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Unmet Needs and Evidence Gaps Among Patients with DLBCL Treated with CAR-T Therapy: A Systematic Literature Review

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Key Takeaways

- This SLR showed that more real-world and comparative research is needed to optimize outcomes for patients with DLBCL treated with CAR-T therapy, including regarding access, site (and transition) of care, bridging therapy, and management of post-CAR-T failure.

Conclusions

- This SLR summarized the efficacy, safety, HRU, costs, and unmet needs of DLBCL patients receiving CAR-T and other innovative treatments, with most evidence focused on descriptive analyses
  - Formal comparisons of these outcomes across different CAR-T therapies and in different settings (i.e., IP vs. OP) in DLBCL are scarce
- More research is needed to identify the most appropriate bridging therapy and treatments post-CAR-T failure to optimize outcomes for patients with different clinical profiles
- Additional real-world evidence is needed to better understand how the administration of CAR-T therapies can be further optimized to improve patient outcomes and support physicians in treatment decisions for DLBCL patients

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Background

- Chimeric antigen receptor T-cell (CAR-T) therapies have changed the treatment landscape for several malignancies, including diffuse large B-cell lymphoma (DLBCL)[1, 2]
- CAR-T therapy involves the genetic modification of a patients' T-cells *ex-vivo*, generating specificity of the patients' T-cells to the specific proteins on the patients' tumor cells[1, 3]
- Since the approval of the first CAR-T therapy for DLBCL in 2017[4], many other innovative treatments have been approved for the treatment of DLBCL, but a systematic literature review (SLR) of the current real-world evidence for these treatments is lacking

Objective

- The current study aimed to conduct an SLR of the real-world efficacy, safety, HRU, costs, and unmet needs for innovative treatments, including CAR-T therapies, for patients with DLBCL

Methods

Data Source and Search Strategy

- An SLR was conducted using MEDLINE and Embase databases (January 1 2017 – April 9 2024) to identify real-world studies published in English that evaluated the efficacy, safety, HRU, costs, and unmet needs of innovative treatments for DLBCL (axicabtagene ciloleucel [axi-cel], lisocabtagene maraleucel [liso-cel], tisagenlecleucel [tisa-cel], polatuzumab vedotin [pola], tafasitamab [tafa], loncastuximab tesirine [lonca], selinexor, epcoritamab, and glofitamab) among adults with DLBCL in the United States
- The following PICOS-T criteria were used to identify relevant studies:
  - **Population:** US adult patients (aged ≥ 18 years) with DLBCL
  - **Intervention:** Innovative treatments for DLBCL (axi-cel, liso-cel, tisa-cel, pola, tafa, lonca, selinexor, epcoritamab, glofitamab)
  - **Comparators:** Not applicable
  - **Outcomes:** Efficacy, safety, HRU, costs
  - **Study Design:** Real-world observational studies (non-interventional)
  - **Time Frame:** January 1 2017 – April 9 2024

Study Selection and Data Extraction

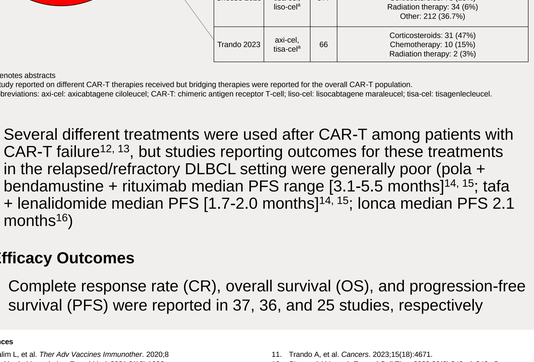
- Each study was independently assessed for inclusion by two reviewers, with an additional third reviewer resolving any discrepancies
- Information on relevant articles was extracted systematically using a data extraction form in Microsoft Excel
- Studies that included LBCL populations without separately reporting DLBCL-specific results were excluded

Results

Search Results

- Of the 1,256 records identified, 92 real-world studies (21 journal articles [22.8%] and 71 [77.2%] conference abstracts) were selected for inclusion (**Figure 1**)

Figure 1. PRISMA Flow Diagram



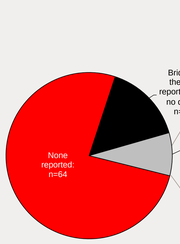
Abbreviations: DLBCL: diffuse large B-cell lymphoma; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; US: United States.

- 86 studies reported on patients receiving CAR-T therapies specifically, with the majority (N=48) reporting on axi-cel

Bridging Therapy and Treatment Sequencing

- Twenty studies reported on the use of bridging therapy prior to CAR-T; however, few studies reported on the specific regimen received; among these, the most commonly reported bridging therapies included chemotherapy, radiotherapy, and corticosteroids[5-11] (**Figure 2**)
- Overall, no preferred option or clear guidance on the use of bridging therapies emerged

Figure 2. Bridging Therapies Reported in CAR-T Studies



Study	Innovative Treatment	N	Bridging Therapy, N (%)
Chihara 2023	CAR-T	551	Chemotherapy or targeted therapy: 160 (29%) Corticosteroids: 73 (28%) Radiotherapy: 29 (11%)
Gaut 2021	axi-cel	22	Rituximab/gemcitabine-oxaliplatin: 7 (32%) Cytarabine/thiotepa: 1 (5%) Rituximab/dexamethasone/cytarabine/cisplatin: 1 (5%) Rituximab/ifosfamide/carboplatin/etoposide: 1 (5%) Rituximab/cyclophosphamide/dexamethasone: 1 (4.5%)
Manzar 2023[a]	axi-cel	40	Radiotherapy: 40 (100%)
Major 2023	CAR-T	96	Any before CAR-T: 66 (69%) Radiation therapy before CAR-T: 3 (3%)
Ravella 2021*	CAR-T	20	Chemotherapy: 8 (40%) Radiation therapy: 5 (25%)
Shouse 2023	axi-cel, tisa-cel, liso-cel[a]	577	Bendamustine: 62 (11%) Non-bendamustine chemotherapy: 112 (19%) Corticosteroids: 73 (13%) Radiation therapy: 34 (6%) Other: 212 (36.7%)
Trando 2023	axi-cel, tisa-cel[a]	66	Corticosteroids: 31 (47%) Chemotherapy: 10 (15%) Radiation therapy: 2 (3%)

*Denotes abstracts
[a]Study reported on different CAR-T therapies received but bridging therapies were reported for the overall CAR-T population.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; liso-cel: lisocabtagene maraleucel; tisa-cel: tisagenlecleucel.

- Several different treatments were used after CAR-T among patients with CAR-T failure[12, 13], but studies reporting outcomes for these treatments in the relapsed/refractory DLBCL setting were generally poor (pola + bendamustine + rituximab median PFS range [3.1-5.5 months][14, 15]; tafa + lenalidomide median PFS [1.7-2.0 months][14, 15]; lonca median PFS 2.1 months[16])

Efficacy Outcomes

- Complete response rate (CR), overall survival (OS), and progression-free survival (PFS) were reported in 37, 36, and 25 studies, respectively

Efficacy Outcomes (Cont.)

- CRs were generally higher in studies reporting on axi-cel (40-58%; five studies[7, 9, 17-19]) than those reporting on liso-cel (15%; one study[20]) or tisa-cel (25-38%; two studies[21, 22]) (**Table 1**)
- Respectively, five and three studies reported on median OS and PFS for axi-cel
  - Median OS ranged from 16.4-25.5 months among three studies[7, 17, 18], with two studies reporting that OS was not reached (**Table 1**)[19, 23]
  - Median PFS ranged from 4.5-8.9 months in two studies,[7, 18] with one study reporting that PFS was not reached[19] (**Table 1**)
- Three studies reported efficacy outcomes in patients treated with axi-cel vs. tisa-cel and found longer OS (Kittai 2021: hazard ratio [HR] 0.61; 95% confidence interval [CI]: 0.31-1.20; p=0.15[24]) and PFS (Fitzgerald 2020: HR: 0.12; 95% CI: 0.04-0.36; p<0.001[25]; Kittai 2021: HR: 0.60; 95% CI: 0.34-1.05; p=0.07[24]; Shouse 2023 HR: 1.42; p=0.011[10]) for axi-cel based on adjusted analyses (**Table 1**)

Table 1. Summary of Efficacy Outcomes Reported in Studies Evaluating Specific CAR-T Therapies

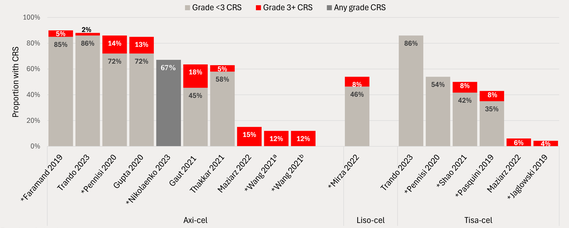
Study	Study Design	Data Source	Follow-Up (median number of months)	Sample Size	Complete Response N (%)	Overall Survival (median number of months)	Progression-Free Survival (median number of months)
Axi-cel							
Fitzgerald 2020*	Retrospective cohort	Multicenter	5.2	axi-cel: 61 tisa-cel: 16	NA	NA	HR: 0.12 (95% CI: 0.04-0.36; p<0.001) (in favor of axi-cel)[a]
Kittai 2021	Retrospective cohort	4 academic institutions	13	axi-cel: 94 tisa-cel: 36	NA	HR: 0.61 (95% CI: 0.31-1.20; p=0.15)[b]; (in favor of axi-cel)	HR: 0.60 (95% CI: 0.34-1.05; p=0.07)[b]; (in favor of axi-cel)
Lunning 2024	Prospective cohort	CIBMTR and SCHOLAR-1	24.5	response rate analysis: 493 survival analysis: 659	NA (58%)	25.5 (95% CI: 19.3-32.6)	NA
Manzar 2023*	Retrospective cohort	Medical record reviews	NA	40	At 30 days: 23 (58%)	22 (95% CI: NA)	8.9 (95% CI: NA)
Nikolaenko 2023*	Retrospective cohort	City of Hope	19	6	At 30 days: 3 (50%)	16.4 (95% CI: 1.3-NR)	4.5 (95% CI: 1.0-NR)
Ravella 2021*	Retrospective cohort	Single institution database	NA	20	Days post-infusion: 30 days: 9 (45%) 90 days: 8 (40%)	NA	NA
Shouse 2023	Retrospective cohort	9 academic medical centers	21	axi-cel: 393 tisa-cel: 120	NA	NA	HR: 1.42 (95% CI: NA; p=0.011)[b]; (in favor of axi-cel)
Tabbara 2021*	Retrospective cohort	Single-center	NA	54	NA	NR	NA
Thakkar 2021	Retrospective cohort	Montefiore Medical Center	7.7	19	11 (58%)	NR	NR
Tisa-cel							
Jaglowski 2019*	Retrospective cohort	CIBMTR CT registry	5.8	70	18 (38%)	NA	NA
Shao 2021*	Retrospective cohort	Karmanos Cancer Center	6.7	12	3 (25%)	NA	NA
Liso-cel							
Mirza 2022*	Prospective cohort	Yale School of Medicine Hematologic Disease Tissue Bank	3	13	2 (15%)	NA	NA

*Denotes abstracts
[a]Estimate was adjusted via propensity score matching.
[b]Estimate was adjusted via multivariable modelling.
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CIBMTR: Center for International Blood and Marrow Transplant Research; CI: confidence interval; HR: hazard ratio; liso-cel: lisocabtagene maraleucel; NA: not available; tisa-cel: tisagenlecleucel.

Safety

- Cytokine release syndrome (CRS) was a commonly reported safety outcome for CAR-T (N=32 studies) with grade 3+ CRS reported in 0-32% of patients treated with CAR-T therapies overall; these rates were 2-18% for axi-cel[6, 11, 18, 19, 26-31], 8% for liso-cel[20], and 0-8% for tisa-cel[11, 21, 22, 27, 29, 32] (**Figure 3**)

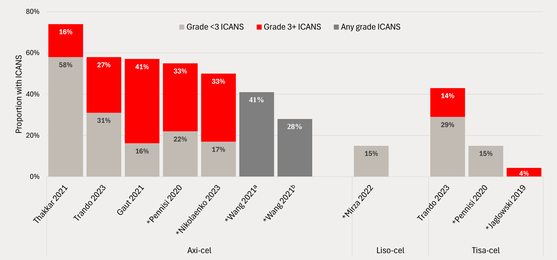
Figure 3. Studies Reporting on CRS Among Patients with DLBCL Treated with CAR-T



*Denotes abstracts
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; tisa-cel: tisagenlecleucel.

- Immune effector cell-associated neurotoxicity syndrome (ICANS) was another commonly reported outcome for CAR-T (N=20 studies), with grade 3+ ICANS reported in 0-39% of patients treated with CAR-T therapies overall; these rates were 16-41% for axi-cel[6, 11, 18, 19, 27, 30, 31], 0% for liso-cel[20], and 0-14% for tisa-cel[11, 21, 27] (**Figure 4**)

Figure 4. Studies Reporting on ICANS Among Patients With DLBCL Treated With CAR-T



*Denotes abstracts
Abbreviations: axi-cel: axicabtagene ciloleucel; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; ICANS: immune effector cell-associated neurotoxicity syndrome; liso-cel: lisocabtagene maraleucel; tisa-cel: tisagenlecleucel.

- One study reported on secondary primary malignancies, with 4.7% of patients developing acute myeloid leukemia/myelodysplastic syndrome[33]
- No studies formally compared incidence of AEs across CAR-T therapies using covariate-adjusted analyses

HRU and Costs

- Patients who received CAR-T in the outpatient (OP) vs. inpatient (IP) setting had lower use of IP[5, 34, 35] and intensive care unit (ICU) services post-infusion[34]
- One study reported that post-CAR-T, 44% of patients had unplanned re-hospitalizations and 25% had unplanned emergency room visits (results not stratified by OP vs. IP administration)[36]
- Based on 14 studies evaluating costs, total costs (including medical services and treatment) for CAR-T therapies were generally higher than other innovative treatments
- One analysis found lower pre-administration and higher post-administration HRU and medical costs for CAR-T relative to autologous hematopoietic stem cell transplant (HSCT), and lower pre- and post-administration HRU and medical costs compared to allogeneic HSCT[37]
- While a descriptive study found tisa-cel to have lower non-CAR-T costs than axi-cel, no studies formally compared HRU or costs between CAR-T therapies in DLBCL using covariate-adjusted analyses[29]

Unmet Needs and Evidence Gaps

- Unmet needs and evidence gaps were broken down into four key themes: treatment sequencing, effectiveness, access, and transition of care (**Table 2**)

Table 2. Summary of Unmet Needs and Evidence Gaps

Theme	Unmet Needs	Evidence Gap
Treatment sequencing	• Poor outcomes of treatments used in lines of therapy after CAR-T highlight the **unmet needs** for better treatments post CAR-T	• Studies evaluating appropriate **treatment sequencing** before (e.g., bridging therapy) and after CAR-T therapy is needed
Effectiveness	• **Prognosis** for patients with DLBCL **remains poor** • Patients continue to experience severe **AEs**	• Studies **comparing outcomes** between different CAR-T therapies are limited • Studies **evaluating safety** across different CAR-T therapies are limited
Access	• **Patient access** to CAR-T administration varies by patient subgroups (e.g., age, comorbidities) and region of residence, and is reduced by administrative barriers • Access-related concerns can be separated into financial, socio-economic, and prescribing/recommending barriers • Access to novel therapies **remains limited**	• Studies **evaluating outcomes** in important patient subgroups are needed • Studies **evaluating costs across different CAR-T** therapies are limited • Information on clinical outcomes in the **IP vs. OP setting** is limited
Transition of care	• Need for **accessible,** and **less health care resource intensive** interventions in DLBCL patients	• Studies evaluating **transition of care** and related clinical outcomes among patients treated with CAR-T in the OP vs. IP setting are limited

Abbreviations: AE: adverse event; CAR-T: chimeric antigen receptor T-cell; DLBCL: diffuse large B-cell lymphoma; IP; inpatient; OP: outpatient.

Study Limitations

- Due to the heterogeneity of reported outcomes and populations evaluated, no statistical or other quantitative comparisons were conducted
- This SLR was only conducted among articles published in English and focusing on patients in the United States, thus limiting the generalizability to other countries

References

1. Halim L, et al. *Ther Adv Vaccines Immunother*. 2020;8
2. Narkhede M, et al. *Ann Transl Med*. 2021;9(12):1036.
3. Manier S, et al. *Blood Reviews*. 2022;54:100929.
4. Yescarta (axicabtagene ciloleucel) [package insert]. (Kite Pharma Inc.; Santa Monica, California, 2017).
5. Chihara D, et al. *Blood*. 2023;142(12):1047-1055.
6. Gaut D, et al. *Int J Cancer*. 2021;148(5):1192-1196.
7. Manzar GS, et al. *Int J Radiat Oncol Biol Phys*. 2023;117(2):S53-S54.
8. Major A, et al. *Blood Advances*. 2023;7(16):4528-4538.
9. Ravella R, et al. *Int J Radiat Oncol Biol Phys*. 2021;111(3):e305-e306.
10. Shouse G, et al. *Blood Advances*. 2023;7(14):3516-3529
11. Trando A, et al. *Cancers*. 2023;15(18):4671.
12. Sigmund AM, et al. *Transpl Cell Ther*. 2022;28(6):342.e1-342.e5.
13. Jalbert JJ, et al. *Advances in Therapy*. 2022;39(6):2630-2640.
14. Hamadani M, et al. *Blood*. 2022;140(Supplement 1):8058-8060.
15. Crombie JL, et al. *J Clin Oncol*. 2023;41(16_suppl):7552-7552.
16. Ayers E, et al. *Blood*. 2023;142(Supplement 1):312-312.
17. Lunning MA, et al. *Am J Hematol*. 2024;99(5):880-889.
18. Nikolaenko L, et al. *Transpl Cell Ther*. 2023;29(2, Supplement):S222-S223.
19. Thakkar A, et al. *Stem Cell Investigation*. 2021;8
20. Mirza A-S, et al. *Blood*. 2022;140(Supplement 1):10410-10412.
21. Jaglowski S, et al. *Blood*. 2019;134(Supplement_1):766-766.
22. Shao YF, et al. *Blood*. 2021;138(Supplement 1):4828-4828.
23. Tabbara N, et al. *Blood*. 2021;138(Supplement 1):3869-3869.
24. Kittai AS, et al. *Transpl Cell Ther*. 2021;27(1):46-52.
25. Fitzgerald L, et al. *J Clin Oncol*. 2020;38(15_suppl):8039-8039.
26. Faramand R, et al. *Blood*. 2018;132:95.
27. Pennisi M, et al. *Biol Blood Marrow Transplant*. 2020;26(3):S40-S41.
28. Gupta S, et al. *Am J Kidney Dis*. 2020;76(1):63-71.
29. Maziarz RT, et al. *Leukemia & Lymphoma*. 2022;63(9):2052-2062.
30. Wang M, et al. *Transfusion*. 2021a;
31. Wang M, et al. *Clin Pharmacol Ther*. 2021b;109:S50-S50.
32. Pasquini M, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19:S267.
33. Khouri IF, et al. *Blood*. 2022;140(Supplement 1):7502-7503.
34. Yang H, et al. *Leukemia & Lymphoma*. 2023;64(2):339-348.
35. Zhao J, et al. *J Clin Oncol*. 2021;39(15_suppl):e19550-e19550.
36. Kenzik K, et al. *Blood*. 2021;138(Supplement 1):569-569.
37. Mohammadi I, et al. *Blood*. 2020;136(Supplement 1):4-4.

B-cell Malignancies

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