≥3 ICANS, N (%)[#]						
No	20 (80.0)	160 (80.4)	27 (96.4)	46 (95.8)	1.00 (0.38 – 2.60)	0.99
Yes	5 (20.0)	39 (19.6)	1 (3.6)	2 (4.2)		
Grade ≥3 neutropenia at 3 months, N (%)						
No	11 (84.6)	73 (78.5)	9 (90.0)	12 (80.0)	0.88 (0.41 – 1.89)	0.73
Yes	2 (15.4)	20 (21.5)	1 (10.0)	3 (20.0)		
Missing/unknown/patient relapsed or died	12	106	18	33		
Grade ≥3 thrombocytopenia at 3 months, N (%)						
No	12 (92.3)	79 (84.9)	9 (90.0)	12 (80.0)	0.91 (0.43 – 1.94)	0.81
Yes	1 (7.7)	14 (15.1)	1 (10.0)	3 (20.0)		
Missing/unknown/patient relapsed or died	12	106	18	33		

*Adjusted for product; ICU, Intensive Care Unit

[#]Risk of ICANS according to age (for an increase of 10 years): any ICANS OR: 1.50 (1.21 – 1.86), p <0.0001, grade ≥3 ICANS: OR 1.06 (0.83 – 1.37), p = 0.63

14

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

15

Figure 2: Long-term outcomes according to ASCT-fitness. (A) PFS in unfit vs. fit. (B) OS in unfit vs. fit. (C) PFS according to reason for being deemed unfit. (D) PFS according to CAR T product in ASCT-unfit. (E) OS of ITT cohort unfit vs. fit. (F) PFS for the over 75 cohort.

A

Number at risk

No	53	22	20	12	6	2	0
Yes	247	112	91	70	44	19	0

Median PFS:
Unfit: 3.6 months (2.4 – 20.3)
Fit: 3.4 months (3.1 – 6.6)

12-month PFS:
Unfit: 37.7% (24.9 – 50.5)
Fit: 36.8% (330.9– 42.8)

Unfit vs. fit: HR (95% CI): 1.02 (0.70 – 1.47), p=0.93

B

Number at risk

No	53	40	30	19	8	2	0
Yes	247	173	139	102	58	21	0

Median OS:
Unfit: 25.5 months (8.4 – NR)
Fit: 18.3 months (11.6 – NR)

12-month OS:
Unfit: 56.6% (42.3 – 68.7)
Fit: 56.3% (49.9 – 62.2)

Unfit vs. fit: HR (95% CI): 0.92 (0.60 – 1.41), p=0.69

C

Number at risk

Unfit: age alone	24	10	9	4	2	0	0
Unfit: frailty	7	3	3	2	0	0	0
Unfit: comorbidities	22	9	8	6	4	2	0
Fit for SCT	264	118	92	70	44	19	0

HR (95% CI) for PFS vs. ASCT-fit cohort (p=0.86):
Unfit by age: 0.96 (0.57 - 1.63)
Unfit by frailty: 0.77 (0.28 – 2.07)
Unfit by comorbidities: 1.19 (0.70 - 2.01)

D

PFS by age group (main cohort)

Number at risk

Under 70	252	114	95	73	47	20	0
70-74	41	18	14	8	2	1	0
75+	7	2	2	1	1	0	0

HR (95% CI) for PFS vs. <70 cohort (p=0.81):
Age 70-75: 1.02 (0.68 - 1.53)
Age 75+: 1.13 (0.46 – 2.76)*

*The additional cohort of patients aged 75+ treated in 2021 were not included in this comparison.

E

Number at risk

Unfit for SCT	81	51	36	30	13	5	0
Fit for SCT	323	210	152	125	74	35	6

F

Number at risk

Axi-cel	25	12	10	8	5	1	0
Tisagen	28	10	10	4	1	1	0

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| **Median OS (ITT cohort):**
Unfit: 8.5 months (6.8 – 13.4)
Fit: 11.0 months (8.7 – 13.6)

12-month OS:
Unfit: 38.3% (27.8 – 48.7)
Fit: 38.3% (32.9 – 43.7)

Unfit vs. fit: HR (95% CI): 1.07 (0.78 – 1.45), p=0.69 | **Median PFS:**
Tisa-cel: 3.5 months (1.0 – 20.3)
Axi-cel: 5.1 months (2.3 – NR)

12-month PFS:
Tisa-cel: 35.7% (18.8 – 53.0)
Axi-cel: 40.0% (21.3 – 58.1)

Tisa-cel vs. Axi-cel: HR (95% CI): 1.25 (0.64 – 2.47) , p=0.52 |