Poster #3346

Network Meta-Analysis (NMA) of Chimeric Antigen Receptor (CAR) T-Cell Therapy for the Treatment of Relapsed / Refractory Diffuse Large B-Cell Lymphoma (DLBCL) after 2 Prior Treatments using Published Comparative Studies

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BACKGROUND

- Historically, the clinical prognosis for patients with relapsed/ refractory (r/r) diffuse large B-cell lymphoma (DLBCL) has been poor, with limited curative treatment options. However, the introduction of chimeric antigen receptor CAR T-cell (CAR-T) therapies are changing how r/r DLBCL patients are treated. Axicabtagene ciloleucel (axi-cel), for example, is showing encouraging efficacy results, with five year overall survival rate of 43%.[1]
- Regulatory approvals of axi-cel, lisocabtagene maraleucel (liso-cel) and tisagenlecleucel (tisa-cel) in patients with r/r DLBCL with two or more prior lines of treatment were based on single-arm, non-comparative, clinical trials: ZUMA-1, JULIET, TRANSCEND NHL 001 (TRANSCEND) and TRANCEND WORLD.
- In the absence of randomized controlled trials (RCT), the efficacy of these CAR-T therapies have been compared with historical standard-of-care (SoC) cohorts.[2,3,4] This allows the estimate of comparative efficacy of CAR-T to other available therapies in an earlier timeframe than would be possible with an RCT.
- However, to understand the comparative efficacy of the three approved CAR-T therapies, treatment comparisons across trials are necessary. In the absence of direct evidence, several matching-adjusted indirect comparisons (MAICs) have been conducted. This method matches the individual patient data (IPD) from one trial, with the patient characteristics of the second trial. However, these comparisons have led to conflicting results.
- This may be, in part, due to the lack of a common comparator. By using existing comparisons of CAR-T to historical SoC, it may be possible to overcome the limitations of the existing MAICs by creating a network with a common SoC comparator.
- Here, we conduct an adjusted indirect comparison of axi-cel, liso-cel, and tisa-cel using published comparative studies of CAR-T products to historical SoC cohorts.

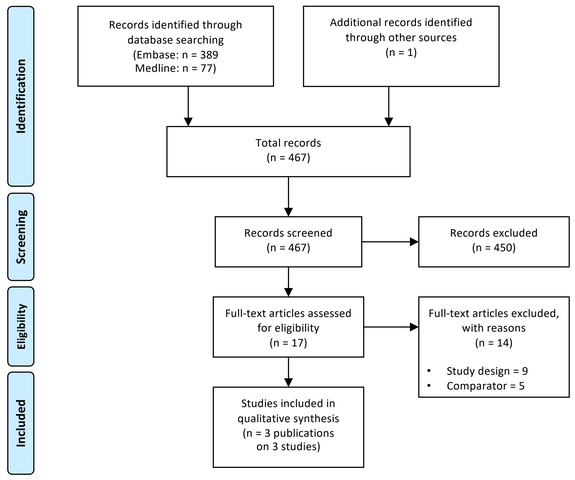
METHODS

- On 17th September 2021, we systematically searched EMBASE and MEDLINE databases. Subsequent conferences were searched, and additional relevant literature was added upon publication.
- Eligible studies enrolled patients with r/r DLBCL and compared approved CAR-T therapies to SoC. Outcomes of interest were response and time-to-event outcomes. Safety outcomes were not reported in SCHOLAR-1 and published comparisons to SCHOLAR-1 so safety could not be explored in this analysis.
- The systematic search followed the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All study selection and data extraction steps were conducted in dual and independently.
- For indirect treatment comparisons, network meta-analyses (NMA) were conducted using a Bayesian framework. For dichotomous outcomes, we used logistic regression with binomial link function. A linear regression on log-transformed hazard ratios (HR) were used for available time-to-event outcomes. The NMA used an anchored network with the historical SoC serving as the common comparator.

RESULTS

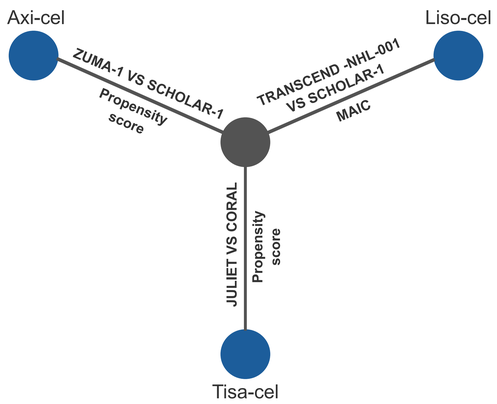
- The search identified 467 publications, of which 3 were included in the evidence base (**Figure 1**).
- The included studies were all published after 2020.

Figure 1. Systematic literature review



- The three studies were a comparison of a CAR-T therapy to a historical SoC. One study was available for each of the approved CAR-T treatments.
- This allowed the creation of a connected network, with SoC as the common comparator (**Figure 2**).

Figure 2. Network of evidence



Axi-cel: axicabtagene ciloleucel; Liso-cel: lisocabtagene maraleucel: MAIC: Matching-adjusted indirect comparison; SoC: standard of care; Tisa-cel: Tisagenlecleucel

- Two of the studies (comparing axi-cel or liso-cel to SoC) used SCHOLAR-1, a historical SoC cohort designed to act as a control for ZUMA-1. SCHOLAR-1 pooled data from two clinical trials and two observational cohorts.
- The study comparing tisa-cel to SoC used CORAL. CORAL was one of the trial cohorts used to build SCHOLAR-1.
- Characteristics of SoC cohorts are outlined in **Table 1**.

Table 1. Characteristics of control cohorts

Trial	Patient group	SoC
SCHOLAR-1	r/r DLBCL r/r defined as one of the following: • Best PD (≥4 cycles of first LoT) • Best SD (2 cycles of subsequent LoT) • ≥12 months post ASCT relapse)	• Salvage chemotherapy
CORAL	r/r CD20(+) DLBCL after first LoT	• Salvage chemotherapy

DLBCL: diffuse large B cell lymphoma; LoT: line of therapy; PD: progressive disease; SD: Stable disease; SoC: standard of care

- The axi-cel and tisa-cel studies both used IPD. Patients from the respective clinical trial and the SoC cohorts were matched using propensity score methods. Liso-cel was compared to published SoC summary data using an MAIC.
- Variables included when matching the groups varied across all three studies. Age, sex, disease stage and prior autologous SCT were adjusted for in at least two studies (**Table 2**).
- Outcomes available for analysis were overall survival (OS_, overall response rate (ORR), and complete response (CR).

Table 2. Study characteristics of included publications

CAR-T	Sample size*	Method	Variables included in adjustment
Axi-cel	Axi: 80 SoC: 340	Propensity scoring	Age, sex, NHL subtype, relapse post auto SCT, refractory to ≥2 lines of therapy, primary refractory, number prior lines.
Liso-cel	Liso: 248 SoC: 636	MAIC	Age, sex, NHL subtype, prior auto SCTs, disease stage, IPI score, refractory to last therapy
Tisa-cel	Tisa: 111 SoC: 145	Propensity scoring	Age at diagnosis, disease stage, extranodal site involvement, r/r status (last line, all lines), time to 2nd line after diagnosis, prior auto SCT, number of relapses

*Sample size is based on adjusted results; Axi-cel sample size is for response outcomes, survival had a separate set with axi-cel: 81 and SoC: 331; SCT: stem cell transplantation

- As expected, all three CAR-T therapies resulted in significantly improved outcomes across OS, ORR and CR when compared to SoC (**Table 3**).
- Axi-cel demonstrated significantly longer OS compared to both liso-cel (HR: 0.54) and tisa-cel (HR: 0.47). There was no difference between liso-cel and tisa-cel for OS (**Table 3**).
- Axi-cel (OR: 5.62) and liso-cel (OR: 4.24) had significantly higher probability of objective response compared to tisa-cel, but there was no significant difference between axi-cel and liso-cel.
- Complete response was not reported for tisa-cel vs. SoC, so comparisons were limited.

Table 3. Network Meta-analysis results

	OS (HR, 95% CrI)	ORR (OR, 95% CrI)	CR (OR, 95% CrI)
Compared to historical SoC:			
Axi-cel vs SoC	0.27 (0.00, 0.38)*	9.32 (5.11, 18.08) *	8.57 (4.96, 15.05) *
Liso-cel vs SoC	0.50 (0.40, 0.60) *	7.05 (4.71, 10.74) *	12.90 (8.17, 20.73) *
Tisa-cel vs SoC	0.57 (0.44, 0.73) *	1.66 (1.05, 2.65) *	--
Between CAR-T comparison:			
Axi-cel vs tisa-cel	0.47 (0.26, 0.88) *	5.62 (2.64, 12.42) *	--
Axi-cel vs liso-cel	0.54 (0.37, 0.79) *	1.32 (0.64, 2.87)	0.67 (0.32, 1.37)
Liso-cel vs tisa-cel	0.87 (0.42, 1.78)	4.24 (2.28, 7.91) *	--

*Indicates a statistically significant result. Axi-cel: axicabtagene ciloleucel; Liso-cel: lisocabtagene maraleucel; SoC: standard of care; Tisa-cel: Tisagenlecleucel; CAR: Chimeric antigen receptor; CR: complete response; CrI: credible interval; ORR: overall response rate; OS: overall survival; SoC: standard of care

CONCLUSIONS

- Results of the analyses suggest that axi-cel leads to improved OS in patients with r/r DLBCL after 2 prior treatments relative to liso-cel and tisa-cel.
- Axi-cel and liso-cel were comparable with respect to response outcomes, showing favorable ORR relative to tisa-cel.
- These results are in line with existing MAIC results, where efficacy between CAR-T treatments have been directly compared, but offer the advantage of being able to include a common comparator in the absence of placebo controlled RCTs.

REFERENCES

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