Comparative Effectiveness of Second-Line Immune Targeted Treatments in Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL): A Network Meta-Analysis

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INTRODUCTION

- Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) undergo multiple lines of burdensome therapies.
- Multiple FDA approved platinum-based chemoimmunotherapy regimens, immune-targeted therapies, and novel agents (CAR T- cell therapy) are available.
- Lack of head-to-head trials, however, impose challenges in identifying the most effective treatment option(s) among guideline recommended second-line therapies.

OBJECTIVES

- To evaluate the efficacy of second-line (2L) immune-targeted treatments (ITTs),, including chimeric antigen receptor (CAR)-T cell therapies, in the management of R/R DLBCL patients, with a focus on overall survival (OS) and event-free survival (EFS) outcomes.

METHODS

- **Database**: PubMed, Embase, and Cochrane Library, covering the period from January 2016 to September 2023.
- **Eligibility**:
  - Studies reporting on adult patients (≥18 years) with DLBCL who R/R to first-line were anti-CD20 and anthracycline-containing regimens.
  - RCTs comparing investigational targeted therapies (ITTs) with the standard of care (SOC), including 2L salvage chemoimmunotherapy regimens, followed by stem cell transplantation.
- **Statistical Approach**: Frequentist fixed-effect model to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).
- **Treatment Ranking**: Ranked based on the surface under the cumulative ranking curves (SUCRA).We performed a cluster analysis for the included interventions with respect to SUCRA

RESULTS

Search and Study Selection:

• 4 RCTs contributed to the network meta-analysis:

- 3 trials compared CAR-T therapies (axicabtagene ciloleucel [axicel], lisocabtagene maraleucel [lisocel], and tisagenlecleucel [tisacel]) with the standard of care (SOC).
- 1 trial compared ofatumumab + cisplatin, cytarabine, and dexamethasone (O-DHAP) with SOC.
- SOC in included studies are R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin); R-ICE (rituximab,ifosfamide, carboplatin, and etoposide); R-GDP (rituximab, gemcitabine, dexamethasone, and cisplatin); R-GemOx (rituximab, gemcitabine, oxaliplatin); or R-GEM-P (Rituximab ,methylprednisolone ,gemcitabine , cisplatin)

RESULTS

Overall Survival (OS):

• Axi-cel significantly improved OS compared to both:

• Tisacel (HR, 0.59; 95% CI, 0.36-0.96)

• SOC (HR, 0.73; 95% CI, 0.55-0.98)

• No significant differences in OS were observed for other ITTs vs. SOC.

Event-Free Survival (EFS):

• Axicel (HR, 0.38; 95% CI, 0.27-0.53) and liso-cel (HR, 0.32; 95% CI, 0.21-0.51) showed significant improvement compared to O-DHAP.

• Axicel and lisocel also improved EFS significantly when compared individually to both tisacel and SOC.

SUCRA Rankings:

• For OS: Axicel ranked as the most effective therapy.

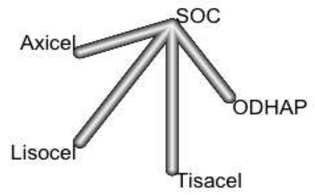
• For EFS: Lisocel ranked as the most effective therapy.

Table 1: Study characteristics

Author	Trial name	Single (S)/ Multicenter (M)	Country	% of DLBCL patients	Intervention	N (ITT)	Male n (%)	Int (median age and range)	IPI range	Ann Arbor stage
Abramson JS_2023	TRANSFORM	M	Global	64%	Liso-cel	184	66	60 (20-74)	0-3*	I-IV
Westin JR_2023	ZUMA-7	M	Global	69%	Axi-cel	359	71	58 (21-80)	2-3*	I-IV
Bishop MR_2021	BELINDA	M	Global	66.1%	Tisa-cel	322	61.2	59.5(19-79)	>=2	I-IV
Van Imhoff GW_2016	ORCHARRD	M	Global	93%	O-DHAP	445	62	57.5(23-83)	0-3*	I-IV

Legend: IPI (International Prognostic Index); * (sAAIPI second-line age-adjusted IPI); axi-cel (axicabtagene ciloleucel); liso-cel (lisocabtagene maraleucel); tisa-cel (tisagenlecleucel); O-DHAP (ofatumumab + cisplatin, cytarabine, dexamethasone)

Fig. 1: Network plots of OS and EFS



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RESULTS

Table 2: League table and SUCRA values for EFS

Axicel				
1.17 [0.74; 1.87]	Lisocel			
0.38 [0.27; 0.53]	**0.32 [0.21; 0.51]**	ODHAP		
0.42 [0.32; 0.54]	**0.36 [0.24; 0.53]**	1.11 [0.89; 1.37]	SOC	
0.39 [0.27; 0.57]	0.33 [0.21; 0.54]	1.03 [0.73; 1.46]	0.93 [0.71; 1.23]	Tisacel

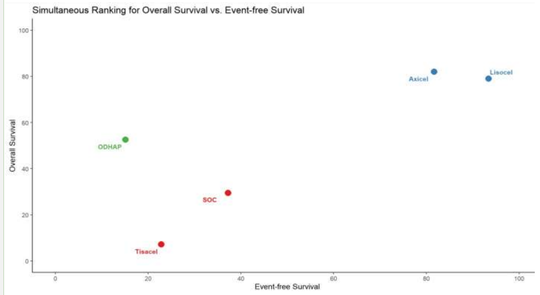
Rank	Treatment	SUCRA	P-score
1	Lisocel	0.93	0.93
2	Axicel	0.82	0.81
3	SOC	0.37	0.37
4	Tisacel	0.22	0.22
5	ODHAP	0.15	0.15

Table 3: League table and SUCRA values for OS

Axicel				
1.01 [0.57; 1.79]	Lisocel			
0.82 [0.55; 1.21]	0.81 [0.47; 1.41]	ODHAP		
0.73 [0.55; 0.98]	0.73 [0.44; 1.19]	0.90 [0.69; 1.16]	SOC	
0.59 [0.36; 0.96]	0.58 [0.31; 1.09]	0.72 [0.45; 1.15]	0.80 [0.54; 1.19]	Tisacel

Rank	Treatment	SUCRA	P-score
1	Axicel	0.82	0.82
2	Lisocel	0.79	0.78
3	ODHAP	0.52	0.52
4	SOC	0.29	0.29
5	Tisacel	0.07	0.07

Fig. 2: Cluster ranking plot for OS vs EFS



SUCRA indicates surface under the cumulative ranking. Each plot shows SUCRA values on a scale of 0% to 100% for 2 outcomes (OS and EFS). Drugs with the same color belong to a similar effectiveness profile. The upper right quadrant represents the more favorable interventions on the joint outcomes; lower right quadrant, more favorable on the horizontal axis outcome but less on the vertical axis outcome; lower left quadrant, less favorable on both outcomes; the upper left quadrant, more favorable on the vertical axis outcome but less on the horizontal axis outcome.

LIMITATIONS

Results are constrained by lack of multiple studies for each treatment comparison.

Although we assumed transitivity a priori , there are clinical and methodological differences which may affect the transitivity assumption.

CONCLUSION

Axi-cel was consistently associated with improved OS and EFS when compared to tisa-cel and SOC, while liso-cel improved EFS over tisa-cel, ODHAP and SOC.

Future studies are needed to include individual patient data on various prognostic and clinical characteristics, such as DLBCL molecular subgroups, age, and IPI which would further allow the clinicians to select regimens for patients with varying characteristics.