Cost effectiveness of the chimeric antigen receptor (CAR) T cell treatment lisocabtagene maraleucel (liso-cel), as second-line (2L) treatment of relapsed or refractory (R/R) large B-cell lymphoma (LBCL) in Switzerland

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Background

- Non-Hodgkin lymphoma represents the sixth most incident cancer in Switzerland, with 1,700 new cases annually.[1]
- Diffuse large B-cell lymphoma (DLBCL) accounts for around 30% of all adult non-Hodgkin lymphoma cases globally, establishing the disease as a major aggressive subtype.[2]
- Compared to DLBCL, other large B-cell lymphoma (LBCL) subtypes are less prevalent.
- About 50-60% of patients experience a long-lasting response to existing first-line standard of care (SoC) treatments for LBCL, while the remaining patients either don't respond or relapse post-treatment.[3-5]
- Second-line SoC involves salvage chemotherapy followed by high-dose chemotherapy (HDCT) and hematopoietic stem cell transplantation (HSCT); around 50% of patients experience relapse after HSCT.[6,7]
- The Swissmedic-approved CAR T-cell therapies lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) offer alternative treatment options for LBCL patients who are refractory or relapse (R/R) within 12 months after first-line chemoimmunotherapy.[8,9]
- Both liso-cel and axi-cel have shown superior efficacy in second-line (2L) treatment for this patient population compared to SoC in the TRANSFORM[10,11] and ZUMA-7[12,13] trials, respectively.

Objective

- An economic model was developed to evaluate the cost effectiveness of liso-cel versus SoC and axi-cel in 2L treatment of patients with R/R LBCL from the perspective of the Swiss statutory health insurance system.

Methods

Model Overview and Structure

- A partitioned survival model was built in Microsoft Excel® in accordance with the best practice guidelines from the International Society for Pharmacoeconomics and Outcomes Research.[14]
- The model population was comprised of transplant-eligible adults diagnosed with R/R LBCL whose prognosis is poor as per the TRANSFORM trial definition (i.e., refractory disease to first-line immune-chemotherapy or relapse within 12 months).
- Three distinct health states were modelled: event-free survival (EFS), post-event survival, and death, with patient partitioning based on overall survival (OS) and EFS projections.

Survival Projections

- Individual patient-level data (IPD) from TRANSFORM[10,11] (17.5 months median follow-up; NCT03575351) and reconstructed IPD from ZUMA-7[12,13] (24.9 months median follow-up; NCT03391466) were used to project OS and EFS.
- Given the survival heterogeneity among CAR T-cell recipients, mixture-cure modeling (MCM) was used to capture the curative effect (materialized by a plateau in the data) experienced by some patients with 2L treatment.
- MCM is a statistical framework that assumes the patient population consists of both cured and non-cured individuals.
  - MCM estimates the proportion of patients who are cured (to whom the general population OS is applied) and the survival pattern of patients who are non-cured, based on parametric distributions, judged by their statistical goodness-of-fit and the predicted probability of long-term events of relevance (e.g., death).[15]
- MCM is widely recognized by health technology assessment (HTA) organizations for CAR T-cell therapies in R/R LBCL.[16-23]

Comparative Efficacy

- Liso-cel was compared with SoC based on evidence from the TRANSFORM trial.
- The unadjusted Bucher indirect-treatment comparison (ITC) method was employed to estimate the treatment effect of axi-cel versus liso-cel, as both the TRANSFORM and ZUMA-7 trials used SoC as a common comparator and had similar cross-over proportions. To project survival outcomes for axi-cel, the ITC-derived treatment effects were applied to the liso-cel MCM curves.

Other Inputs

- The model accounted for costs related to the pre-treatment period associated with CAR T-cell therapies, CAR T-cell acquisition, administration, all-grade AE management, post-infusion hospital stay, monitoring, and end-of-life care (Table 1).
- The analysis presents a 'base case' in which it is assumed that axi-cel and tisa-cel (a subsequent therapy option in the model) have identical prices, both of which are higher than liso-cel's price. In the 'alternative base case', while axi-cel and tisa-cel are still assumed to have prices exceeding that of liso-cel, the difference is not as large; furthermore, tisa-cel is priced higher than axi-cel. In the model, the prices for individual CAR-T therapies are the same in 2L and third line (3L).
- EQ-5D-5L data from TRANSFORM were utilized to estimate health-state utility values and utility decrements for AEs. French tariffs were used given the absence of Swiss-specific values.[24]

Analyses

- Uncertainty was explored through deterministic (DSA) and probabilistic sensitivity analyses (PSA).
- Scenarios analyses included different drug acquisition assumptions for CAR T-cell therapies.

Results

Base Case

- Over the model's time horizon, liso-cel generated 5.1% and 13.7% more QALYs compared to axi-cel and SoC, respectively (Figure 1).
- When comparing liso-cel to axi-cel, liso-cel incurs higher costs for 2L pre-treatment (CHF3,946) and subsequent therapy (CHF9,469). Yet, in terms of 2L AE management, it offers a cost saving of CHF9,964. In the base case, cost savings for liso-cel versus axi-cel were primarily attributable to a lower assumed acquisition cost for liso-cel.
- For liso-cel relative to SoC, the key differences in costs are higher direct treatment costs (CHF108,137) and lower subsequent therapy expenses (−CHF155,263).
- Overall, liso-cel dominated axi-cel (incremental costs −CHF17,586, incremental QALYs 0.5) in the base case, and was associated with an ICER of CHF3,942 (incremental costs CHF1,962, incremental QALYs 0.5) in the alternative base case. Compared with SoC, liso-cel's ICER was CHF9,553/QALY (incremental costs CHF12,887, incremental QALYs 1.35).

Probabilistic Sensitivity Analysis

- PSA, carried out with 3,000 replications using a Markov chain Monte Carlo simulation, indicated a 57% likelihood that liso-cel would be more effective than axi-cel and a 74% probability that liso-cel would be more effective than SoC.
- The probability that liso-cel would be cost effective at a $100,000 threshold was 44% vs. axi-cel and SoC (Figure 2).

Deterministic Sensitivity Analysis

- DSA shows the most influential drivers of cost effectiveness were the parameters determining the cure proportions for liso-cel and SoC from TRANSFORM, with a range of incremental net monetary benefit (INMB), at a CHF100,000/QALY threshold, from approximately −CHF200,000 to CHF500,000, while the remaining parameters, in both comparisons, showed a more limited impact, with INMBs ranging between CHF50,000 and CHF150,000.

Scenario Analyses

- Versus axi-cel, all scenarios resulted in liso-cel dominating axi-cel, except for the scenario where the price for all CAR-Ts was assumed to be equal to liso-cel (Table 2). In this scenario, the ICER was CHF14,057; liso-cel's higher subsequent treatment costs were offset by its lower acquisition cost.
- If a greater proportion of patients receive 3L CAR T-cell therapy after SoC, then liso-cel in 2L is a dominant strategy vs SoC (Table 2). Liso-cel is also dominant in a short time horizon of 10 years as patients are not accruing substantial 3L costs.

Inputs

Table 1. Key Inputs

	Liso-cel[A]	Axi-cel[B]	SOC	Source
CAR-T				
Pre-treatment flow				
% patients receiving planned treatment	96.74%	95.51%	NA	A: TRANSFORM CSR (13 May 2022 DCO), Figure 5.1-1 B: Locke et al., 2021. Primary analysis of ZUMA-7 Figure 1
Leukapheresis				
Unit cost (CHF)	24,600		NA	Swiss DRG 11, case A42B[25]
Bridging therapy				
% receiving	63.0%	38.2%	NA	A: TRANSFORM CSR (13 May 2022 DCO), Table 14.3.1.1.1.1.2; Composition: B Expert opinion B: Expert opinion
Composition of treatment for those receiving				
Composition of treatment	49% R-GDP, 18% R-DHAP, 33% R-ICE	Same as liso-cel	NA	
Cost per patient (CHF)	9,284	5,631		Calculation, includes acquisition and administration
Lymphodepleting chemotherapy				
3 days of Fludarabine 30mg/ m^2 and 3 days of Cyclophosphamide 300mg/m^2 (CHF)				TRANSFORM CSR (8 March 2021 data cut-off) - Section 9.4.1.2.1
% receiving	98%	96%	NA	Given to the proportion that go on to receive CAR T-cell therapy
Cost per patient (CHF)	2,070	2,020		Calculation, includes acquisition and administration
SOC				
Pre-treatment flow				
Stem cell harvest autoHSCT unit cost (CHF)	NA	NA	24,600	Expert Opinion, Swiss DRG for inpatient cost
% receiving			50%	Assumed the same as those that receive HS
Salvage chemotherapy				
Composition	NA	NA	58% R-ICE, 42% R-DHAP	Swiss Expert opinion, Müller et al.2023[26]
Average cost per cycle (CHF)			9,736	Calculation
HDCT				
BEAM one cycle (CHF)	NA	NA	12,479	Calculation, includes acquisition and administration
% receiving			50%	Assumed the same as those that receive HSCT
HSCT (2L)				
% receiving	NA	NA	50%	Swiss expert opinion
Cost of auto HSCT per patient (CHF)			45,894	Expert Opinion, Swiss DRG for inpatient cost
SUBSEQUENT TREATMENT DISTRIBUTION				
Distribution of 3L therapies	8% auto HSCT, 18% allo HSCT, 75% chemo, 10% radio-therapy	13% auto HSCT, 0% allo HSCT, 71% chemo, 15% radio-therapy	3% allo HSCT, 33% chemo, 88% CAR T	A: TRANSFORM CSR (13 May 2022 data cut-off) Data Tables 14.1.10.1.1 and 14.1.10.4.1; novel treatment proportion assumed the same as for axi-cel B: YESCARTA Biologics License Application Clinical Review and Evaluation, pg. 78; reweighted
KEY AES GRADE ≥3 AES				
CRS (G3)	1.1%	4.7%	0.0%	A: TRANSFORM CSR (13 May 2022 DCO) - Data Table 14.3.1.3 B: Yescarta EPAR, CRS: pg. 106; NT:Table 24
CRS (G4)	0.0%	1.8%	0.0%	
Neurotoxicity (G3)	4.3%	15.3%	0.0%	
Neurotoxicity (G4)	0%	5.9%	0.0%	
AE MANAGEMENT COST (CHF)				
CRS management (G3)	57,231			Swiss DRG[25]
CRS management (G4)	169,304			
Neurotoxicity management (G3)	Same as CRS management (G3)			
Neurotoxicity management (G4)	Same as CRS management (G4)			
UTILITY VALUES				
Event-free	0.949			TRANSFORM EQ-5D analysis (13 May 2022 data cut-off); French tariffs
Post-event	0.925			
CRS	−0.228 (QALY decrement)			Howell et al. 2022[27]
Neurotoxicity	−0.178 (QALY decrement)			
All other AEs	−0.038 (QALY decrement)			TRANSFORM EQ-5D analysis (13 May 2022 data cut-off); French tariffs

Figure 1: Cumulative QALY by Treatment Arm

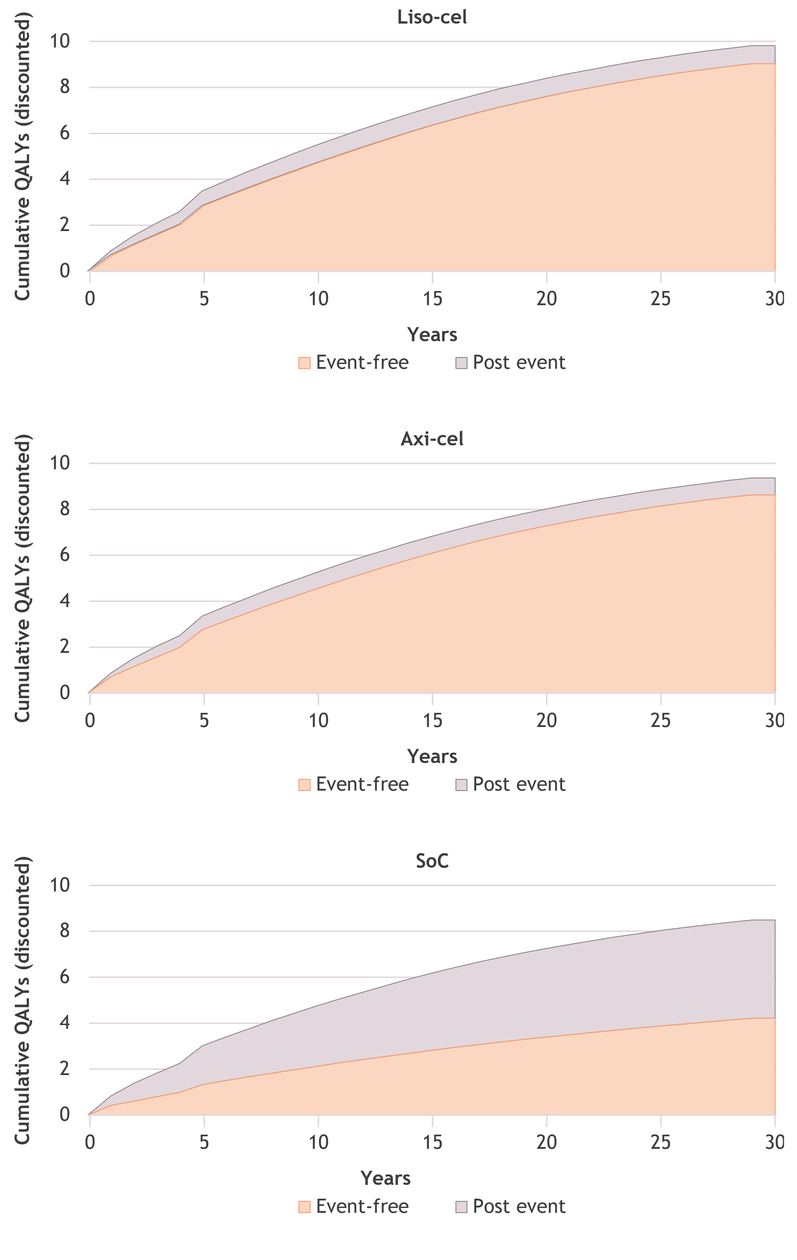

Figure 2. Cost-effectiveness Acceptability Curves

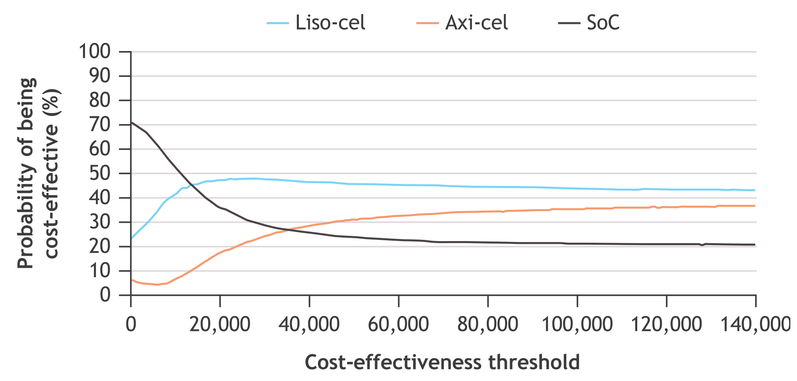

Table 2. Scenario Analyses

Scenario	ICER vs. axi-cel	ICER vs. SoC
Base-case	Dominant	CHF9,553
Time horizon: 10 years	Dominant	Dominant
Time horizon: 20 years	Dominant	CHF11,109
Time horizon: 40 years	Dominant	CHF9,088
Cost Discount: 5%	Dominant	CHF9,650
Health Discount: 5%	Dominant	CHF11,672
Bridging therapy for axi-cel 100% corticosteroids	Dominant	CHF10,719
Equal price for all CAR Ts	CHF14,057	CHF16,394
100% of SoC patients receive 3L CAR T	Dominant	Dominant

Discussion

- Compared to axi-cel, liso-cel had higher life years (LYs) and QALYs while being less expensive or marginally more expensive.
- Liso-cel's more favorable safety profile resulted in both lower AE management costs and lower QALY decrements due to AEs.
- Pre-treatment costs were higher for liso-cel over axi-cel due to higher bridging therapy costs.
- The analysis had several limitations, including uncertainty emanating from the limited follow-up for OS (especially for liso-cel), the absence of head-to-head data for liso-cel versus axi-cel, a high degree of missingness in the EQ-5D-5L data from TRANSFORM, and the reliance on price assumptions for CAR-T therapies.

Conclusions

- Liso-cel emerged as cost effective against axi-cel and SoC for 2L LBCL treatment. Its superior safety profile relative to axi-cel's contributed to higher QALYs and reduced costs when comparing the 2 CAR T therapies.

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