A national service for delivering CD19 CAR-T in large B-cell lymphoma – the UK real-world experience

A Kuhnl,[1] C Roddie,[2,3] AA Kirkwood,[4] E Tholouli,[5] T Menne,[6] A Patel,[7] C Besley,[8] S Chaganti,[9] R Sanderson,[1] M O'Reilly,[2] J Norman,[5] W Osborne,[6] A Bloor,[7] S Lugthart,[8] R Malladi,[9,10] PEM Patten,[1,11] L Neill,[2] N Martinez-Cibrian,[5] H Kennedy,[6] EH Phillips,[12,13] C Jones,[14] K Sharplin,[8] D El-Sharkawi,[15] A-L Latif,[16] A Mathew,[9] B Uttenthal,[10] O Stewart,[1] MAV Marzolini,[2] W Townsend,[2] K Cwynarski,[2] K Ardeshna,[2] A Ardavan,[17,18] K Robinson,[17] A Pagliuca,[1] GP Collins,[19] R Johnson,[20] A McMillan[21]

1 Department of Haematology, King's College Hospital, London, UK
2 Department of Haematology, University College London Hospitals, London, UK
3 UCL Cancer Institute, University College London, London, UK
4 Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, University College London, London, UK
5 Department of Haematology, Manchester Royal Infirmary, Manchester, UK
6 Department of Haematology, Freeman Hospital, Newcastle, 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, Addenbrookes Hospital, Cambridge, UK
11 Comprehensive Cancer Centre, King's College London, London, UK
12 Department of Medical Oncology, The Christie Hospital, Manchester, UK
13 Division of Cancer Sciences, University of Manchester, Manchester, UK
14 Department of Haematology. University Hospital of Wales, Cardiff, UK
15 Department of Haematology, Royal Marsden Hospital, London, UK
16 Department of Haematology, Queen Elizabeth II Hospital, Glasgow, UK
17 NCRI Consumer Forum, London, UK
18 Department of Physics, University of Oxford, UK
19 Department of Haematology, Oxford University Hospital, Oxford, UK
20 Department of Haematology, St. James's Hospital, Leeds, UK
21 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

Abstract

CD19 CAR-T have emerged as a new standard treatment for relapsed/refractory (r/r) large B-cell lymphoma (LBCL). CAR-T real-world (RW) outcomes published to date suggest significant variability across countries. We provide results of a large, national cohort of patients intended to be treated with CAR-T in the UK.

Consecutive patients with r/r LBCL approved for CAR-T by the National CAR-T Clinical Panel between December 2018-November 2020 across all UK CAR-T centres were included. 404/432 patients were approved (292 axicabtagene ciloleucel (axi-cel), 112 tisagenlecleucel (tisa-cel)), 300 (74%) received the cells. 110/300 (38.3%) patients achieved complete remission (CR) at 6 months (m). The overall response rate was 77% (52% CR) for axi-cel, 57% (44% CR) for tisa-cel. The 12-month progression-free survival was 41.8% (axi-cel) and 27.4% (tisa-cel). Median overall survival for the intention-to-treat population was 10.5m, 16.2m for infused patients. The incidence of grade≥3 cytokine release syndrome and neurotoxicity were 7.6%/19.6% for axi-cel and 7.9%/3.9% for tisa-cel.

This prospective RW population of CAR-T eligible patients offers important insights into the clinical benefit of CD19 CAR-T in LBCL in daily practice. Our results confirm long-term efficacy in patients receiving treatment similar to the pivotal trials, but highlight the significance of early CAR-T failure.

Introduction

Chimeric Antigen Receptor (CAR) T-cell therapies targeting CD19 have transformed treatment options for patients with relapsed/refractory (r/r) large B-cell lymphoma (LBCL) who have failed two or more lines of treatment, a patient population with historically dismal outcome.[1] Two CD19 CAR-T products, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) have been licensed in this indication; FDA approval for a third product, lisocabtagene maraleucel,[2] has recently been granted and European approval is expected imminently.

Results from the registrational trials, ZUMA-1 and JULIET, suggest that 35-40% of patients receiving CD19 CAR-T achieve long-term remission.[3,4] Two retrospective US axi-cel real-world (RW) datasets have been published showing outcomes similar to ZUMA-1.[5,6] Preliminary results from European RW cohorts appear more heterogeneous, likely reflecting differences in patient selection, bridging approaches and manufacturing times.[7–9] Collection of larger registry datasets of axi-cel and tisa-cel treated patients are underway.[10,11] Most datasets are restricted to the "intention-to-manufacture" or infused patient cohorts, not providing results of the intention-to-treat (ITT) population, which should be the benchmark for comparing CAR-T to emerging therapies such as bispecific antibodies.

A clear understanding of the determinants of long-term outcome after CD19 CAR-T in the RW setting will be critical to assess cost-effectiveness and define criteria for future funding. Several disease and patient characteristics have been identified to be associated with inferior outcome after CAR-T, including LDH, ECOG performance status (PS), total metabolic tumour volume, and extranodal involvement pre-infusion.[5–7] However, there is no established predictive model or consensus about how such risk factors should guide upfront decision-making. Of note, none of these studies have assessed the risk of early drop-out pre-infusion as part of the primary failure rate, which is a highly relevant endpoint for CAR-T patients.

England was the first European country to implement a national service for the delivery of CD19 CAR-T. Treatment is approved by the National CAR-T Clinical Panel (NCCP) and delivered at geographically spread commissioned CAR-T centers.[12] This centralized structure enabled the collection of prospective clinical data from a national cohort of patients intended to be treated with CAR-T, fulfilling uniform eligibility criteria. We report results of the first 404 patients with r/r LBCL enrolled on the UK national CAR-T program.

Methods

Patients

Consecutive patients with r/r LBCL submitted to the NCCP for approval of treatment with licensed CD19 CAR-T between December 2018 and November 2020 were included. An additional 12 patients approved by the Scottish CAR-T centre based on the same eligibility criteria were included (NCCP equivalent). Eligibility criteria for receiving CAR-T treatment via the National Health Service (NHS) Cancer Drug Fund are provided in the Supplement. Patients were required to have an ECOG PS of 0-1 at the time of submission and PS 0-2 at the time of infusion. All NCCP-approved patients were included in the ITT population. Patients were treated at commissioned CAR-T centres (see Supplement). The choice of CAR-T product was at the centre's discretion (both products available at all centres). Data were collected retrospectively from electronic hospital records at the treating centre as a National Service Evaluation.

Treatment and Assessments

Bridging therapy was defined as any lymphoma-directed therapy administered between leukapheresis and lymphodepletion chemotherapy. Lymphodepletion with cyclophosphamide and fludarabine was delivered as per SmPC and local guidelines. Cytokine release syndrome (CRS) and Immune effector cell-associated neurotoxicity syndrome (ICANS) grading was performed as per ASTCT consensus guidelines.[13] Management of treatment-related toxicities was as per centre's local practice. Treatment response was assessed locally according to the Lugano 2014 classification at month 1, 3, and 6 after infusion.[14]

Statistical considerations

Pre-treatment factors and toxicity were compared using Wilcoxon Mann-Whitney/Kruskal Wallis (continuous variables) or Chi-squared/Fisher's exact tests (discrete variables). Logistic regression was used to assess the risk of primary treatment failure (failure to receive cells, death or progressive disease (PD) by the first response assessment). Progression-free survival (PFS, events: progression and death) and overall survival (OS, event: death) were analysed using Kaplan-Meier survival analysis and Cox regression. Competing risk analysis by the method of Fine and Gray was used to analyse progression and non-relapse mortality (NRM) cumulative incidence rates, with death in remission and relapse counted as competing risks, respectively. Times were measured from the date of infusion until the date of the first event with patients who did not experience an event censored at the date last seen, except for the ITT analysis of OS where time was measured from the date of NCCP approval, and analyses for responders, which are measured from the date of response. Multivariable models used stepwise selection techniques (see Table 3 for further details).

Results

Patient characteristics

Between December 2018 and November 2020, 432 patients with r/r LBCL were submitted to the NCCP for consideration of CD19 CAR-T, of which 404 were approved (Figure 1), 292 for axi-cel and 112 for tisa-cel. 300 patients (224 axi-cel, 76 tisa-cel) successfully received CAR-T. 104/404 (26%) did not proceed to infusion, mainly due to rapid disease progression (Figure 1). The reasons for drop-out did not significantly differ between products (p=0.17), The median follow-up was 13.9 months (interquartile range (IQR) 9.1-19.4).

Patients' baseline characteristics at the time of approval and at lymphodepletion are provided in Table 1. Patients undergoing tisa-cel treatment were significantly older, had a lower incidence of bulky disease at baseline and a higher lymphocyte count pre-lymphodepletion. Other variables were comparable between the cohorts.

The median time from CAR-T approval to infusion was 57 days (IQR 49-71; 56 days for axi-cel (IQR 49-69), 69 days for tisa-cel (IQR 58-89); p<0.001) and 42 days (IQR 37-53) from apheresis to infusion (40 days for axi-cel (IQR 35-48), 50 days for tisa-cel (IQR 43-64; p<0.001)). 260/300 (86.7%) patients received bridging therapy: 29 corticosteroids only, 167 systemic therapies, 54 radiotherapy, and 10 combined modality treatment. The use and modality of bridging therapy was comparable between the axi-cel and tisa-cel cohorts (Table 1B). Details of systemic bridging regimens are provided in the Supplement.

Efficacy

Of 300 infused patients, the 3-month response rate was 48% (40% CR; Table 2). 111/294 (37.8%) patients were in ongoing CR at 6 months (40% for axi-cel, 32% for tisa-cel; Table 2, Supplementary Figure S1). Of those with CR as best response, 76.4% had achieved CR by month 1, with a further 18.1% and 5.6% achieving CR by month 3 and month 6, respectively. Most progression events (143/161 (88.8%)) occurred early, i.e. by the 3-month response assessment, and in 84/161 (52%) of cases, progression followed a transient response. The best ORR was 77% (52% CR) for axi-cel treated patients and 57% (44% CR) for tisa-cel (Table 2). The median duration of response (DOR) has not been reached, but the 12-month PFS rate in responders was 52.0% (95% CI 44.7-58.8). We observed an improvement of outcomes when comparing the first and second year of the CAR-T programme: 6-month ORR 34.6% vs 49.6 % (p=0.011; axi-cel: 37.6% vs 52.3%; tisa-cel: 27.1% vs 35.7%).

Survival estimates are shown in Figure 2. Median PFS for all treated patients was 3.5 months (5.5 months (95% CI 3.3-10.1) for axi-cel and 2.9 months (95% CI 1.7-3.6) for tisa-cel). The 12-month PFS was 41.8% (95% CI 35.0-48.4) in the axi-cel and 27.4% (95% CI 17.5-38.3) in the tisa-cel cohort. Patients who achieved CR had significantly longer PFS than patients with PR as best response (Supplementary Figure S2A). Patients in CR at 6 months had a 89.8%

(95% CI 80.6-94.8) PFS rate at 18 months post-infusion, with no events reported after 1 year, though median follow-up is short at 9.5 months (Supplementary Figure S2B).

Median OS from the time of infusion was 14.8 months (axi-cel: 15.6 months (95% CI 11.1-NR (not reached)), tisa-cel: 10.2 months (95% CI 7.7-NR), with a 12-month OS of 53.9% (axi-cel: 57.1% (95% CI 49.8-63.8); tisa-cel: 43.8% (95% CI 31.1-55.9)). Median OS for the ITT population was 10.5 months (95% CI 8.3-12.0) from the time of approval, 16.2 months (95% CI 12.4-NR) for infused patients, and 2.1 months (95% CI 1.94-2.69) for patients not infused (Figure 2D).

Risk factors for early failure and long-term outcome

We aimed to identify patients at risk of early failure, as defined by failure to receive cells, death or PD by the first response assessment, i.e. a group of patients who appeared to lack benefit from CAR-T. Early failure was seen in 164/395 (41.5%) of the evaluable ITT population, less commonly in primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (tFL) compared to the other subtypes (Table 3A). ECOG PS, LDH >2 ULN, and liver involvement at the time of CAR-T approval were independently associated with early failure in multivariable analysis (Table 3A). We grouped the three factors conferring high risk and considered them separately by disease subtype. The presence of one factor increased the risk of early failure within the DLBCL cohort but there was no evidence of an increased risk within the PMBCL/tFL/t-other groups. Patients with two or more of the factors had an increased risk of early failure for DLBCL and tFL groups, with more than 65% having early failure (odds ratios of 5.46 (95% CI 2.61- 11.43) and 11.0 (95% CI 2.83 – 42.7)). There was no evidence of a difference for PMBL and t-other, however numbers were too small to draw strong conclusions (Table 3B). For patients who underwent infusion, presence of ≥3 extranodal sites at baseline and high LDH at lymphodepletion (>ULN) were significantly associated with shorter PFS in multivariable analysis (Table 3C). Patients with presence of both these risk factors had a 12-month PFS of only 9.5% (Supplementary Figure S3). High LDH, impaired ECOG PS and low platelet count at lymphodepletion were associated with inferior OS (Table 3C; Supplementary Figure S4). There was no significant association of age, bulk, histological/molecular subgroups and turnaround times on outcome (univariable analysis for PFS and OS shown in the Supplement).

We also assessed associations between involvement of specific extra nodal sites at baseline and survival (Supplementary Table S4). Patients with liver and bone marrow involvement had significantly worse PFS and OS (HRs >2). However, numbers of patients with certain anatomical sites were small, so firm conclusions about a lack of association are difficult to draw.

Toxicities

CAR-T related toxicities are shown in Table 4. Grade ≥3 CRS occurred in 7.6% of axi-cel and 7.9% of tisa-cel treated patients, grade ≥3 ICANS in 19.6% and 3.9%, respectively. 27.8% of patients required ICU admission (31.4% axi-cel; 17.1% tisa-cel), but this was limited to observation/inotropes for the majority of patients (Table 4). Tocilizumab and corticosteroids were used in 66.9% and 38.8% of patients, respectively. The NRM rate was 7.3% at 12 months (Supplementary Figure S5). Most deaths were related to infectious complications (6/21 COVID19-related; Supplementary Table S5). Ongoing grade ≥3 neutropenia and thrombocytopenia at 3 months were observed in 20.8%/14.2% of axi-cel and 16.0%/16.0% of tisa-cel treated patients (Table 4).

Discussion

Identifying LBCL patient subgroups who derive clinical benefit from CD19 CAR-T in the RW setting is key to a patient-centred and cost-effective use of this novel treatment. This is the first RW dataset providing ITT outcomes from a national cohort of CAR-T eligible patients selected by uniform, centrally reviewed criteria. Since a significant number of eligible patients, 26% in our cohort, fail to proceed with CAR-T treatment, results from the infused ("modified ITT") population will inherently over-estimate the clinical benefit of CAR-T and thus be of limited value for upfront decision-making. ITT outcomes are not published for most CAR-T datasets, apart from the French RW experience and the JULIET trial (drop-out rates of 15% and 33%, respectively),[4,15] but should be the benchmark to compare CAR-T against alternative treatments. The unique CAR-T approval system in the UK through a central, independent panel not only provides transparent treatment access, but also ITT outcomes from a consecutive national cohort.

Efficacy outcomes in our cohort of infused patients were similar to results from the pivotal trials and other RW datasets,[4,5,8,16] with a 12-month PFS for axi-cel treated patients of 42% (ZUMA-1: 44%), and 27% for tisa-cel (JULIET: 31%). Patients who achieved CR at 6 months had an about 90% chance of ongoing remission 18 months post-infusion. However, 52% of responding patients had only transient response and progressed by month 6, which highlights the limited value of best ORR in this setting. We observed an improvement of outcomes during the analysis period, without a change in disease risk, reflecting the learning curve and evolving experience after implementing a new and complex treatment.

When investigating predictors of outcome, we wanted to consider two distinct clinical questions. To identify factors associated with high risk of primary failure in the ITT population (drop-out pre-infusion or early progression/death post-infusion), where clinical benefit from CAR-T is unlikely, and factors associated with long-term survival post-CAR-T. While our simplified model requires further validation, it showed that DLBCL and tFL patients with 2 or

more high risk factors (high LDH (>2 ULN), ECOG PS 1 or liver involvement at CAR-T approval) had a more than 5-fold increased risk of primary failure (54/77 failed) compared to those with no risk factors. For these patients, appropriate counselling will be important, and novel bridging approaches or alternative therapies/palliation could be considered. Vercellino *et al.* demonstrated that high total metabolic tumor volume pre-infusion and extranodal involvement of two or more sites were associated with the risk of progression within one month of CAR-T infusion, but they did not include the risk of pre-infusion drop-out.[7] Moreover, a main limitation of pre-lymphodepletion models aiming to predict primary failure is deferring risk assessment to a late timepoint on the pathway rather than informing decision-making upfront. Our second outcome analysis focused on factors associated with long-term survival after CAR-T. Consistent with previous datasets, high LDH (>ULN) and involvement of ≥3 extranodal sites were found to be strongly associated with PFS, whereas ECOG PS was only independently predictive for OS in our cohort.[5,7,8] We further assessed the risk of specific extranodal sites, an analysis which has not been performed in other studies. Interestingly, liver and bone marrow involvement were associated with inferior PFS and OS. However, numbers of events precluded multivariable analyses including involved sites and larger datasets are needed to fully assess the clinical benefit of CAR-T in these specific subgroups.

Most of the risk factors we identified are known prognostic factors in LBCL and not specific to the CAR-T setting. It is therefore difficult to draw conclusions for daily practice, e.g. whether the presence of certain high-risk features should preclude CAR-T in the absence of better alternative treatments. Interestingly, a recent single-centre analysis from Memorial Sloan Kettering Cancer Centre indicated that long-term clinical benefit of CAR-T over standard third-line therapies was not convincing when adjusting for high-risk patient characteristics.[17]

There was clear evidence for selection bias of the two products in the UK RW setting, and outcomes of the axi-cel and tisa-cel cohorts cannot be directly compared. Tisa-cel was less commonly used in patients with bulky disease and more commonly used in elderly patients, reflecting the favourable toxicity profile.[4] Data from the French RW experience suggested a potentially higher rate of early progressions after tisa-cel vs. axi-cel,[7] which is somewhat mirrored in our dataset, with a 40% early PD rate and a relatively short median PFS in tisa-cel treated patients. However, long-term survival appears similar and potential differences between products are likely over-estimated when looking at markers of early response.

CAR-T turnaround times were longer compared to the US cohorts, similar to what has been reported in other European centres.[7,8] This will likely lead to a higher drop-out rate in the ITT population and might have a negative impact on efficacy if patients have a more proliferative, high-burden disease by the time they receive the cells. Interestingly, time-to-infusion did not impact on outcome in our cohort, which might reflect planned delays for patients who were

stable on bridging therapy and does not necessarily argue against the importance of rapid turnaround times for individual patients.

The incidence of high-grade CAR-T toxicities was favourable for both products compared to the pivotal trials and other RW datasets. For tisa-cel, a consistently low rate of severe CRS and ICANS was observed across different RW datasets,[8,11,9] in line with the more permissive use of tocilizumab and corticosteroids in daily practice. For axi-cel, no difference in high-grade ICANS between ZUMA-1 and the two large US RW cohorts was seen, but there was a lower rate in European datasets including ours.[5,6,15,18] Similar to the German RW cohort,[9] we observed ongoing NRM events beyond month 1, with a 12-month rate of 7%, mainly caused by complications from long-term cytopenia and infections (6/21 were COVID19-related deaths).

In conclusion, this large, national dataset of standard-of-care CAR-T treatment for LBCL provides valuable insights into clinical outcomes of patients and specific subgroups intended for CAR-T therapy. Our results significantly add to existing RW datasets and may help to optimize patient selection and to assess the clinical benefit of CAR-T against alternative treatments. From a structural perspective, we demonstrate that implementation of a national service for delivering a novel, complex therapy is feasible and facilitates collection of prospective IIT outcomes.

Acknowledgements

The authors would like to thank the patients, their relatives and caregivers, and investigators and staff involved in this analysis. W.T. receives funding from the NIHR UCLH Biomedical Research Centre.

Declaration of interests: A.K. and C.R. have served on advisory boards and received honoraria from Kite/Gilead, Novartis and Celgene/BMS. A.A.K. received honoraria from Kite/Gilead. E.T. has received speaker and consultancy fees from Novartis, Kite/Gilead, Celgene/BMS and Janssen. C.B. has served on advisory boards for Novartis and Kite/Gilead and received honoraria from Kite/Gilead, Novartis and Janssen. S.C, has served on advisory boards, provided consultancy services, and received meeting attendance support from Takeda, Novartis, Celgene/BMS, Kite/Gilead, Atara Bio, Incyte, and Roche. R.S. and M.O. have 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. W.O. has received honoraria from Roche, Takeda,

Pfizer, Servier, Kite/Gilead, MSD, Novartis, Beigene, Astra Zeneca, Syneos, Autolus, Kyowa Kirin, Abbvie, Incyte, BMS. R.M. has served on advisory boards and received honoraria from Kite/Gilead and Novartis. A.B. has received speaker fees from Novartis and conference fees from Kit/Gilead. P.E.M.P. has received research funding from Roche, Kite/Gilead, has served on advisory boards for Novartis and Abbvie, has received honoraria from Abbvie, Astra Zeneca, Gilead, Janssen, Novartis and has received support for attending meetings from Abbvie and Janssen. E.H.P. has received speaker fees from Kite/Gilead and conference fees from Celgene/BMS. D.E.-S. has served on advisory boards for Abbvie, ASTEX, AstraZeneca, Beigene, Janssen, Kyowa Kiirin and received honoraria from Abbvie, AstraZeneca, Kite/Gilead, Janssen, Roche, Takeda and support for attending meetings from Abbvie and Novartis. A.-L.L. has received honoraria from Kite, Jazz, Daiichi Sankyo, Novartis, Amgen, AbbVie, Astellas and participated in company-sponsored speaker's bureau for Kite, Takeda UK, Astellas. B.U. has served on advisory boards and received conference sponsorship from Kite/Gilead, Novartis and Celgene/BMS and served on advisory boards for Atara. O.S. has received honoraria from Kite/Gilead and Novartis. W.T. has received honoraria and consultancy fees from Celgene/BMS, Incyte, and Roche. K.C. has received consultancy fees from Atara, Celgene/BMS, Kite/Gilead, Incyte, Janssen, Takeda, has participated in company-sponsored speaker's bureau for Kite/Gilead, Incyte, Roche, Takeda, and conference fees from Celgene/BMS, Kite/Gilead, Roche and Takeda. G.P.C. has served on advisory boards and received honoraria from Kite/Gilead and Novartis. R.J. has served on advisory boards and received honoraria from Kite/Gilead and Novartis.

The remaining authors have no conflict of interests to declare.

Data sharing

Deidentified clinical data will be made available upon request to the corresponding author.

References

1. Crump, M. *et al.* Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood* **130**, 1800–1808 (2017).

2. Abramson, J. S. *et al.* Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet* **396**, (2020).

3. 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).

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

5. 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).

6. 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).

7. 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).

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

9. Dreger, P. *et al.* Ootcome determinants of commercial CAR-T cell therapy for large B-cell lymphoma: Results of the GLA/DRST real world analysis. *Hematol. Oncol.* **39**, (2021).

10. Pasquini, M. C. *et al.* Post-Marketing Use Outcomes of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma (LBCL) in the United States (US). *Blood* **134**, (2019).

11. Jaglowski, S. *et al.* Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy (CT) Registry. *Blood* **134**, (2019).

12. Kuhnl, A. *et al.* Real-World Data of High-Grade Lymphoma Patients Treated with CD19 CAR-T in England. *Blood* **134**, (2019).

13. Lee, D. W. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol. Blood Marrow Transplant.* **25**, 625–638 (2019).

14. Cheson, B. D. *et al.* Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J. Clin. Oncol.* **32**, 3059–3067 (2014).

15. Gouill, S. *et al.* First results of DLBCL patients treated with CAR-T cells and enrolled in DESCAR-T registry, a French real-life database for CAR-T cells in hematologic malignancies. *Hematol. Oncol.* **39**, (2021).

16. Locke, F. L. *et al.* Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol.* **20**, 31–42 (2019).

17. Sermer, D. *et al.* Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. *Blood Adv.* **4**, (2020).

18. Rejeski, K. *et al.* CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma. *Blood* (2021) doi:10.1182/blood.2020010543.

Tables

Table 1: Baseline characteristics (A) at the time of approval and (B) at the time of lymphodepletion.

(A)

Characteristics	**All** **N=300**	**Axi-cel** **N=224**	**Tisa-cel** **N=76**	***P***
Age, years (median, range)	59.0 (18 - 78)	57.0 (18 - 78)	63.5 (30 - 77)	0.0001
Sex, male, N (%)	185 (61.7)	143 (63.8)	42 (55.3)	0.18
ECOG PS, N (%)				0.39
0	147 (49.0)	113 (50.4)	34 (44.7)	
1	153 (51.0)	111 (49.6)	42 (55.3)	
Stage, N (%)				0.64
I-II	64 (21.6)	49 (22.3)	15 (19.7)	
III-IV	232 (78.4)	171 (77.7)	61 (80.3)	
Missing/unknown	4	4	0	
Bulk (≥7.5cm, N (%)	81 (27.0	71 (31.7)	10 (13.2)	0.0017
LDH, N (%)				0.12**
Normal	68 (23.7)	48 (22.3)	20 (27.8)	
>ULN	156 (54.4)	115 (53.5)	41 (56.9)	
>2 ULN	63 (22.0)	52 (24.2)	11 (15.3)	
Missing/unknown	13	9	4	
Extranodal involvement, N (%)				0.90**
None	109 (36.5)	84 (37.7)	25 (32.9)	
1 site	112 (37.5)	79 (35.4)	33 (43.4)	
2 sites	47 (15.7)	35 (15.7)	12 (15.8)	
≥3 sites	31 (10.4)	25 (11.2)	6 (7.9)	
Missing/unknown	1	1	0	
IPI score, N (%)				0.56
0-2	149 (52.3)	114 (43.3)	35 (49.3)	
3-4	136 (47.7)	100 (46.7)	36 (50.7)	
Missing/unknown	13	10	5	
Refractoriness, N (%)				0.43
Previous response	160 (55.4)	123 (56.7)	37 (51.4)	
Refractory	129 (44.6)	94 (43.3)	35 (48.6)	
Missing/unknown	11	7	4	
SD/PD to last treatment	218 (72.7)	160 (71.4)	58 (76.3)	0.41
Previous treatment lines, N (%)				0.39
≥3	112 (37.3)	83 (37.1)	32 (42.1)	
Prior transplant, N (%)				0.41*

No	250 (83.3)	183 (81.7)	67 (88.2)	
Autologous	45 (15.0)	37 (16.5)	8 (10.5)	
Allogeneic	5 (1.7)	4 (1.8)	1 (1.3)	
Histological subtypes, N (%)				0.13
De novo DLBCL	200 (66.7)	143 (63.8)	57 (75.0)	
Transformed FL	64 (21.3)	49 (21.9)	15 (19.7)	
Transformed, other[#]	17 (5.7)	13 (5.8)	4 (5.2)	
PMBCL	19 (6.3)	19 (8.5)	0	
COO subtype, N (%)				0.68
GCB	150 (61.5)	109 (62.3)	41 (59.4)	
Non-GCB	94 (38.5)	66 (37.7)	28 (40.6)	
Missing/unknown	56	49	7	
Molecular risk groups, N (%)				0.78
Normal	181 (70.4)	133 (70.0)	48 (71.6)	
Double/triple hit	33 (12.8)	26 (13.7)	7 (10.4)	
Double/triple expresser	43 (16.7)	31 (16.3)	12 (17.9)	
Missing/unknown	43	34	9	

*****N=289

IPI= International Prognostic Index. DLBCL= Diffuse large B-cell lymphoma. COO= Cell-of-origin. GCB= germinal center B-cell.

Discrete variables are compared using chi-squared, Fisher's (*) or chi squared for trend (**). Continuous variables are comparted using the Wilcoxon Mann Whitney test. PMBCL patients were excluded from the subtype comparison. [#]transformed other: transformed lymphoplasmacytic lymphoma (N=1), transformed marginal zone lymphoma (N=16), transformed nodular LP Hodgkin lymphoma (N=4), Richter's transformation (N=1).

(B)

Characteristics	**All** **N=300**	**Axi-cel** **N=224**	**Tisa-cel** **N=76**	***P***
Bridging, N (%)				0.59
None	40 (13.3)	26 (11.6)	14 (18.4)	
Corticosteroids only	29 (9.7)	22 (9.8)	7 (9.2)	
Systemic treatment (ST) +/- steroids	167 (55.7)	125 (55.8)	41 (54.0)	
RT +/- corticosteroids	54 (18.0)	43 (19.2)	11 (14.5)	
CMT	10 (3.3)	8 (3.6)	3 (4.0)	
Response to ST, N (%)	**N=177**	**N=133**	**N=44**	0.51
CR/PR	66 (39.5)	48 (38.1)	18 (43.9)	
SD/PD	101 (60.5)	78 (61.9)	23 (56.1)	
Missing/unknown	10	7	3	
ECOG PS, N (%)				0.88
0-1	271 (90.3)	202 (90.2)	69 (90.8)	
2	29 (9.7)	22 (9.8)	7 (9.2)	
LDH, N (%)				0.18
Normal	72 (28.3)	54 (28.9)	18 (26.9)	
>ULN	130 (51.2)	90 (48.1)	40 (59.7)	

>2 ULN	52 (20.5)	43 (23.0)	9 (13.4)	
Missing/unknown	46	37	9	
CRP, median (range)	14.0 (.5 - 286)	14.0 (.5 - 248)	14.0 (1 - 286)	0.85
Lymphocyte count, N (%)				0.014
<0.5	127 (42.8)	104 (46.8)	23 (30.7)	
≥0.5	170 (57.2)	118 (53.2)	52 (69.3)	
Missing/unknown	3	2	1	
Platelet count, N (%)				0.60
<50	24 (8.0)	19 (8.5)	5 (6.6)	
≥50	276 (92.0)	205 (91.5)	71 (93.4)	

ST= Systemic therapy.

Table 2: Treatment response.

Characteristics	All	Axi-cel	Tisa-cel
Response at 3 months, N (%)	**N=300**	**N=224**	**N=76**
CR*	120 (40.0)	94 (42.0)	26 (34.2)
PR#	24 (8.0)	22 (9.8)	2 (2.6)
PD	143 (47.7)	95 (42.4)	48 (63.2)
-PD before 3-month assessment	63 (21)	35 (15.6)	28 (36.8)
Not known (death before 3-month ass.)	12 (4.0)	12 (5.4)	0
Not assessed	1 (0.3)	1 (0.5)	0
3-month ORR (CR) rate	**48% (40%)**	**52% (42%)**	**37% (26%)**
Response at 6 months, N (%)	**N=294§**	**N=218**	**N=76**
CR$	111 (37.8)	87 (39.9)	24 (31.6)
PR##	10 (3.4)	10 (4.6)	0
PD	158 (53.7)	107 (49.1)	51 (67.1)
-PD before 6m	143	95	48
Death before 6m	15 (5.1)	14 (6.4)	1 (1.3)
6-month ORR/CR rate	**41%/ 38%**	**44%/ 40%**	**32%/ 32%**
Median duration of response, months	NR	NR	10.5 (3.1-NR)
Best ORR (CR) rate	**72% (50%)**	**77% (52%)**	**57% (44%)**

***** *Includes 5 clinically assessed remissions (with confirmation of CR on 1- or 6-month PET scan)*
 # includes one not assessed (PR at 1 month, CR at 6 months)
§ Evaluable (6 months post infusion at data cut off)
$ Includes 13 "clinical remission" who were in CMR at 3 months.
Includes 2 "clinical remission" (PR at 1 and 3)

Table 3: Multivariable analysis on efficacy outcomes. (A) Multivariable analysis of early CAR-T failure. (B) Combined risk score for early failure within histological subgroups. (D) Multivariable analysis for progression-free and overall survival.

(A)

	OR (95% CI)	*P*
PMBCL (vs t-other or *de novo* DLBCL)	0.18 (0.05 – 0.70)	0.013
tFL (vs t-other or *de novo* DLBCL)	0.55 (0.31 – 0.97)	0.039
LDH (>2ULN vs LDH ≤2ULN)	3.12 (2.90 – 5.14)	<0.0001
ECOG PS (1 vs 0)	1.72 (1.09 – 2.74)	0.021
Liver involvement (yes vs no)	2.51 (1.09 – 5.81)	0.031

Variables at baseline (CAR-T approval). variable considered: age, sex, ECOG, stage, bulky disease, extra nodal sites, LDH, lymphoma subtype, double hit status, refractoriness, response last line, 3 lines + previous therapy, HCTCI-score and the following specific extra nodal sites: reproductive organs, GI, peritoneum, muscle, soft tissue, bone/chest wall , renal/adrenal/urinary, skin and subcutaneous, lung/pleura, peri-pancreatic/pancreas/gallbladder, liver and bone marrow. Models were reduced with backwards selection with p=0.05 for inclusion.

(B)

Number of risk factors	DLBCL N=249	PMBL N=20	t-FL N=81	t-other N=20	All N=370
No factors	**N=81**	**N=8**	**N=28**	**N=7**	**N=124**
Early failures, N (%)	23 (26.4)	1 (12.5)	6 (21.4)	3 (42.9)	33 (26.6%)
OR (95% CI)	1.00	1.00	1.00	1.00	1.00
1 factor	**N=111**	**N=7**	**N=33**	**N=9**	**N=160**
Early failures, N (%)	50 (45.1)	1 (14.3)	5 (15.2)	4 (44.4)	60 (37.5%)
OR (95% CI)	2.07 (1.12 - 3.81)	1.17 (0.06 – 22.94)	0.65 (0.18 – 2.43)	1.07 (0.15 – 7.82)	1.65 (0.99 - 9.86)
2 or more factors	**N=57**	**N=5**	**N=20**	**N=4**	**N=86**
Early failures, N (%)	39 (68.4)	1 (20.0)	15 (75.0)	2 (50.0)	57 (66.3%)
OR (95% CI)	5.46 (2.61 – 11.43)	1.75 (0.08 – 36.3)	11.0 (2.83 – 42.70)	1.33 (0.11 – 15.70)	5.42 (2.98 - 9.86)

(C)

Factor		Events/N	HR (95% CI)	p-value
PFS				
LDH at LD				
	Normal	31/72	1.00	0.0001
	>ULN	80/130	1.78 (1.17 – 2.69)	
	>2ULN	41/51	2.81 (1.76 – 4.49)	
Extra nodal sites				
	<3	130/226	1.00	0.002
	≥3	22/27	2.04 (1.30 – 3.22)	
OS				
LDH at LD				
	Normal	17/72	1.00	<0.0001
	>ULN	59/130	2.27 (1.32 – 3.91)	
	>2ULN	37/52	3.69 (2.05 – 6.64)	
ECOG PS				
	0	24/82	1.00	0.0002
	1	73/151	1.88 (1.18 – 2.99)	
	2	16/21	3.99 (2.09 – 7.62)	
Low platelets				
	≥50	98/236	1.00	0.002
	<50	15/18	2.54 (1.42 – 4.55)	

LD= lymphodepletion.

The models above, are the final reduced models for PFS and OS. Variables considered: age, sex, ECOG, stage (submission), bulky disease, extra nodal sites, LDH (pre-LD), CRP, low platelets, low lymphocytes, lymphoma subtype, double hit status, refractoriness, response last line, 3 lines + previous therapy. Models were reduced with backwards selection with p=0.05 for inclusion.

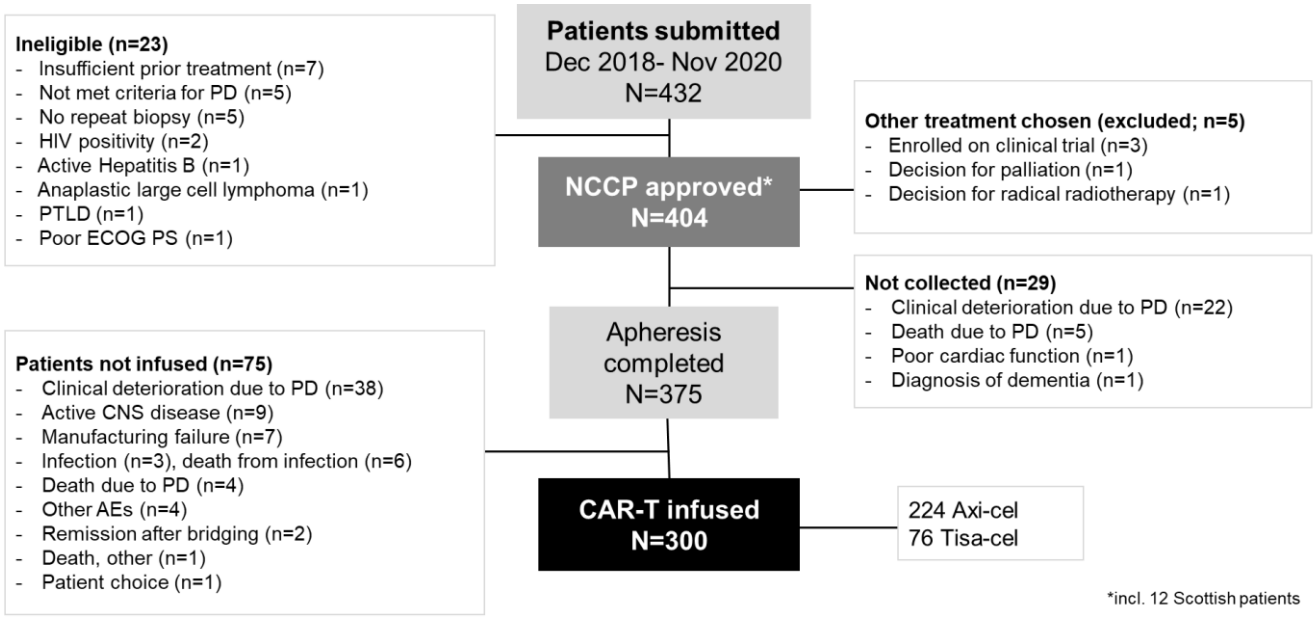
Table 4: Toxicity of treatment.

	All N=300	Axi-cel N=224	Tisa-cel N=76
CRS, N (%)			
Any grade	264 (88.0)	208 (92.9)	56 (73.7)
Grade ≥3	23 (7.7)	17 (7.6)	6 (7.9)
ICANS, N (%)			
Any grade	110 (36.8)	99 (44.4)	11 (14.5)
Grade ≥3	47 (15.7)	44 (19.6)	3 (3.9)
Toxicity management, N (%)			
Tocilizumab use	200 (66.9)	164 (73.5)	36 (47.4)
Corticosteroid use	116 (38.8)	97 (43.5)	19 (25.0)
ICU support, N (%)			
None	217 (72.3)	154 (68.8)	63 (82.9)
Observation only	25 (8.3)	21 (9.4)	4 (5.3)
Inotropes	33 (11.0)	26 (11.7)	7 (9.2)
Organ support/ventilation	24 (8.0)	22 (9.9)	2 (2.6)
Missing/unknown	1	1	0
Cytopenia at 3 months*, N (%)			
Grade ≥3 neutropenia	26 (19.8)	22 (20.8)	4 (16.0)
Grade ≥3 thrombocytopenia	19 (14.5)	15 (14.2)	4 (16.0)
1-year non-relapse mortality	7.3%	8.7%	3.1%

* N=131

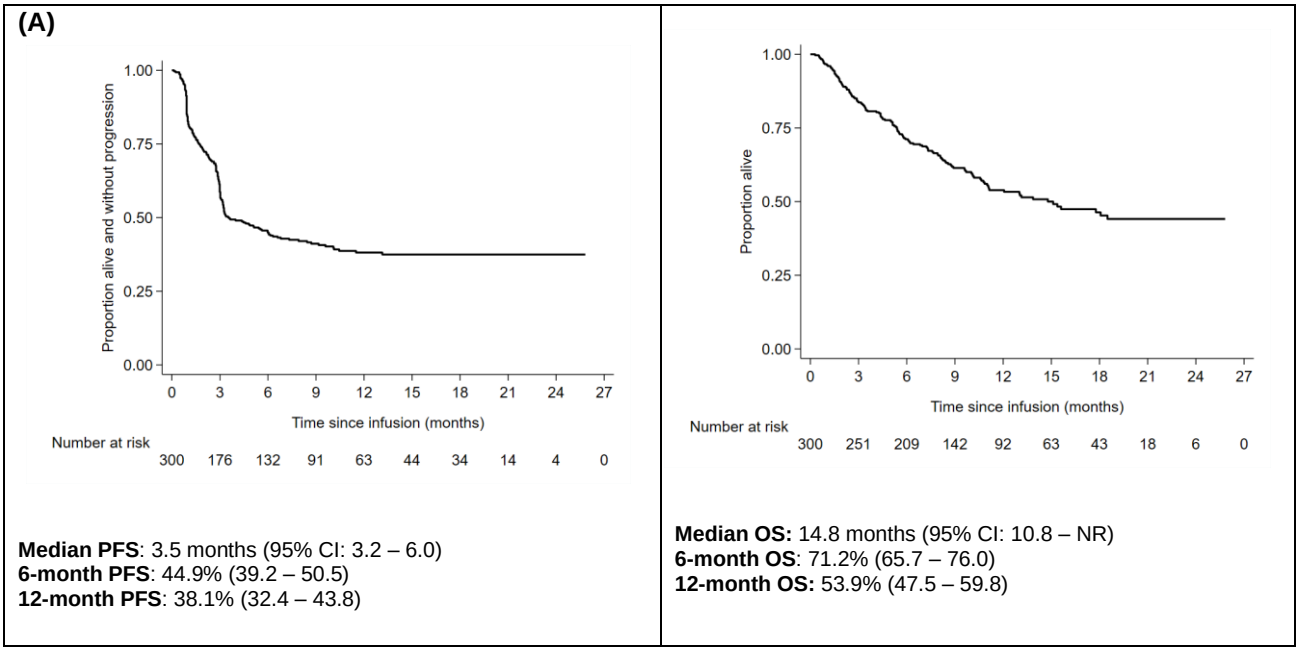
Figures

Figure 1: Flow chart of patients submitted for CAR-T approval.

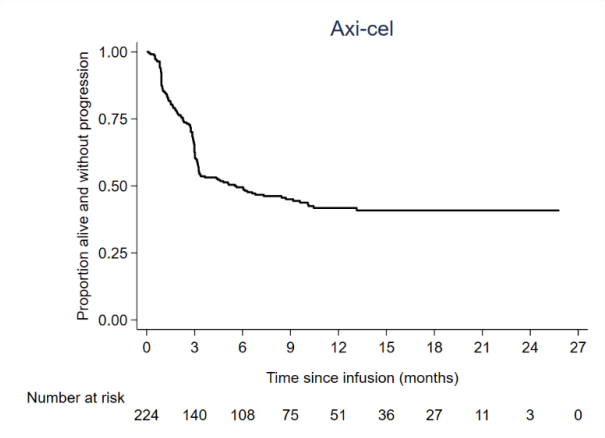


PTLD= Post transplant lymphoproliferative disorder.

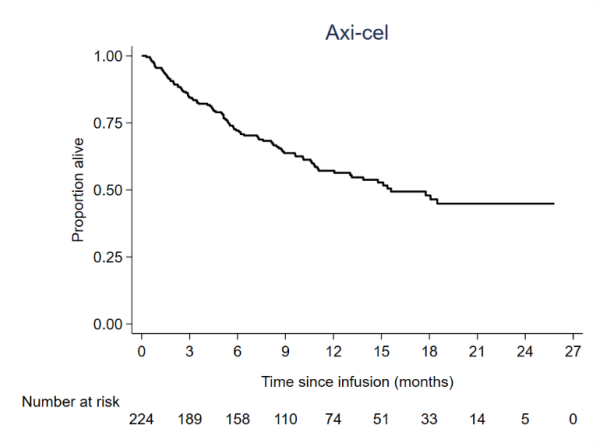
Figure 2: Kaplan-Meier curves of progression-free and overall survival for A) total cohort of infused patients, (B) Axi-cel, (C) Tisa-cel. (D) Overall survival of the intention-to-treat population.



(B)

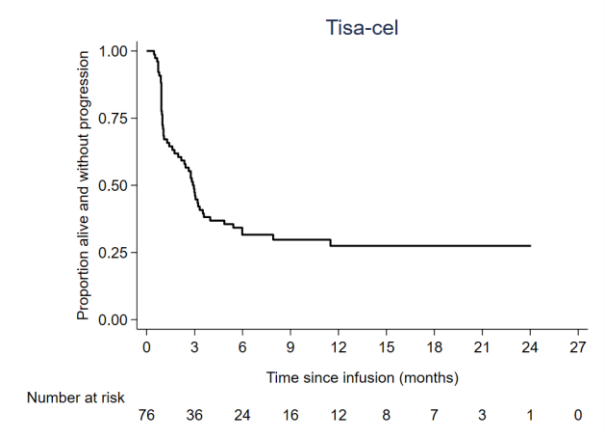


Median PFS: 5.5 months (95% CI: 3.3 – 10.1)
6-month PFS: 49.5% (42,8 – 55.9)
12-month PFS: 41.8% (35.0 – 48.4)

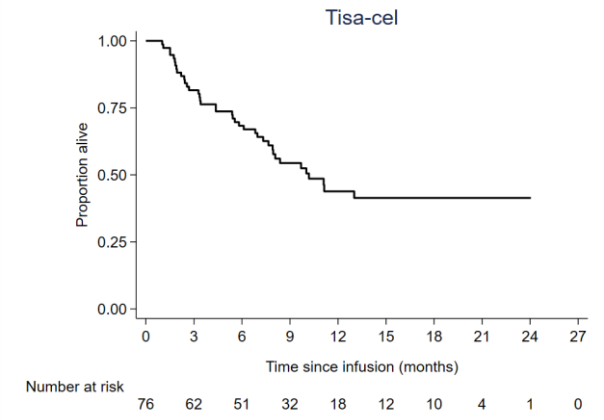


Median OS: 15.6 months (95% CI: 11.1 – NR)
6-month OS: 72.1% (65.7 – 77.5)
12-month OS: 57.1% (49.8 – 63.8)

(C)

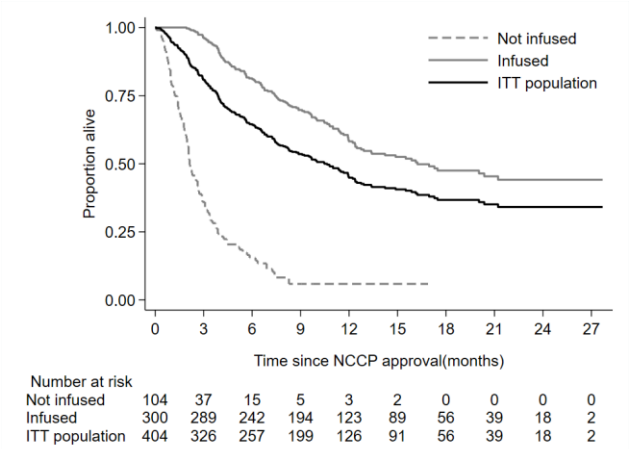


Median PFS: 2.9 months (95%: 1.7 – 3.6)
6-month PFS: 31.6% (21.5 – 42.1)
12-month PFS: 27.4% (17.5 – 38.3)



Median OS: 10.2 months (95%: 7.7 - NR)
6-month OS: 68.3% (56.6 – 77.5)
12-month OS: 43.8% 31.1 – 55.9)

(D)



ITT:
Median OS 10.5 months (8.3 – 12.0)
12-month OS: 44.9% (39.7 – 49.9)
24-month OS: 34.1% (28.4 – 40.0)

Infused:
Median OS: 16.2 months (12.4 – NR)
12-month OS: 58.2% (52.1 – 63.9)
24-month OS: 44.1% (36.8 – 51.2)

Not infused:
Median OS: 2.1 months (1.94 – 2.69)
12-month OS: 5.9% (2.3 – 11.9)
24-month OS: N/A