CT-107

Cost-effectiveness of the chimeric antigen receptor T cell treatments, lisocabtagene maraleucel versus axicabtagene ciloleucel, as second-line treatment of large B-cell lymphoma

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Introduction

- Diffuse large B-cell lymphoma (LBCL) is the most common non-Hodgkin lymphoma subtype worldwide (≈30%—60%) and is included in a group of aggressive lymphomas referred to as LBCL[1–4]
- While ≈50%—60% of patients with LBCL achieve a sustained long-term response to the current first-line standard of care (SOC), the remaining patients have disease refractory to first-line treatment or that relapsed after exhibiting a response[1]
- Second-line (2L) SOC consists of platinum-based immunochemotherapy and high-dose chemotherapy followed by autologous stem cell transplantation (ASCT)[5]; roughly half of patients proceed through ASCT, and only a fraction of those are cured[5,6]
- The autologous, CD19-directed chimeric antigen receptor (CAR) T cell therapies lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) have demonstrated superior efficacy as 2L treatment for patients with relapsed or refractory LBCL versus SOC in the TRANSFORM[7,8] and ZUMA-7[9,10] trials, respectively
- This study assessed the cost-effectiveness of liso-cel versus axi-cel as 2L treatment for patients with primary refractory or early relapsed (within 12 months of first-line therapy) (R/R) LBCL using an economic model informed by the respective pivotal trials TRANSFORM and ZUMA-7

Methods

Model overview and structure

- A partitioned survival model was constructed in Microsoft Excel® following the modeling good practice guidelines of the International Society for Pharmacoeconomics and Outcomes Research[11]
- The model population comprised transplant-intended adults with R/R LBCL with a poor prognosis as defined in the TRANSFORM and ZUMA-7 trials followed for a lifetime (up to 50-year time horizon for a cohort starting at 56.3 years and 42.9% female)
- The United States (US) commercial third-party payer-based model included the following 3 health states: event-free survival (EFS), post-event survival, and death. Patients were partitioned to the death state based on overall survival (OS) projections and assigned to the EFS and post-event survival states based on EFS projections

Survival projections

- Individual patient-level data (IPD) from TRANSFORM[8] (17.5 months median follow-up; NCT03575351) and reconstructed[12] IPD from ZUMA-7[9] (24.9 months median follow-up; NCT03391466) were used to project OS and EFS for liso-cel and axi-cel, respectively, beyond the observed trial period
  - The data cuts that most closely aligned according to median, on-study follow-up time were chosen
- Given that some patients receiving 2L LBCL treatments may achieve long-term remission, mixture cure modeling (MCM) was employed to extrapolate EFS and OS to capture the observed plateau[6] of the Kaplan-Meier (KM) data
- MCM is a statistical framework that assumes the population comprises both cured patients (patients with an overall standard mortality similar to that in the general population) and noncured patients
  - The statistical model estimates the proportion of patients who are cured and predicts the survival of noncured patients using parametric survival distributions selected based on their statistical goodness-of-fit and the clinical plausibility of the long-term projections[13]
- MCM is widely accepted in R/R LBCL by health technology assessment (HTA) bodies in assessing cost-effectiveness for CAR T cell therapies[13] and was the most common approach used to extrapolate clinical outcomes in published models and HTA submissions

Comparative efficacy

- Given that both randomized, controlled studies, TRANSFORM and ZUMA-7, had a common comparator SOC arm and similar crossover proportions, an unadjusted Bucher[14] indirect treatment comparison (ITC) was used to derive the treatment effect of axi-cel versus liso-cel
  - For MCM , treatment effects of axi-cel versus liso-cel were derived corresponding to the effect on the cure proportion and the effect on the survival curve of noncured patients
  - Treatment effects were then applied to the liso-cel MCM to project survival outcomes for axi-cel

Table 1. Key inputs

Treatment costs (USD) and monitoring	Liso-cel	Axi-cel	Sources
Pretreatment cost[a]	$20,409	$9325	InHealth Professional Services[15]; Merative Micromedex® RED BOOK®[16]
CAR T cell treatment acquisition cost	$447,227	$424,000	Merative Micromedex® RED BOOK®[16]
CAR T cell treatment administration inputs			
Percent receiving CAR T cell - inpatient	78.7%	97.0%	TRANSFORM trial: May 13, 2022 DCO[17]; ZUMA-7 trial[18]
Cost for day of administration - inpatient	$16,764		Analysis of Medicare claims data 2019, inflated to 2022[19]; HCUPnet[20]
Cost for day of administration - outpatient	$12,207		Analysis of Medicare claims data 2019, inflated to 2022[19]
Inpatient LOS after inpatient CAR T cell administration, days	13	15[b]	TRANSFORM trial: May 13, 2022 DCO[17]; ZUMA-7 trial[9]
Percent admitted to hospital after outpatient CAR T cell administration	68.4%	100%	TRANSFORM trial: May 13, 2022 DCO[17]; ZUMA-7 trial[18]
Inpatient LOS after outpatient CAR T cell administration, days	9	15[b]	TRANSFORM trial: May 13, 2022 DCO[17]; ZUMA-7 trial[9]
Subsequent treatments in 3L+ inputs			
Treatment distribution	0% CAR T cell, 25% ASCT/allo-HSCT, 75% chemo, 10% radiotherapy	Assumed the same as for liso-cel	TRANSFORM trial: May 13, 2022 DCO[17]
Chemotherapy and radiotherapy - average cost per weekly cycle	$3313		InHealth Professional Services[15]; Merative Micromedex® RED BOOK®[16]
ASCT cost	$36,478		HCUPnet[20]
Key AEs	**Liso-cel**	**Axi-cel**	**Sources**
Grade ≥ 3 AEs			BREYANZI® USPI[21]; YESCARTA® USPI[22]
CRS	1.1%	7.0%	
NEs	7.0%	25.0%	
Grade 1—2 AEs			
CRS	47.9%	85.0%	
NEs	20.0%	49.0%	
Grade ≥ 3 CRS management	3 days ICU + tocilizumab and dexamethasone treatment		BREYANZI® USPI[21]; YESCARTA® USPI[22]; TRANSFORM trial microcosting analysis[23]
Grade ≥ 3 NE management	3 days ICU + dexamethasone treatment		
Utilities			**Sources**
Health state utilities			TRANSFORM trial: May 13, 2022 DCO[17]; 17.5 months median follow-up
EFS	0.886		
Post-event survival	0.840		
Utility decrement			Howell et al. 2022[24]
CRS	0.228		
NEs	0.178		

[a]Leukapheresis, bridging therapy, and lymphodepleting chemotherapy costs; [b]LOS not reported separately for inpatient and outpatient infusion for axi-cel.
3L+, third line or later; AE, adverse event; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CRS, cytokine release syndrome; DCO, data cutoff; ICU, intensive care unit; LOS, length of stay; NE, neurological event; USD, United States dollars; USPI, United States Food and Drug Administration Prescribing Information.

Inputs

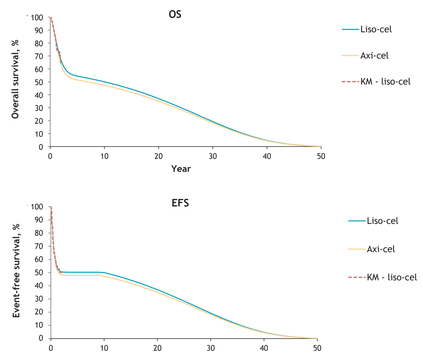
- Costs: The model includes costs for pretreatment (leukapheresis, bridging therapy, and lymphodepleting chemotherapy), acquisition and administration of CAR T cell therapies, subsequent-line treatment, all-grade AE management, post-infusion hospitalization and monitoring, and end-of-life care (**Table 1**)
- Utilities: EQ-5D-5L data from TRANSFORM, mapped to US utilities using the value set by Pickard et al.,[25] were used to estimate utilities for health states and utility decrements for AEs

Analyses

- Uncertainty was explored using deterministic sensitivity analyses (DSA), probabilistic sensitivity analyses (PSA), and scenario analyses
- There are 2 key differences between the ZUMA-7 and TRANSFORM trials
  - Only corticosteroids were allowed as bridging therapy in ZUMA-7 per protocol
  - More patients in ZUMA-7 were administered CAR T cell therapy in an inpatient setting
- Scenario analyses were conducted to explore the impact of these differences:
  - The same proportion receiving bridging therapy and distribution of treatments for axi-cel as liso-cel
  - All patients were administered CAR T cell therapy in an outpatient setting (for liso-cel and axi-cel)
    - In scenario 2, inpatient LOS after outpatient infusion was assumed the same for liso-cel and axi-cel (9 days per TRANSFORM data)

Results

Figure 1. KM curves and extrapolated OS and EFS curves using MCM (capped by the US population standard mortality rate)



Base case

- Patients receiving liso-cel achieved improved 5-year survival compared with axi-cel (54% vs 51%, respectively), and slightly better EFS in the long-term (**Figure 1**)

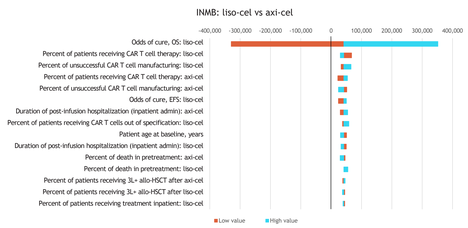
Table 2. Base-case cost-effectiveness results[a]

Treatment	Costs	LYs	QALYs	ICER per QALY	INMB[b]
Liso-cel	$663,798	10.00	8.82	–	–
Axi-cel	$656,977	9.51	8.34	–	–
Incremental	$6821	0.49	0.48	$14,084	$41,608

[a]Discounted at 3% per year; [b]Willingness-to-pay threshold of $100,000.
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life-year; QALY, quality-adjusted life-year.

- Higher total cost for liso-cel than axi-cel was primarily driven by the higher CAR T cell therapy acquisition costs and pretreatment costs (due to bridging therapy)
- However, liso-cel was cost-saving compared with axi-cel for the following components:
  - CAR T cell administration (including post-infusion hospitalization): −$14,277
  - AE management: −$11,746
  - Subsequent treatment: −$4451
- The favorable safety profile of liso-cel, including lower rates of CRS and NEs, also yielded QALY gains (0.05) when compared with axi-cel
- Overall, liso-cel was associated with a QALY gain of 0.48 and a minimal cost increase of $6821, yielding an ICER per QALY of $14,084 (**Table 2**)

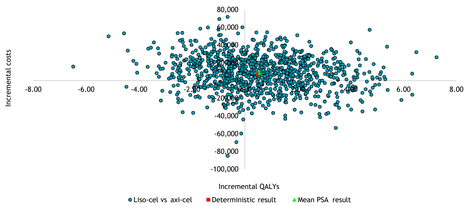
Figure 2. One-way sensitivity analysis tornado diagram (INMB)



Deterministic sensitivity analysis

- DSA was performed to assess variability around key parameters
- Parameters were varied by the upper and lower bounds of the 95% confidence intervals or by ±10% of the base-case value
- The key driver of cost-effectiveness was the OS cure fraction (**Figure 2**)

Figure 3. Incremental cost-effectiveness scatter plot



Probabilistic sensitivity analysis

- PSA was performed to assess the joint uncertainty of key parameters by simultaneously varying multiple parameters using a Markov chain Monte Carlo simulation with 1000 replications
- The probability that liso-cel was more effective than axi-cel was 59% (**Figure 3**)
- The probability that liso-cel was cost-effective at a threshold of $100,000 was 58%

Table 3. Key scenarios cost-effectiveness results[a]

Treatment	Costs	LYs	QALYs	ICER per QALY	INMB[b]
Same bridging therapy for axi-cel as liso-cel					
Liso-cel	$663,798	10.00	8.82	–	–
Axi-cel	$667,846	9.51	8.34	–	–
Incremental	−$4047	0.49	0.48	Dominant	$52,476
All patients received CAR T cell infusion as outpatient					
Liso-cel	$636,385	10.00	8.82	–	–
Axi-cel	$626,717	9.51	8.34	–	–
Incremental	$9669	0.49	0.48	$19,965	$38,760

[a]Discounted at 3% per year; [b]Willingness-to-pay threshold of $100,000.

Scenario analyses

- The scenario on bridging therapy predicted cost savings for liso-cel versus axi-cel and the scenario on outpatient CAR T cell infusion resulted in a slightly greater cost increase for liso-cel over axi-cel than in the base case (**Table 3**)

Discussion

- Compared with axi-cel, liso-cel yielded higher LYs and QALYs and marginally higher overall costs over a lifetime horizon in the model
- Less burdensome toxicity associated with liso-cel resulted in lower AE management costs
- Higher overall costs for liso-cel over axi-cel were driven by higher pretreatment costs due to bridging therapy in the trial setting; when assuming the same bridging therapy for both CAR T cell therapies, which is reflective of the real-world setting,[26] liso-cel was cost-saving
- CAR T cell infusion site of care and subsequent hospitalization LOS were drivers of results that yielded cost savings for liso-cel, but LOS data were more limited for axi-cel

Limitations

- No head-to-head data were available to inform the comparison of liso-cel versus axi-cel
- There was uncertainty in the OS data with the current follow-up available, especially for liso-cel
- A high degree of missing EQ-5D-5L data from TRANSFORM used to inform the health state utilities limited the dataset and, therefore, may have biased the results

Conclusions

- This analysis estimated that liso-cel is cost-effective versus axi-cel for 2L R/R LBCL as informed by pivotal trials
  - Liso-cel generated increased QALYs at a minimal cost increase, partly owing to the favorable safety profile of liso-cel versus axi-cel
- Liso-cel was cost-effective compared with axi-cel assuming the same bridging therapy rates (ie, real-world setting)

References

1. Gisselbrecht C, et al. *Br J Haematol* 2018;182:633—643.
2. American Cancer Society. Types of B-cell lymphoma. https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/b-cell-lymphoma.html. Updated January 29, 2019. Accessed August 18, 2023.
3. Tilly H, et al. *Ann Oncol* 2015;26(suppl 5):v116—v125.
4. Chihara D, et al. *Br J Haematol* 2014;164:536—545.
5. Gisselbrecht C, et al. *J Clin Oncol* 2010;28:4184—4190.
6. van Den Neste E, et al. *Bone Marrow Transplant* 2016;51:51—57.
7. Kamdar M, et al. *Lancet* 2022;399:2294—2308.
8. Abramson JS, et al. *Blood* 2023;141:1675—1684.
9. Locke FL, et al. *N Engl J Med* 2022;386:640—654.
10. Westin JR, et al. *N Engl J Med* 2023;389:148—157.
11. Caro JJ, et al. *Value Health* 2012;15:796—803.
12. Guyot P, et al. *BMC Med Res Methodol* 2012;12:9.
13. National Institute for Health and Care Excellence (NICE). Flexible methods for survival analysis TSD. https://www.sheffield.ac.uk/nice-dsu/tsds/flexible-methods-survival-analysis. Accessed August 18, 2023.
14. Bucher HC, et al. *J Clin Epidemiol* 1997;50:683—691.
15. InHealth 2022 Physicians' Fee & Coding Guide. InHealth Professional Services. Atlanta, GA. Commercial Fee Range.
16. Merative Micromedex® RED BOOK®, 2023.
17. Bristol Myers Squibb. Data on file. TRANSFORM. May 13, 2022 data cutoff.
18. United States Food and Drug Administration. BLA 125643/394 clinical review and evaluation axicabtagene ciloleucel (Yescarta). https://www.fda.gov/media/157687/download. Accessed December 28, 2022.
19. Centers for Medicare & Medicaid Services. www.cms.gov. Accessed August 18, 2023.
20. HCUPnet - Hospital Inpatient National Statistics 2020 National, Statistics by Clinical Classification Software Refined (CCSR) Principal Diagnosis Code All Payers, Incl. Private Insurance, inflated to 2022. https://hcup-us.ahrq.gov/. Accessed August 22, 2023.
21. BREYANZI® (lisocabtagene maraleucel) [package insert]. Bothell, WA: Juno Therapeutics Inc., a Bristol-Myers Squibb Company; June 2023.
22. YESCARTA® (axicabtagene ciloleucel) [package insert]. Santa Monica, CA: Kite Pharma; November 2022.
23. BMS. Data on file. Burden of cytokine release syndrome (CRS) and neurological toxicity (NT) in transplant intended relapsed/refractory large-B-cell lymphoma patients receiving second-line lisocabtagene maraleucel in the TRANSFORM trial - Technical Document. 2022.
24. Howell TA, et al. *Pharmacoecon Open* 2022;6:367—376.
25. Pickard AS, et al. *Value Health* 2019;22:931—941.
26. Pinnix CC, et al. *Blood Adv* 2020;4:2871—2883.

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