Locally manufactured *versus* commercial CAR T therapy for large B-cell lymphoma: a multicenter propensity score-matched analysis

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Received: June 11, 2025.
Accepted: December 16, 2025.
Early view: December 24, 2025.

https://doi.org/10.3324/haematol.2025.288419

Abstract

Locally manufactured chimeric antigen receptor T-cell (CAR T) therapy enables rapid manufacturing and a substantially shorter vein-to-vein time. However, its clinical efficacy compared to commercial CAR T products remains unclear. This retrospective study compared outcomes in patients with large B-cell lymphoma (LBCL) treated with a CD19-directed autologous locally manufactured CAR T product (CD28-based co-stimulation) *versus* axicabtagene-ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) across three academic centers. All patients had received at least two prior lines of therapy. Propensity score analysis for CAR T product adjusted for age, Karnofsky performance status, lactate dehydrogenase (LDH) level, primary refractory disease, and transformed histology was performed to account for underlying differences in treatment groups. Among 330 patients (132 axi-cel, 104 tisa-cel, 94 locally manufactured products), those treated with locally manufactured CAR T were younger, had higher performance status, and were more likely to present with elevated LDH and primary refractory disease. The median time from apheresis to CAR T infusion was significantly shorter with locally manufactured CAR T (11 days) than with axi-cel (38 days) or tisa-cel (44 days) (P<0.001). In adjusted analysis, a trend to improved progression-free survival with axi-cel was found when comparing locally manufactured products versus axi-cel (weighted hazard ratio [WHR]=1.54; 95% confidence interval [95% CI]: 1.00-2.37; P=0.051) and no difference between those given a locally manufactured product *versus* tisa-cel (WHR=0.71; 95% CI: 0.45-1.11; P=0.13). Overall survival was comparable across treatment groups: locally manufactured product *versus* axi-cel (WHR=1.35, 95% CI: 0.87-2.10; P=0.18) and locally manufactured product *versus* tisa-cel (WHR=0.85, 95% CI: 0.53-1.34; P=0.48). Rates of grade ≥2 cytokine release syndrome were lower with locally manufactured CAR T. These findings support locally manufactured CAR T as a clinically comparable alternative to commercial products for LBCL, with the potential advantage of rapid availability for patients with aggressive disease.

Introduction

Chimeric antigen receptor T-cell (CAR T) therapies targeting CD19 have transformed the treatment landscape for B-cell malignancies, offering potential cure for patients with otherwise poor prognosis.[1] However, widespread use of commercial CAR T products is constrained by high costs, limited availability, and extended production times, which is a particular drawback for patients with rapid disease progression.[2-4] A promising alternative is locally manufactured cell production, which may alleviate some of these limitations. Although establishing facilities for local manufacture requires significant investment in infrastructure and personnel, production costs are substantially lower, logistical processes are minimized by eliminating the need for complex multi-step shipping and traceability,[5] and the quality control period may be more efficient and shortened.[6,7] Importantly, the time from apheresis to infusion is considerably shorter with locally manufactured cells compared to 30-40 days for most commercial products. Additionally, the use of fresh cells, without freezing and storage, may improve product quality and efficacy.[8]

Despite these potential advantages, locally manufactured products can pose challenges. Smaller centers may find it difficult to justify the high start-up costs and training requirements. Moreover, the lack of standardization across such facilities and the operator-dependent nature of production may raise concerns about product consistency and safety.[9-11] Locally manufactured products often rely on decentralized production settings with greater variability in protocols, instrumentation, and operator expertise. This variability can affect multiple critical aspects of product quality. For instance, differences in T-cell subset composition, transduction efficiency, and expansion kinetics may lead to inconsistencies in potency, persistence, and *in vivo* expansion of the final product – key factors that influence clinical outcomes.[12] Additionally, locally manufactured products may also be more susceptible to contamination or batch failure, due to less robust infrastructure and automation. To date, large-scale comparative data on the safety and efficacy of locally manufactured *versus* commercial CAR T therapies are lacking.

Sheba Medical Center has operated a locally manufactured CAR T program since 2016, using an anti-CD19 construct with CD28-based co-stimulation.[13] With the availability of commercial CAR T products in Israel, a subset of patients with large B-cell lymphoma (LBCL) have received either locally manufactured or commercial therapies based on factors such as insurance coverage, clinical urgency, and manufacturing availability.

This international multicenter study provides the first direct comparison of locally manufactured and commercial CAR T products in LBCL, analyzing key clinical outcomes such as efficacy and toxicity, along with logistical considerations including time to infusion. A retrospective study using an inverse probability weights design was conducted to evaluate an autologous CD19 locally manufactured CAR T product in comparison to commercial alternatives in patients with LBCL who had received at least two prior lines of therapy.

Methods

Patients and study design

Adults with relapsed/refractory aggressive B-cell lymphomas in whom at least two prior treatment lines had failed were included in this study. The histological types of lymphoma included were diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma. Patients with primary central nervous system lymphoma, Burkitt lymphoma, and Richter transformation were excluded.

Patients given locally manufactured products were treated at Sheba Hospital between 2016 and 2024. The locally manufactured product, a CD28-based academic CAR T and FMC63-scFv directed against CD19, was administered as part of a phase I/II clinical trial (NCT02772198).[13] Patients received 1×10^6 fresh CAR-positive cells/kg following lymphodepletion. Commercial CAR T products were administered at Sheba Hospital, Memorial Sloan Kettering Cancer Center (MSKCC) and Rambam Health Care Campus between 2017 and 2024. The treatment was administered in accordance with the product leaflet and local protocols. For axicabtagene-ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), lymphodepletion included fludarabine 30 mg/m^2 for 3 days (days –5 to –3) and cyclophosphamide 300-500 mg/m^2 also for 3 days (days –5 to –3). In some cases, bendamustine 90 mg/m^2 for 2 days (days –4 to –3) was administered. For locally manufactured products, lymphodepletion included fludarabine 25 mg/m^2 for 3 days (days –4 to –2) and a single dose of cyclophosphamide 900 mg/m^2 (day –2).

The study was approved by the local institutional review boards of all participating centers.

Data collection and definitions

Data were collected using the REDCap database.[14,15] Response to therapy was assessed by investigators using positron emission tomography-computed tomography scans at 100 days after CAR T infusion, according to Lugano response criteria.[16] Overall response rate at day 100 was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). Overall survival (OS) was measured from CAR T infusion to death. Progression-free survival (PFS) was measured from CAR T infusion to first documented progression or death. Patients were censored at the time of the next treatment without a preceding progression or at last follow-up. Time to relapse was defined from CAR T infusion until relapse, such that death without relapse was considered a competing event. Time to non-relapse mor-

tality (NRM) was defined from CAR T infusion until death without a preceding relapse, where relapse was considered a competing event. Toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), were recorded as per the American Society of Transplantation and Cellular Therapy (ASTCT) consensus guidelines.[17]

Statistical analysis

Continuous variables are reported as medians and ranges, while categorical data are presented as percentages. Baseline characteristics were compared using a Pearson χ^2, Fisher exact, or Kruskal-Wallis rank sum test, as appropriate. Propensity score modeling for CAR T product assignment (locally manufactured *vs*. axi-cel and locally manufactured *vs*. tisa-cel) was conducted using logistic regression models that adjusted for the following factors: age, transformed lymphoma, primary refractory disease prior to apheresis, lactate dehydrogenase levels before lymphodepletion, and Karnofsky performance status (KPS). OS and PFS were estimated using Kaplan-Meier methods. Associations between CAR T products and survival endpoints were calculated using Cox proportional hazards models. Relapse and NRM were estimated using the cumulative incidence function. Associations between CAR T products and relapse and NRM were calculated using the cause-specific hazards approach for competing risks regression, which were weighted using the inverse probabilities derived from the propensity score models. Associations between CAR T products and CRS and ICANS were estimated using logistic regression models. To account for potential differences in CAR T product assignment, all models were inverse probability weighted (IPW) using the estimated propensity scores. Presenting both sets of estimates allows readers to assess the impact of adjustment, evaluate the robustness of the findings, and better understand the influence of patient selection on outcomes. For sensitivity analysis, unadjusted estimates are reported as well. Statistical significance was set at a two-sided *P* value <0.05. Data were analyzed using R version 4.3.2.

Results

Patients' characteristics

Data were collected from 330 patients treated with anti-CD19 CAR T cells at the participating centers. The CAR T products used were axi-cel (N=132, 40%), tisa-cel (N=104, 32%), and Sheba locally manufactured (N=94, 28%). The most common diagnosis across the groups was DLBCL NOS, with frequencies of 77%, 86%, and 76% for the groups given axi-cel, tisa-cel, and locally manufactured products, respectively (Table 1).

Patients who received locally manufactured CAR T were younger, with a median age of 51 years, compared to 62 years for those given axi-cel and 69 years for those given tisa-cel (*P*<0.001). Additionally, they had better KPS, with 71% of patients receiving a locally manufactured product having a KPS score ≥90, compared to 48% for axi-cel and 50% for tisa-cel (*P*=0.001). More patients who received the locally manufactured product had elevated lactate dehydrogenase levels (64%) before lymphodepletion compared to 46% and 45% in the axi-cel and tisa-cel groups, respectively (*P*=0.015). Furthermore, patients who received the locally manufactured product had a higher rate of primary refractory disease (54%) compared to 48% in the axi-cel and 36% in the tisa-cel groups (*P*=0.024). The frequencies of CAR T therapy product by site are shown in *Online Supplementary Table S1*.

Production efficiency of the locally manufactured product was 98.6%,[13] but data are unavailable for commercial products. The time from apheresis to infusion (vein-to-vein time) was significantly shorter for the locally manufactured product, with a median of 11 days (interquartile range [IQR], 10-11), compared to 38 days (IQR, 30-46) for axi-cel and 44 days (IQR, 38-53) for tisa-cel (*P*<0.001). Consequently, only 21% of patients given a locally manufactured product received bridging therapy (primarily steroids) compared to 67% for axi-cel and 78% for tisa-cel recipients (*P*<0.001). Most patients had progressive or stable disease before CAR T infusion across all groups, with 72%, 74%, and 72% in the groups given axi-cel, tisa-cel, and a locally manufactured product, respectively.

Lymphodepletion therapy consisted primarily of fludarabine and cyclophosphamide in 99% of axi-cel patients, 96% of tisa-cel patients, and 100% of those given the locally manufactured product. Bendamustine was used as lymphodepletion for one patient (0.8%) in the axi-cel group and four patients (3.8%) in the tisa-cel group.

Response

Disease response at day 100 is shown in *Online Supplementary Table S2*. The overall response rate was highest with axi-cel (64% CR, 17% PR), followed by tisa-cel (50% CR, 11% PR) and the locally manufactured product (42% CR, 22% PR). In adjusted analyses using IPW, the locally manufactured product was associated with a significantly lower overall response compared to axi-cel (weighted odds ratio [WOR]=0.17; 95% confidence interval [95% CI]: 0.07-0.38; *P*<0.001). No significant difference was observed between those who received a locally manufactured product and those who received tisa-cel (WOR=0.41; 95% CI: 0.15-1.03; *P*=0.075).

Overall survival and progression-free survival

The median follow-up was 39 months (95% CI: 29-46), 35 months (95% CI: 31-51) and 49 months (95% CI: 43-51) in the groups that received axi-cel, tisa-cel and the locally manufactured CAR T, respectively.

The median OS was longest for patients given axi-cel (31 months, 95% CI: 20-not reached), followed by those given

Table 1. Patients' characteristics.

Characteristic	Axicabtagene ciloleucel N=132	Tisagenlecleucel N=104	Local manufacture N=94	P[a]
Age at pre-CAR-T, years, median (IQR)	62 (52-69)	69 (60-75)	51 (38-63)	<0.001
Sex, N (%) Male Female	 89 (67) 43 (33)	 55 (53) 49 (47)	 55 (59) 39 (41)	0.070
Pre-CAR-T KPS (categorized), N (%) ≥90 <90 Unknown	 63 (48) 67 (52) 2	 51 (50) 52 (50) 1	 66 (71) 27 (29) 1	0.001
Diagnosis, N (%) DLBCL NOS High-grade BCL with *MYC* and *BCL2* and/or *BCL6* rearrangements Primary mediastinal BCL High-grade BCL, NOS EBV-positive DLBCL T-cell rich DLBCL Intravascular large BCL	 101 (77) 10 (7.6) 11 (8.3) 6 (4.5) 1 (0.8) 2 (1.5) 1 (0.8)	 89 (86) 8 (7.7) 0 (0) 4 (3.8) 1 (1.0) 2 (1.9) 0 (0)	 71 (76) 5 (5.3) 13 (14) 4 (4.3) 0 (0) 1 (1.1) 0 (0)	
Transformed NHL, N (%) *De novo* LBCL Transformed LBCL Unknown	 76 (58) 55 (42) 1	 70 (67) 34 (33) 0	 61 (65) 33 (35) 0	0.3
Cell of origin, N (%) Non-GCB GCB Unknown	 53 (45) 64 (55) 15	 62 (63) 37 (37) 5	 37 (51) 35 (49) 22	0.038
Disease stage at apheresis, N (%) ≤II III-IV Unknown	 29 (23) 98 (77) 5	 28 (27) 75 (73) 1	 19 (20) 74 (80) 1	0.5
LDH level before lymphodepletion, N (%) Normal Elevated Unknown	 68 (54) 58 (46) 6	 53 (55) 44 (45) 7	 33 (36) 58 (64) 3	0.015
Bulky disease[b], N (%)	22 (17)	10 (9.7)	13 (14)	0.3
Previous auto-HCT, N (%)	35 (27)	24 (23)	25 (27)	0.8
Previous allo-HCT, N (%)	6 (4.5)	3 (2.9)	4 (4.3)	0.8
Primary refractory - pre-apheresis, N (%) Unknown, N	64 (48) 0	37 (36) 0	49 (54) 4	0.024
Bridging, N (%)	89 (67)	81 (78)	20 (21)	<0.001
Pre-CAR-T disease response, N (%) Complete response Partial response Stable/progressive disease Unknown	 4 (3.0) 33 (25) 95 (72) 0	 9 (8.7) 18 (17) 76 (74) 1	 2 (2.1) 24 (26) 68 (72) 0	0.13
Lymphodepletion, N (%) Cyclophosphamide/fludarabine Bendamustine	 131 (99) 1 (0.8)	 100 (96) 4 (3.8)	 94 (100) 0 (0)	0.070
Days from apheresis to CAR-T infusion, median (IQR)	38 (30-46)	44 (38-53)	11 (10-11)	<0.001

[a]Kruskal-Wallis rank sum test; Pearson χ^2 test; Fisher exact test; [b]A mediastinal mass >1/3 intra-thoracic diameter on a posteroanterior chest X-ray or any mass ≥10 cm) before apheresis. CAR-T: chimeric antigen receptor T-cell therapy; IQR: interquartile range; KPS: Karnofsky performance status; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; BCL: B-cell lymphoma; EBV: Epstein-Barr virus; NHL: non-Hodgkin lymphoma; LBCL: large B-cell lymphoma; GCB: germinal center B-cell-like; LDH: lactate dehydrogenase; auto-HCT: autologous hematopoietic cell transplant; allo-HCT: allogeneic hematopoietic cell transplant.

tisa-cel (16 months, 95% CI: 13- not reached]) and those given the locally manufactured product (15 months, 95% CI: 9-38) (Figure 1A). In IPW-adjusted Cox models for OS (Figure 2A), there were no significant differences between patients given locally manufactured and commercial CAR T products (locally manufactured *vs*. axi-cel weighted hazard ratio [WHR]=1.35, 95% CI: 0.87-2.10; *P*=0.18; locally manufactured *vs*. tisa-cel (WHR=0.85, 95% CI: 0.53-1.34; *P*=0.48). Unadjusted Cox models yielded similar results, with no significant associations found.

The median PFS was also longest with axi-cel (11 months, 95% CI: 7.5-27), followed by tisa-cel (3.3 months, 95% CI: 2.5-6.6) and locally manufactured products (3.0 months, 95% CI: 2.0-17) (Figure 1B). In IPW models (Figure 2B), a trend to improved PFS with axi-cel was found when comparing locally manufactured products to axi-cel (WHR=1.54, 95% CI: 1.00-2.37; *P*=0.051) and no difference comparing the locally manufactured product to tisa-cel (WHR=0.71, 95% CI: 0.45-1.11; *P*=0.13). Results were similar in the unadjusted models.

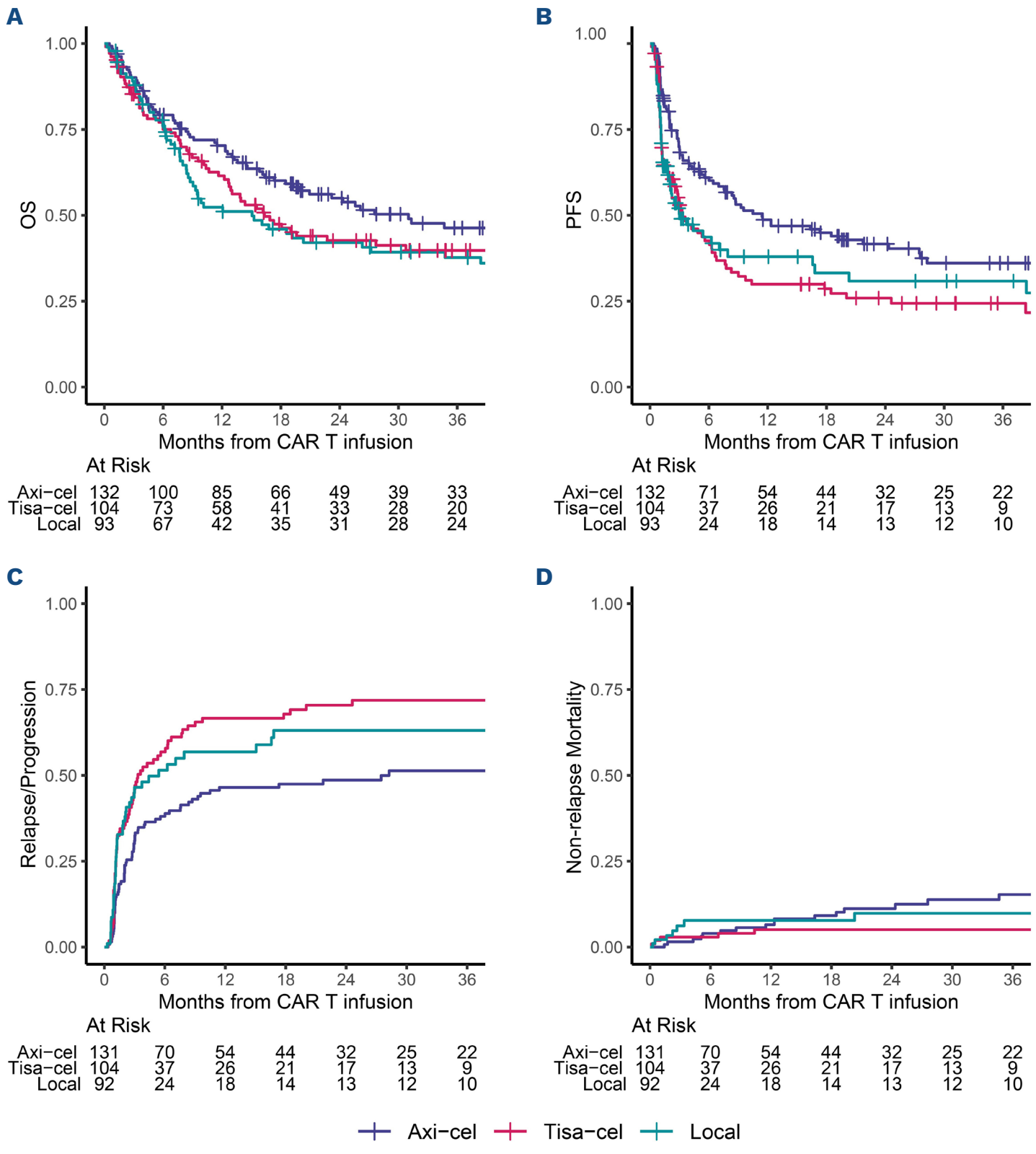

Figure 1. Unadjusted clinical outcomes by chimeric antigen receptor T-cell product. (A) Overall survival and (B) progression-free survival by chimeric antigen receptor T-cell (CAR T) product, estimated using Kaplan-Meier methods. (C) Cumulative incidence of relapse or progression and (D) non-relapse mortality, stratified by CAR T product and analyzed using competing risks methodology. One patient who received locally manufactured CAR T with incomplete survival data is excluded from Figure 1A-D. One additional patient who received locally manufactured CAR T and one patient who received axicabtagene ciloleucel were excluded from Figure 1C, D because of incomplete relapse data. OS: overall survival; PFS: progression-free survival; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Local: locally manufactured chimeric antigen receptor T cells.

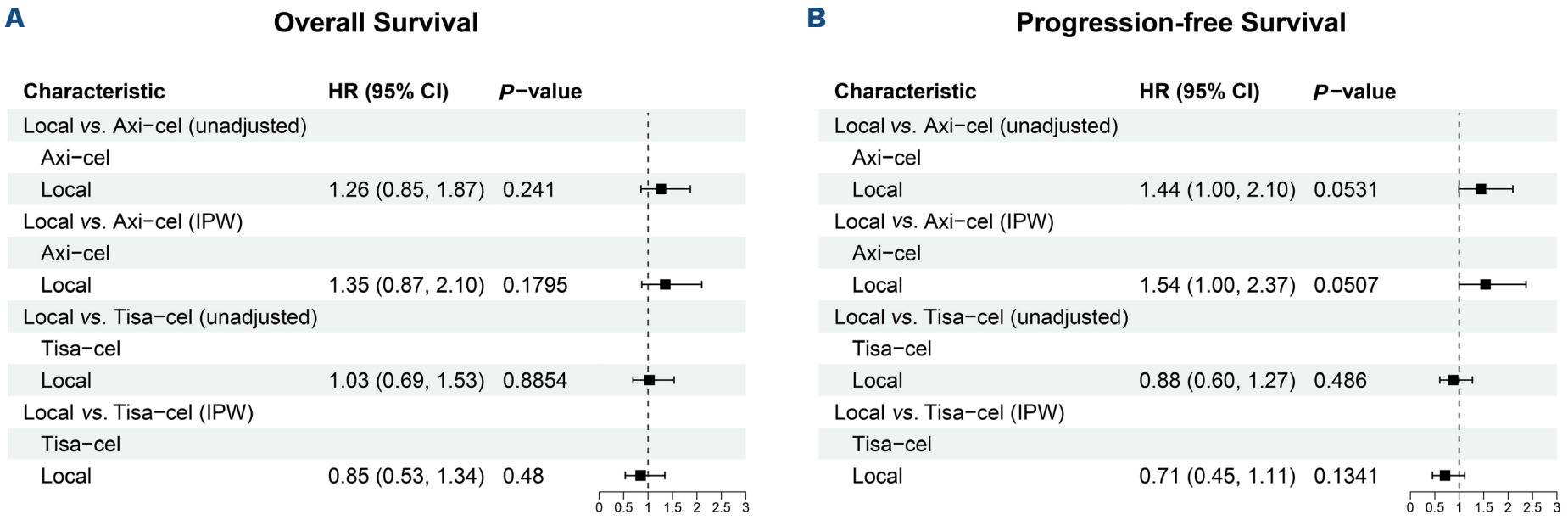

Figure 2. Hazard ratios for outcomes by chimeric antigen receptor T-cell product. (A) Overall survival and (B) progression-free survival by chimeric antigen receptor T-cell (CAR T) product, estimated using unadjusted and inverse probability weighted (IPW)-adjusted Cox models. (C) Cumulative incidence of relapse or progression and (D) non-relapse mortality, analyzed using IPW-adjusted Cox models stratified by CAR T product. HR: hazard ratio; 95% CI: 95% confidence interval; Local: locally manufactured chimeric antigen receptor T cells; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel.

Relapse and non-relapse mortality

At 1 year after the CAR T infusion, the cumulative incidence of relapse (Figure 1C) was highest with tisa-cel (67%, 95% CI: 56-75), followed by the locally manufactured product (57%, 95% CI: 44-67) and axi-cel (46%, 95% CI: 38-55). In both unadjusted and IPW analyses (Figure 2C), relapse risk was higher with the locally manufactured product compared to axi-cel (WHR=1.71, 95% CI: 1.08-2.70; *P*=0.021), but comparable to that with tisa-cel (WHR=0.68, 95% CI: 0.43-1.07; *P*=0.095).

The 1-year cumulative incidence of NRM (Figure 1D) was 7.8% (95% CI: 3.1-15.0) with the locally manufactured product, 6.5% (95% CI: 3.0-12.0) with axi-cel, and 5.1% (95% CI: 1.9-11.0) with tisa-cel. In unadjusted and IPW analyses (Figure 2D), NRM risk with the locally manufactured product was comparable to that with both axi-cel (WHR=1.02, 95% CI: 0.38-2.77; *P*=0.96) and tisa-cel (WHR=0.98, 95% CI: 0.28-3.37; *P*=0.97).

Toxicity

Grade ≥2 CRS occurred in 26% of patients treated with the locally manufactured product (N=24), 52% with axi-cel (N=68), and 37% with tisa-cel (N=38) (Table 2). In both unadjusted and weighted logistic regression models, the risk of grade ≥2 CRS was lower with the locally manufactured product than with axi-cel (WOR=0.31, 95% CI: 0.17-0.56; *P*<0.001). The locally manufactured product was also associated with a lower odds of grade ≥2 CRS compared to tisa-cel in unadjusted analysis (*P*=0.018), but comparable odds in the IPW model (WOR=0.57, 95% CI: 0.28-1.14; *P*=0.12). Grade ≥2 ICANS was least common in patients treated with tisa-cel (12%, N=12), followed by those given a locally manufactured product (29%, N=27) or axi-cel (36%, N=47). The odds of grade ≥2 ICANS with the locally manufactured product was comparable to that with axi-cel (WOR=0.60, 95% CI: 0.33-1.09; *P*=0.10), while patients treated with the locally manufactured product had a significantly higher odds

Table 2. Chimeric antigen receptor T-cell therapy-associated toxicities.

Characteristic, N (%)	Axicabtagene ciloleucel N=132	Tisagenlecleucel N=104	Local manufacture N=94
CRS			
0	12 (9.1)	30 (29)	13 (14)
1	52 (39)	36 (35)	57 (61)
2	45 (34)	25 (24)	13 (14)
3	21 (16)	11 (11)	8 (8.5)
4	2 (1.5)	1 (1)	2 (2.1)
5	0 (0)	1 (1)	1 (1.1)
ICANS			
0	74 (56)	84 (81)	57 (61)
1	11 (8.3)	7 (6.8)	10 (11)
2	15 (11)	8 (7.8)	4 (4.3)
3	27 (20)	4 (3.8)	18 (19)
4	5 (3.8)	0 (0)	5 (5.3)
Unknown	0 (0)	1 (0.9)	0 (0)
ICU admission within first 30 days after CAR-T infusion	17 (14)	6 (6.1)	3 (3.4)
Unknown	13	5	7

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: Intensive Care Unit. ; CAR-T: chimeric antigen receptor T-cell.

of grade ≥2 ICANS in comparison to that of patients given tisa-cel (WOR=4.85, 95% CI: 1.90-14.4; *P*=0.002).

Discussion

This international multicenter study provides the first direct comparison of a locally manufactured CAR T product with commercially available CD19-directed CAR T therapies in patients with LBCL treated after at least two prior lines of therapy. Our findings demonstrate that despite being administered to a younger and more high-risk population – characterized by superior performance status, elevated lactate dehydrogenase levels, and a higher incidence of primary refractory disease – the locally manufactured product yielded clinical outcomes comparable to those of tisa-cel and, in some respects, approaching those of axi-cel. Notably, the locally manufactured CAR T was associated with a substantially shorter vein-to-vein time and lower rates of high-grade CRS. PFS and OS were similar to those achieved with commercially available CAR T. These results suggest that locally manufactured CAR T therapies can offer a viable and timely alternative to commercial products.

These findings are consistent with other reports on local manufacturing CAR T programs. The high rate of successful cell production and the short vein-to-vein times in our cohort, ranging from 7 to 13 days, align with previous studies.[18,19] Recently, a systematic literature review and meta-analysis assessed vein-to-vein time in patients with relapsed/refractory LBCL treated with commercial CAR T therapies: axi-cel, tisa-cel, and lisocabtagene maraleucel (liso-cel). Axi-cel was associated with the shortest median vein-to-vein time (30.6 days), compared to tisa-cel (48.4 days) and liso-cel (35.9 days). Longer vein-to-vein time (40+ days) was associated with significantly lower CR rates and worse OS compared to shorter vein-to-vein times (<28 days or 28 to <40 days), highlighting the potential benefits of earlier infusion with CAR T therapies.[20] Over the past few years, there has been remarkable development in producing CAR T within just 24-48 hours, representing a dramatic shift from traditional timelines.[21-23] These advances not only support faster production but also preserve greater stemness in the CAR T, potentially improving long-term persistence and efficacy.

Notably, during the COVID-19 pandemic, centers in Spain with local manufacturing programs were able to continue administering CAR T therapy despite global supply chain disruptions, further demonstrating the logistical advantages of local production.[24] Toxicity and efficacy outcomes in these studies were also comparable to both our cohort and real-world data for commercial CAR T products.

The differences between locally manufactured and commercial products observed in our cohort, particularly prior to adjustment for patient-related variables, could be explained by a distinct patient population receiving locally manufactured therapy. As commercial CAR T products became available, only patients who did not meet the approved indications, had rapidly progressing disease, faced production failures, or lacked insurance coverage were enrolled in the Sheba locally manufactured clinical trial. Consequently, patients receiving the locally manufactured products tended to have greater tumor burdens and may have received additional treatments prior to CAR T therapy, as reflected in the baseline characteristics (Table 1). Furthermore, tumor burden in this study was assessed using lactate dehydrogenase levels, which are less informative than metabolic tumor volume and may have limited the accuracy of comparisons.

A noteworthy feature of the locally manufactured product used is the absence of cryopreservation during manufacturing. Preclinical and early clinical studies suggest that cryopreservation may negatively impact CAR T efficacy.[8,18] While our study did not directly address this issue, future research is needed to explore the potential benefits of using fresh, non-cryopreserved cells.

Another key finding was the lower proportion of patients in the locally manufactured cohort receiving bridging therapy, likely due to the shorter vein-to-vein times. Delaying CAR T infusion for additional bridging therapy cycles increases the risk of disease progression or therapy-related complications.[25] However, the impact of foregoing bridging therapy remains unclear, especially in patients with high disease burden.[26] In our study, patients in the cohort receiving the locally manufactured product generally had more advanced disease, raising the question of whether a single cycle of bridging therapy may benefit certain patients with high disease burden, while others with less aggressive disease could benefit from faster production and infusion times.[27,28]

Importantly, our study demonstrated that locally manufactured therapy is safe. While it is well established that CD28-containing CAR T are associated with greater toxicity, in our cohort there were lower rates of high-grade CRS compared to those in the groups that received axi-cel and tisa-cel, as well as fewer cases of high-grade ICANS than in patients receiving axi-cel.

This study highlights a central role of academic locally manufactured models in overcoming some of the limitations of commercial CAR T, while also complementing their use. Academic networks can drive innovation and address unmet needs, but collaboration with the pharmaceutical industry is likely necessary for scaling production and ensuring broader availability. A hybrid approach that combines academic research with industry infrastructure could provide a balanced solution to expand global access to CAR T therapies.[6,10] Notably, a phase II multicenter study is evaluating the feasibility and efficacy of locally manufactured CAR T (ARI-0001) *versus* commercial axi-cel in relapsed or refractory DLBCL (NCT05641428). Success could further support local production as a way to improve access and quality.

This study has several limitations. First, its retrospective design introduces the potential for selection bias and residual confounding, despite the use of propensity score weighting to adjust for key baseline differences. Unmeasured variables – such as disease kinetics, comorbidities, and center-level practices – may have influenced treatment allocation and outcomes. Second, the study included only patients treated in the third-line setting or beyond, and results may not be generalizable to earlier lines of therapy. Given the markedly shorter manufacturing time of locally manufactured CAR T, earlier use – particularly in the second-line setting – may yield even greater clinical benefit. Finally, there are no data on CAR T expansion and persistence, which could be associated with therapeutic response and toxicity. Prospective, randomized studies will be needed to definitively establish the relative effectiveness of locally manufactured *versus* commercial CAR T therapies, although such trials may be constrained by logistical and funding barriers.

To our knowledge, this is the first multicenter, matched comparison of a locally manufactured CD19-directed CAR T therapy with commercial products in patients with relapsed or refractory LBCL. Despite being administered to a higher-risk population, the locally manufactured product demonstrated comparable efficacy and safety to commercial therapies, while offering the logistical advantage of markedly shorter manufacturing times. These findings suggest that locally manufactured products can serve as a clinically effective and operationally feasible alternative, particularly for patients requiring expedited treatment. As global demand for CAR T therapies continues to rise, scalable and timely delivery models such as locally manufactured products may play an increasingly important role in expanding equitable access.

Disclosures

MS has served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., Omeros Corporation, and Bristol-Myers Squibb; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, Amgen Inc., Bristol-Myers Squibb, and Sanofi; served on ad hoc advisory boards for Kite – A Gilead Company, and Miltenyi Biotec; and received honoraria from i3Health, Medscape, CancerNetwork, Intellisphere LLC, Curio Science LLC and IDEOlogy. RS reports speaker's honoraria from Incyte, MSD and Sanofi. OB-K reports speaker's honoraria from Gilead and Novartis. JE reports sponsored research funding from Lonza, Inc. for the development of point-of-care cellular therapy manufacturing devices. XDS has served on advisory boards for Gilead and has received speaker's honoraria from Bristol-Myers Squibb and Hoffmann-La Roche. M-AP reports honoraria from Adicet, Allogene, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Pierre Fabre, Sanofi, Syncopation, Takeda, VectivBio AG and Vor Biopharma; serves on Data Safety Monitoring Boards for Cidara Therapeutics and Sellas Life Sciences; has ownership interests in Omeros and OrcaBio; and has received institutional research support for clinical trials from Allogene, Genmab, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Contributions

RM, AA, UG, SB, OB-K and RS designed and conducted the study, performed the analysis and interpreted data. All other authors (SF, NG-A, NS-T, RY, ID, EJ, AN, AS, OI, JE, OBV, AB, XDS, EL, GS, MS, PD, M-AP, TZ, SMD, DY-O, HK and NS) contributed to data analysis and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Funding

The reported research was supported in part by the National Institutes of Health/National Cancer Institute (NIH/NCI) award number P01CA023766 and Memorial Sloan Kettering Cancer Center support grant (P30 CA008748). RS reports grant support from an NIH-NCI K08CA282987, the Long Island Sound Chapter, Swim Across America, The Lymphoma Research Foundation, and Comedy vs. Cancer.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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