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Contemporary Treatment Options Beyond Chimeric Antigen Receptor T-Cell Therapies for Patients With Relapsed or Refractory Large B-Cell Lymphoma: A Systematic Literature Review

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BACKGROUND

- Approximately 40% of patients with large B-cell lymphoma (LBCL) become refractory to or relapse following initial treatment of immunochemotherapy, and outcomes worsen with older age[1]
- Chimeric antigen receptor (CAR) T-cell therapy has emerged as standard of care for most patients with refractory or relapsed (R/R) LBCL after receiving the initial line of treatment[2]
- Other therapies with different mechanisms of action (monoclonal or bispecific antibodies, antibody-drug conjugates, and selective inhibitors of nuclear export) have also received regulatory approvals as second- or third-line (2L or 3L) treatment in recent years[1]
- It is important to understand the effectiveness of these therapies in real-world settings; however, there are a limited number of studies that report on real-world effectiveness for some therapies used in the R/R LBCL setting

OBJECTIVES

- To conduct a systematic literature review (SLR) to understand the real-world effectiveness of non–CAR T-cell therapies, such as tafasitamab with lenalidomide (tafa/len), polatuzumab vedotin with bendamustine and rituximab (pola-BR), loncastuximab, selinexor, epcoritamab, and glofitamab, in patients with R/R LBCL, including in patients with advanced age

METHODS

Figure 1. Study Design

Data Source

- MEDLINE, Embase, and the Cochrane Library databases were searched to identify clinical trials and real-world studies published from January 1, 2017, through January 12, 2023, that reported on ≥10 patients with LBCL who had received ≥1 of the therapies of interest (tafa/len, pola-BR, loncastuximab, selinexor, epcoritamab, or glofitamab) in the 2L+ or 3L+ settings
- A manual search of major conference databases was also performed from 2020 onward to identify additional abstracts[a]
- Data on commercially available CAR T-cell therapies from pivotal clinical trials and a recent SLR[3] were also included for context

Effectiveness Outcomes of Interest

- ORR, CR rate, PFS, and OS

Statistical Analysis

- Key baseline characteristics and effectiveness outcomes were tabulated and summarized herein

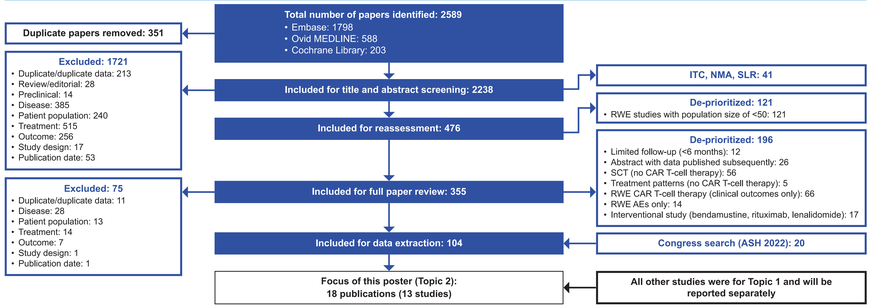
[a]All major congresses from 2020 onward were indexed and captured via Embase, with abstracts from the following conferences of interest: ASCO, ASH, EHA, EBMT, ESMO, ISPOR, and SITC. Conference proceedings from ASH 2022 were not captured in Embase and were hand searched. Abstracts were published in the journal *Blood* and the search was performed within this issue on January 25, 2023 (keywords: B cell, lymphoma, refractory, relapse). Abstracts were selected following the same procedure as abstracts from electronic search.
2L+, second-line or later; 3L+, third-line or later; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; CAR, chimeric antigen receptor; CR, complete response; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LBCL, large B-cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pola-BR, polatuzumab vedotin plus bendamustine and rituximab; SITC, Society for Immunotherapy of Cancer; SLR, systematic literature review; tafa/len, tafasitamab plus lenalidomide.

Analysis Considerations

- Statistical analyses on the significance of differences in baseline characteristics or outcomes between the therapies were not feasible
- The outcomes reported herein were analyzed descriptively; no specific hypothesis was tested
  - Differences between real-world evidence (RWE) and clinical studies (including study design, baseline patient characteristics, and study size) and between non–CAR T-cell therapies and CAR T-cell therapies should be considered when making comparisons of these data

RESULTS

Figure 2. PRISMA Flow Diagram



AE, adverse event; ASH, American Society of Hematology; CAR, chimeric antigen receptor; ITC, indirect treatment comparison; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RWE, real-world evidence; SCT, stem cell transplant; SLR, systematic literature review.

- The literature search, screening, and selection process was performed simultaneously for 2 research topics (**Figure 1**)
  - Topic 1: Treatment sequencing involving non–CAR T-cell therapies
  - Topic 2: Contemporary non–CAR T-cell therapies
- There were 104 publications that met the inclusion but did not meet exclusion criteria for data extraction for both topics (**Figure 2**)
- In total, 13 studies (18 publications) were identified for research Topic 2 and are the focus of this poster (**Figure 2**)
- The studies identified for research Topic 1 will be reported separately

Table 1. Summary of RWE and Clinical Trial Results of Non–CAR T-Cell Therapies for R/R LBCL[a]

Study Information			Baseline Patient Characteristics					Efficacy Outcomes			
Therapy	Study Type	References	N	mFU, mo	Median Age, years (range)	ECOG PS >0, %	Stage 3-4, %	ORR, %	CR Rate, %	Median PFS, mo	Median OS, mo
2L+ Non–CAR T-Cell Therapy Studies											
Tafa/len	Clinical trial (NCT02399085)	Duell et al. 2021[4] Duell et al. 2022[5]	81	≥35	72 (41-86)	–	75	58	40	12	33.5
	RWE	Hamadani et al. 2022[6]	25	12.0	73 (60-84)	–	–	–	9	3	6.6
	RWE	Qualls et al. 2022[7]	82	NR	72 (41-86)	–	90	–	–	3	6.8
Pola-BR	Clinical trial (NCT02257567)	Sehn et al. 2019[8]	40	48.9	67 (33-86)	68	85	63	53	9	12.4
	RWE	Dimou et al. 2021[9]	49	10.8	63 (27-85)	–	57	43	25	4	8.5
	RWE	Northend et al. 2022[10]	133	7.7	72 (18-88)	–	–	57	32	5	8.2
	RWE	Hamadani et al. 2022[6]	60	15.0	72 (60-79)	–	–	–	27	5	7.3
	RWE	Argnani et al. 2022[11]	36	11.0	62 (29-84)	64	83	31	19	6	NR
3L+ Non–CAR T-Cell Therapy Studies											
Pola-BR	RWE	Zurko et al. 2023[12]	18	16	–	–	–	72	33	6	NR
	RWE	Nowakowski et al. 2021[13]	24	–	–	–	–	58	21	5	7
Epcoritamab	Clinical trial (NCT03625037)	Thieblemont et al. 2023[14] Hutchings et al. 2021[15] Clausen et al. 2021[16]	157	11	64 (20-83)	53	75	63	39	4	NR
Glofitamab	Clinical trial (NCT03075696)	Dickinson et al. 2022[17] Dickinson et al. 2022[18] Hutchings et al. 2021[19]	154	13	66 (21-90)	55	75	52	39	4-5	12
Loncastuximab	Clinical trial (NCT03589469)	Caimi et al. 2021[20]	145	–	66 (56-71)	–	77	48	24	5	10
Selinexor	Clinical trial (NCT02227251)	Kalakonda et al. 2020[21]	127	11	67 (35-87)	57	–	28	12	3	9

[a]Data not reported in the source publication are noted with dashes in the table.
2L+, second-line or later; 3L+, third-line or later; CAR, chimeric antigen receptor; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; mFU, median follow-up; mo, months; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; BR, polatuzumab vedotin plus bendamustine and rituximab; R/R LBCL, relapsed/refractory large B-cell lymphoma; RWE, real-world evidence; tafa/len, tafasitamab plus lenalidomide.

Table 2. Summary of RWE and Clinical Trial Results of 3L+ CAR T-Cell Therapy Studies for R/R LBCL[a]

Study Information			Baseline Patient Characteristics					Efficacy Outcomes			
Therapy	Study Type	References	N	mFU, mo	Median Age, years (range)	ECOG PS >0, %	Stage 3-4, %	ORR, %	CR Rate, %	Median PFS, mo	Median OS, mo
3L+ CAR T-Cell Therapy Studies											
Axi-cel	RWE-MA	Jacobson et al. 2023[22]	148-1343	6-25	–	–	–	73	51	7	20
	Clinical trial (ZUMA-1, NCT02348216)	Neelapu et al. 2023[23]	101	63	58 (23-76)	–	–	83	58	6	26
Tisa-cel	RWE-MA	Jacobson et al. 2023[22]	151-682	6-25	–	–	–	58	39	3	12
	Clinical trial (JULIET, NCT02445248)	Schuster et al. 2021[24]	115	40	56 (46-64)	43	77	53	39	3	11
Liso-cel	Clinical trial (TRANSCEND, NCT04245839)	Abramson et al. 2020[25]	344	19	63 (54-70)	59	–	73	53	7	21

[a]Data not reported in the source publication are noted with dashes in the table.
3L+, third-line or later; axi-cel, axicabtagene ciloleucel; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; liso-cel, lisocabtagene maraleucel; MA, meta-analysis; mFU, median follow-up; mo, months; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R LBCL, relapsed/refractory large B-cell lymphoma; RWE, real-world evidence; tisa-cel, tisagenlecleucel.

- Key findings from the identified non–CAR T-cell studies (**Table 1**)
  - Sample size, median follow-up duration, and median age varied across studies
  - One pivotal trial for each therapy of interest in 2L+ or 3L+ was identified
  - In clinical trials in the 3L+ setting
    - Objective response rate (ORR) ranged from 28% for selinexor to 63% for epcoritamab, and complete response (CR) rate ranged from 12% for selinexor to 39% for epcoritamab and glofitamab
    - Median overall survival (OS) ranged from 9 months for selinexor to 12 months for glofitamab and not reached for epcoritamab
  - RWE studies were identified for tafa/len (2 for 2L+) and pola-BR (4 for 2L+; 3 for 3L+)
    - Reported outcomes in 2L+ were numerically lower in RWE studies (pola-BR, 31%-57% ORR, 19%-32% CR rate; tafa/len, ORR not reported, 9% CR rate) versus clinical trials (pola-BR, 63% ORR, 53% CR rate; tafa/len, 58% ORR, 40% CR rate)
- Key findings from 3L+ CAR T-cell therapy studies are included for context (**Table 2**)

Table 3. Clinical Outcomes of Contemporary Therapy for Older Patients with R/R LBCL

Therapy	Study Type	Reference	Subgroup Age, years	N	ORR, %	CR rate, %	OS Rate, % (follow-up time) / Median OS, months (95% CI)
2L+ Studies							
Tafa/len	Clinical trial (NCT02399085)	Salles et al. 2020[26]	≥70	45	58	–	–
		Duell et al. 2022[5]	≥70	45	–	–	OS rate: 45 (2.5 years)
		Zinzani et al. 2021[27]	≥70	43	72	–	–
Pola-BR	RWE	Dimou et al. 2021[9]	>60	–	–	–	OS rate: 52 (1 year)
3L+ Studies							
Glofitamab	Clinical trial (NCT03075696)	Hutchings et al. 2021[19]	>60	62	66	56	–
		Dickinson et al. 2022[18]	≥65	84	–	38	–
Loncastuximab tesirine	Clinical trial (NCT03589469)	Caimi et al. 2021[20]	65-75, DLBCL	59	46	25	–
			≥75, DLBCL	21	52	38	–
	Clinical trial (NCT02669017)	Hamadani et al. 2021[28]	65-75, DLBCL	37	49	–	–
			≥75, DLBCL	27	56	–	–
Selinexor	Clinical trial (NCT02227251)	Kalakonda et al. 2020[21]	≥70	57	25	–	–
		Maerevoet et al. 2021[29]	≥70	60	–	–	Median OS: 7.8 (6.1-13.7)
		Zijlstra et al. 2022[30]	≥65	82	24	–	Median OS: 7.8

2L+, second-line or later; 3L+, third-line or later; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; OS, overall survival; pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R / R LBCL, relapsed/refractory large B-cell lymphoma; RWE, real-world evidence; tafa/len, tafasitamab plus lenalidomide.

- Subgroup analyses of studies that examined outcomes by age in the 3L+ setting found that ORRs in older patients ranged from 24% (selinexor; aged ≥65 years) to 66% (glofitamab; aged >60 years; **Table 3**)
  - In the 2L+ setting, ORRs in older patients were only reported for tafa/len with heterogeneous results
- Median OS was 7.8 months in older patients (aged ≥65 years or ≥70 years) treated with selinexor in 3L+ settings[29,30]
  - Median OS data in older patients were unavailable for the other therapies examined in this analysis
- OS rates were 45% at 2.5 years in older patients treated with tafa/len (aged ≥70 years)[5] and 52% at 1 year in patients treated with pola-BR (aged >60 years)[9] in 2L+ settings
  - OS rates in older patients were unavailable for 3L+ studies

CONCLUSIONS

- Currently, RWE studies reporting on non–CAR T-cell therapies in the R/R LBCL setting are limited
  - Conversely, there have been 78 RWE CAR T-cell therapy studies published,[30] which validate the efficacy findings reported in clinical trials
- In general, the efficacy outcomes from RWE non–CAR T-cell therapy studies were numerically lower than outcomes from the corresponding clinical trials
- ORRs for older patients who received non–CAR T-cell therapy appeared similar to that of their corresponding total study populations; survival data were limited but appeared lower in older patients
- It is important to note that differences in study design, median follow-up duration, and patient populations limit interpretation of these results
- Future studies should explore how best to sequence therapies in the management of R/R LBCL for optimal outcomes

REFERENCES

1. Sehn et al. *N Engl J Med*. 2021;384:842-858.
2. Westin et al. *Blood*. 2022;139:2737-2746.
3. Jacobson et al. *Transplant Cell Ther*. 2021;28(suppl):S9-S10.
4. Duell et al. *Haematologica*. 2021;106:2417-2426.
5. Duell et al. *Blood*. 2022;140(suppl 1):6596-6598.
6. Hamadani et al. *Blood*. 2022;140(suppl 1):8058-8060.
7. Qualls et al. *Blood*. 2022;140(suppl 1):787-789.
8. Sehn et al. *Blood*. 2019;134:4081.
9. Dimou et al. *Hematol Oncol*. 2021;39:336-348.
10. Northend et al. *Blood Adv*. 2022;6:2920-2926.
11. Argnani et al. *HemaSphere*. 2022;6:e798.
12. Zurko et al. *Blood Adv*. 2023;7:2657-2669.
13. Nowakowski et al. *Blood*. 2021;138:183.
14. Thieblemont et al. *J Clin Oncol*. 2023;41:2238-2247.
15. Hutchings et al. *Lancet*. 2021;398:1157-1169.
16. Clausen et al. *J Clin Oncol*. 2021;39(15_suppl):7518.
17. Dickinson et al. *N Engl J Med*. 2022;387:2220-2231.
18. Dickinson et al. *J Clin Oncol*. 2022;40(16_suppl):7500.
19. Hutchings et al. *J Clin Oncol*. 2021;39:1959-1970.
20. Caimi et al. *Lancet Oncol*. 2021;22:790-800.
21. Kalakonda et al. *Lancet Haematol*. 2020;7:e511-e522.
22. Jacobson et al. *Transplant Cell Ther*. 2024;30:77. e1-77.e15.
23. Neelapu et al. *Blood*. 2023;141:2307-2315.
24. Schuster et al. *Lancet Oncol*. 2021;22:1403-1415.
25. Abramson et al. *Lancet*. 2020;396:839-852.
26. Salles et al. *Lancet Oncol*. 2020;21:978-988.
27. Zinzani et al. *Clin Cancer Res*. 2021;27:6124-6134.
28. Hamadani et al. *Blood*. 2021;137:2634-2645.
29. Maerevoet et al. *J Hematol Oncol*. 2021;14:111.
30. Zijlstra et al. *Cancers (Basel)*. 2022;14:791.

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