Cost-Effectiveness Analysis of Second-Line Treatment With Lisocabtagene Maraleucel Versus Standard of Care for Patients With Large B-Cell Lymphoma in the Netherlands

Poster #EE101

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Background

- Non-Hodgkin lymphoma (NHL) is one of the most common forms of cancer worldwide with a global incidence of more than 1.2 million cases per year.[1]
- Large B-cell lymphomas (LBCL) comprise approximately one-third of NHLs and are characterised by the proliferation of large B lymphoid cells and aggressive clinical behaviour.
- In 2021, more than 5,000 patients in the Netherlands had LBCL; approximately 1,500 new cases of LBCL have been recorded annually since 2018.[2]
- LBCLs can be further categorised into subtypes, such as diffuse LBCL (DLBCL), DLBCL, high grade B-cell lymphoma (HGBCL), primary mediastinal LBCL (PMBCL) and follicular lymphoma grade 3B (FL3B).[3]
- Many patients with LBCL have refractory disease or relapse following first-line (1L) treatment. The standard of care (SoC) in the second line (2L) for patients eligible for stem cell transplant is salvage therapy with platinum-based chemotherapy regimens followed by high-dose chemotherapy (HDCT) + haematopoietic stem cell transplant (HSCT). However, response rates after 2L SoC treatment remain low.[4,5]
- Lisocabtagene maraleucel (liso-cel) demonstrated benefits vs. SoC in TRANSFORM, a randomised, phase 3, open-label study in patients with 2L DLBCL, HGBCL, PMBCL and FL3B.[6,7]
- Liso-cel received marketing authorisation in Europe in April 2023 for 2L treatment of transplant eligible and non-eligible, released or refractory DLBCL, HGBCL, PMBCL and FL3B.
- A cost-effectiveness model was developed to demonstrate the cost-effectiveness of liso-cel vs. the SoC as 2L treatment in the Netherlands to support the reimbursement assessment.

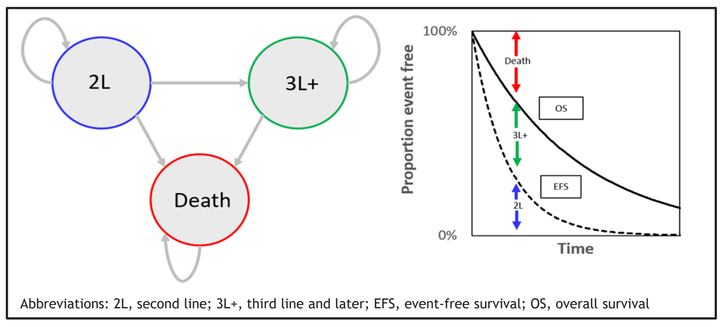
Objectives

- To evaluate the cost-effectiveness of liso-cel vs. SoC as a 2L treatment for transplant-eligible adults with DLBCL, HGBCL, PMBCL and FL3B in the Netherlands from a societal perspective.

Methods

- A partitioned-survival model was developed in R, as part of the R pilot initiated by Zorginstituut Nederland (ZIN). The model comprised three health states: 2L, third-line and later (3L+), and death (Figure 1).
- The model leveraged the primary event-free survival (EFS) and secondary overall survival (OS) endpoints from TRANSFORM. Patients enter the model in the 2L event-free (2L EF) health state; once they have a non-death event defined by EFS, patients move to the 3L+ state. Patients can move to death from either the 2L EF or 3L+ states.
- The target population reflects Dutch adults with 2L LBCL who are transplant eligible, with a poor prognosis defined as having disease that is refractory to 1L immunochemotherapy or that has relapsed within 12 months. The model population was informed by data from TRANSFORM.
- The model adopted a Dutch societal perspective and used an annual discount rate of 4% for costs and 1.5% for health outcomes, in line with the ZIN guidelines.[8]
- As recommended by ZIN,[8] a lifetime horizon (up to 50 years, given the average age of the 2L transplant-eligible TRANSFORM population is 56 years) was applied.
- The SoC arm consisted of rituximab/gemcitabine/dexamethasone/cisplatin (R-GDP), rituximab/dexamethasone/cytarabine/cisplatin (R-DHAP), or rituximab, ifosfamide/carboplatin/etoposide (R-ICE) followed by HDCT and HSCT.
- Based on the burden of the disease, the willingness-to-pay (WTP) threshold was set at €50,000 per quality-adjusted life year (QALY) gained.[9]

Figure 1. Model structure



Abbreviations: 2L, second line; 3L+, third line and later; EFS, event-free survival; OS, overall survival

Clinical Inputs

- Efficacy (i.e., EFS and OS) and safety data from the TRANSFORM trial (13 May 2022 data cut-off, 17.5-month median follow-up) were used in the model.
- Mixture-cure models (MCM) were chosen for survival extrapolations to reflect the natural history of the disease whereby some patients experience prolonged survival even in the absence of chimeric antigen receptor T-cell (CAR-T) therapies.
- MCM is a statistical framework that estimates the proportion cured (with survival assumed to be like the age- and sex-adjusted general population[10]) and predicts the survival of non-cured patients using parametric functions. In the scenario analyses, standardized mortality ratios (SMRs) were used to estimate the survival of cured patients.
- An independent log-normal model was selected for the EFS of liso-cel based on goodness-of-fit to the observed data (**Figure 2A**). The same distribution was used for SoC. All other distributions were tested in scenario analyses.
- Similar to EFS, MCMs were fitted to the liso-cel and SoC OS data from TRANSFORM. Independent gamma models for liso-cel and SoC were selected based on best statistical fit (**Figure 2B**). All other distributions were tested in scenario analyses.
- Model selection was justified based on long-term survival estimates from external data, i.e. CORAL (SoC) and TRANSCEND (liso-cel).[5,7]

Figure 2. EFS (A) and OS (B) survival models used in the base case

Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; OS, overall survival; SoC, standard of care

Utility Inputs

- EQ-5D-5L data from TRANSFORM were collected and analysed using Dutch-specific utility tariffs[11] to estimate the health state utilities (2L EF: 0.872; 3L+: 0.824).
- All health-state utility values were age-adjusted[12] to account for the gradual change in utility due to the aging of the modelled cohort over time; excluding age-adjustment was explored in a scenario analysis.
- The model considers utility values that capture quality of life post-HSCT in 2L, stratified by month 1, months 2 to 6 and months 6 to 12 post HSCT, to capture the short and long-term impact of HSCT on utility.
  - Months 1 to 6 were assumed to have the same utility as 3L+ (0.824) while months 7 to 12 were assumed to have the same utility as 2L EF (0.872).
- AE decrements were applied at the start of the 2L EF health state. Utility decrements due to grade 3+ treatment-related AEs were derived from TRANSFORM EQ-5D-5L data analysis for any AE (-0.059) excluding cytokine release syndrome (CRS) and neurotoxicity (due to low incidence).
  - QALY decrements associated with CRS and neurotoxicity were estimated at -0.228 and -0.178, respectively, based on a vignette study conducted in the United Kingdom.[13]

Resource Use and Cost Inputs

- The following costs were considered in the analysis:
  - Treatment-related costs (at list prices)
    - CAR-T therapy: leukapheresis, bridging therapy, lymphodepleting therapy and additional monitoring for CAR-T therapy post-infusion
    - SoC: HDCT and HSCT
    - Drug acquisition (e.g. SoC salvage chemotherapy) and administration
  - Health care resource use
  - AE management costs for 2L treatments
  - Societal costs including direct non-medical costs (travel, lodging, caregiver) and indirect non-medical costs (due to productivity loss). Indirect medical costs (future costs) were considered in a scenario analysis.
- Resource use frequency was reduced for patients who remained in the 2L EF state after two years as these patients were no longer expected to be at risk of progression or death and, thus, require less monitoring in clinical practice.
- Unit costs were populated for the Netherlands (in 2022 Euros) using national costing databases and other published sources as required.[8]

Sensitivity analysis

- To assess the joint uncertainty of all key parameters, a probabilistic sensitivity analysis (PSA) using 1,000 simulations was performed by simultaneously varying multiple parameters using a Markov chain Monte Carlo simulation.
- One-way deterministic sensitivity analysis (DSA) was performed by varying key parameters by their 95% confidence interval, or 2.5th and 97.5th percentiles of the same probability distribution assumed for the PSA (depending on data availability).

Scenario analysis

- Scenario analyses were performed to assess the impact of a specific scenario/assumption on results (e.g., model settings, efficacy, costs, utilities, application of SMR for cured patients).

Results

Base-case cost-effectiveness results

- In the 2L DLBCL population, patients treated with liso-cel had a total of 13.51 life years (LYs) over the lifetime horizon, compared with 10.87 LYs observed in the SoC arm (discounted). Additionally, liso-cel showed an incremental benefit of 2.51 QALYs compared with SoC (**Table 1**).
- The total costs for liso-cel and SoC were estimated at €481,414 and €379,078, respectively, an increment of €102,337. The disaggregated costs are shown in **Table 2**.
- The resulting incremental cost-effectiveness ratio (ICER) was €40,836 per QALY gained (**Table 1**). This was below the WTP threshold of €50,000/QALY gained.

Table 1. Base-case incremental results for liso-cel vs. SoC

Treatment comparison	Incremental				
	LYs	QALYs	Costs	Costs per LY gained	Costs per QALY gained
Liso-cel vs. SoC	2.73	2.51	€102,337	€37,478	€40,836

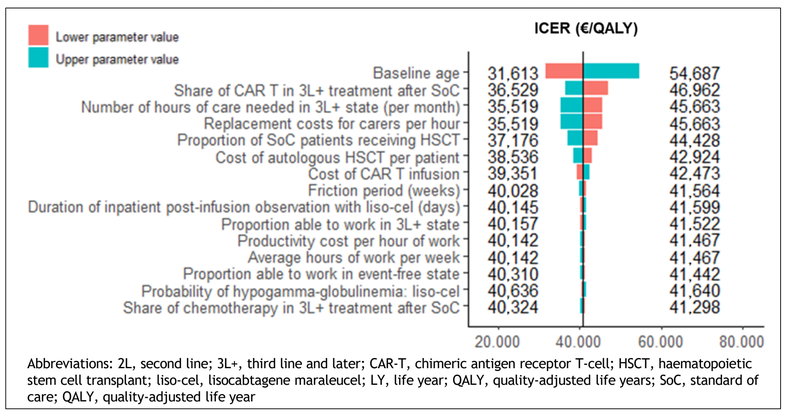
Abbreviations: liso-cel, lisocabtagene maraleucel; LY, life year; QALY, quality-adjusted life year; SoC, standard of care

Table 2. Discounted disaggregated costs by treatment

	Liso-cel	SoC
Total costs (€)	**€481,414**	**€379,078**
Pre-treatment costs (€)	€18,714	€0
2L treatment costs	€370,724	€49,975
Drug acquisition	€332,462	€7,252
Drug administration	€38,262	€6,133
Autologous SCT costs	€0	€36,589
3L+ treatment costs	€9,007	€184,567
Drug acquisition	€2,638	€2,368
Drug administration	€2,325	€2,085
Radiotherapy	€62	€0
Autologous SCT	€3,982	€862
CAR-T cell therapy	€0	€179,252
Adverse event costs	€5,235	€3,491
Routine monitoring resource use	€31,272	€26,717
Post-2L treatment	€10,504	€5,333
2L	€18,798	€9,038
3L+	€1,970	€12,345
End-of-life care	€560	€631
Transportation	€5,627	€38
Productivity loss and informal care	€40,274	€113,658

Abbreviations: 2L, second line; 3L+, third line and later; CAR-T, chimeric antigen receptor T-cell; liso-cel, lisocabtagene maraleucel; LY, life year; QALY, quality-adjusted life year; SCT, stem cell transplant; SoC, standard of care

Figure 3. DSA tornado diagram of liso-cel vs. SoC (€ per QALY gained)



Abbreviations: 2L, second line; 3L+, third line and later; CAR-T, chimeric antigen receptor T-cell; HSCT, haematopoietic stem cell transplant; liso-cel, lisocabtagene maraleucel; LY, life year; QALY, quality-adjusted life years; SoC, standard of care; QALY, quality-adjusted life year

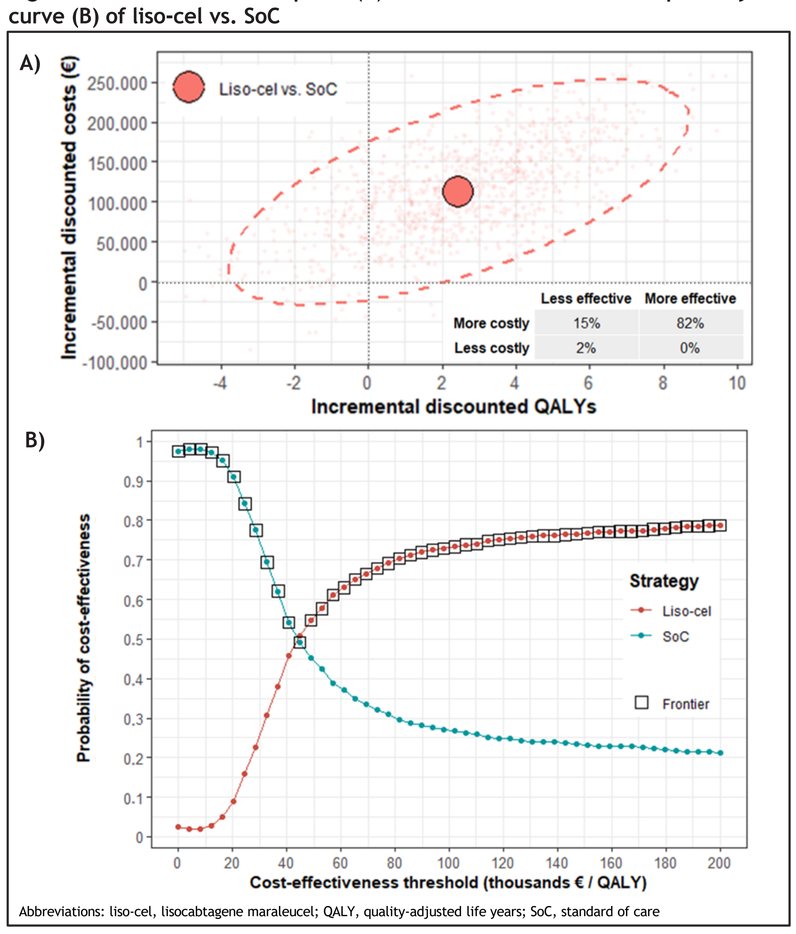
DSAs

- Seven key model parameters had the greatest influence (>2%) on the ICER (€/QALY gained) (**Figure 3**).
- The ICER was most sensitive to the uncertainty around the baseline age of patients, which affects general population mortality and utility. Using the upper limit of this parameter increased the ICER by 34%, reaching €54,687/QALY.
- Other parameters impacting the ICER included the proportion of CAR-T treatment in 3L+ care after SoC and the number of care hours in the 3L+ health state.
- Overall, the DSA tornado diagram illustrates that all ICERs, but one, remained below the WTP threshold of €50,000/QALY.

PSAs

- The results of the PSA (**Figure 4A**) show that liso-cel was more effective than SoC across 82% of the simulations.
- The cost-effectiveness acceptability curve (**Figure 4B**) shows that at the established WTP threshold of €50,000 per QALY gained, liso-cel had a 56% probability of being cost-effective compared with SoC.

Figure 4. Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B) of liso-cel vs. SoC



Abbreviations: liso-cel, lisocabtagene maraleucel; QALY, quality-adjusted life years; SoC, standard of care

Scenario analyses

- The results for the scenario analyses are presented in **Table 4**.
- The ICER was below the €50,000/QALY threshold across all scenarios, except for two scenarios where the time horizon was set to 10 years (€131,436/QALY) and the healthcare perspective was adopted (€67,889/QALY). These scenarios were less relevant as they do not include all costs/benefits till death, or societal costs.
- The scenario where a lower 3L+ utility was applied (0.66 vs. base case 0.824) resulted in the lowest ICER (€33,250/QALY).

Table 4. Scenario results for liso-cel vs SoC

Parameter	Base-case	Scenario	ICER (€/QALY)
Base case			**€40,836**
Time horizon	50 years (lifetime horizon)	25 years	€49,517
		10 years	€131,436
Drug wastage for chemotherapy	Included	Excluded	€41,218
MCM EFS	Log-normal	All other distributions	€39,622 - €42,110
MCM OS	Gamma	All other distributions	€37,876 - €44,664
SMR for cured patients	No SMR applied	SMR of 1.56 to 5 years	€41,838
		SMR of 1.40 to 2 years	€41,140
		SMR of 1.4 for 2 years and 1.18 thereafter	€44,263
Proportion of patients who received liso-cel in an inpatient setting	100%	79% per TRANSFORM	€40,426
Cut-off for long-term remission	2 years	5 years	€41,359
AE decrement for CRS	-0.228	Utility value of zero (i.e., utility decrement equal to EF utility)	€40,951
Age-based utilities	Yes	No	€40,381
Health state utilities	Based on TRANSFORM	10% lower	€45,400
		Lower 3L+ utility of 0.66	€33,250
		Utility from axi-cel NICE submission	€43,216
Indirect medical costs	Excluded	Included	€46,764
Model perspective	Societal perspective	Healthcare perspective	€67,889

Abbreviations: 3L+, third line and later; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; liso-cel, lisocabtagene maraleucel; MCM, mixture-cure model; OS, overall survival; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SMR, standardized mortality rate; SoC, standard of care

Conclusion

- The results from this study present compelling evidence supporting the cost-effectiveness of liso-cel as a valuable addition for the 2L treatment of patients with DLBCL, HGBCL, PMBCL and FL3B in the Netherlands. The ICER of €40,836/QALY gained fell below the relevant WTP threshold of €50,000/QALY.

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