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Cost-effectiveness analysis of lisocabtagene maraleucel in the treatment of patients with refractory or relapsed large B-cell lymphoma within 12 months (LBCL RR≤12) eligible for autologous hematopoietic stem cell transplant (ASCT) in France

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Introduction and objective

- Non-Hodgkin lymphoma (NHL) is a heterogeneous group of diseases defined by an abnormal proliferation of lymphoid cells, most often from the B lineage (85% of cases), divided into "aggressive" and "indolent" forms. Aggressive B-cell NHL can be large B-cell lymphoma (LBCL), including diffuse LBCL, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, or grade 3B follicular lymphoma.[1,2]
- In France, for the treatment of patients with LBCL, CAR-Ts have been available since 2019 in 3rd line and more, but not for patients with LBCL RR≤12.
- Prior to the advent of CAR-Ts, management of patients with LBCL RR≤12 was based on a protocol including autologous hematopoietic stem cell transplant (ASCT) for ASCT-eligible patients (standard of care, SoC).[3-5]
- The arrival of CAR-T cells in the 2nd line of treatment has led to a paradigm shift, with treatment options now being offered according to CAR-T eligibility rather than to ASCT. In France, lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) are the treatment options available. Liso-cel was granted marketing authorization in April 2023 based on data from the TRANSFORM study (#NCT03575351).[6,7]
- The objective of this study was to assess the cost-effectiveness of liso-cel versus SoC in the treatment of adult patients with ASCT-eligible LBCL RR≤12 patients in France.

Methods

Population

- Analysis population corresponded to patients enrolled in the TRANSFORM study (which was simulated) (Table 1).[7]

Table 1. Characteristics of the analysis population

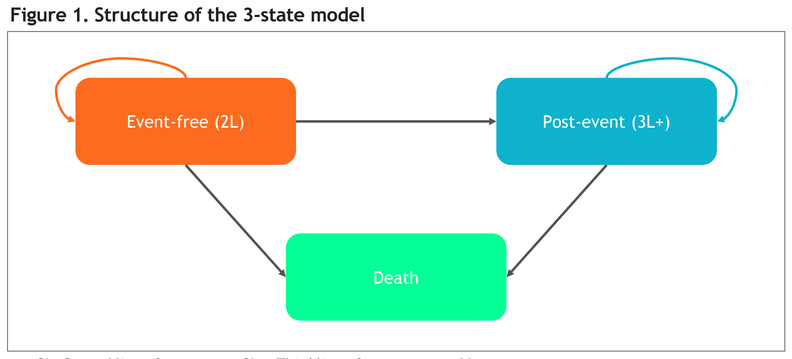
Characteristics	Population (N=184)
Age, mean years	56.3
Men, n (%)	105 (57.1)
Histology, n (%)	
DLBCL	118 (64.1)
HGBCL	43 (23.4)
PMBCL	17 (9.2)
THRBCL	5 (2.7)
FL3B	1 (0.5)

FL3B: Follicular lymphoma 3B; HGBCL: High-grade B-cell lymphoma; DLBCL: Diffuse Large B-cell lymphoma; PMBCL: Primary mediastinal large B-cell lymphoma; THRBCL: T-cell/histiocyte-rich large B-cell lymphoma
Note: Percentages have been rounded

Model

- A semi-Markov model was developed in Excel including 3 distinct mutually exclusive health states: event-free (EF) corresponding to the 2nd line of treatment; post-event (PE) corresponding to the 3rd line of treatment and later; and death (Figure 1).

Figure 1. Structure of the 3-state model



2L: Second line of treatment; 3L+: Third line of treatment and later

- Table 2 presents the main structural choices of the model.

Table 2. Structural choices of the model

Setting	Structural choice
Time horizon	20 years
Intervention	Liso-cel
Comparator	- Standard of care (SoC) consisting of ASCT + salvage chemotherapy - Axi-cel was not considered as a comparator due to the large uncertainty surrounding indirect comparison with liso-cel[8]
Perspective	Restricted to French health system
Safety	Adverse events with a frequency greater than 1% and those specific to CAR-T
Population (simulated)	Patients with relapsed DLBCL, HGBCL, PMBCL or FL3B within 12 months of completion of first-line immunochemotherapy or refractory to this first-line therapy and eligible for ASCT in France
Discount rate	2.5% annually for health costs and outcomes

ASCT: Autologous hematopoietic stem cell transplantation; CAR-T: chimeric antigen receptor-T; DLBCL: Diffuse large B-cell lymphoma; FL3B: Follicular lymphoma 3B; HGBCL: High-grade B-cell lymphoma; PMBCL: Primary mediastinal large B-Cell lymphoma

Survival and safety data

- During the first 5 years, the event-free survival (EFS) data from the TRANSFORM study was extrapolated according to international recommendations and external validity.[9-11]
- In case of disease progression, data from DESCAR-T (French exhaustive registry of patients treated with a CAR-T) and SCHOLAR-1 (2 large randomized trials and 2 academic databases of patients with DLBCL) were used, , to incorporate long-term data into the model.[12,13]
- From 5 years in the same health state (i.e., EF or PE), patients were considered cured. Beyond that, the age- and sex-adjusted mortality of the general French population was considered, increased with a standardized mortality factor (2.2).[14]
- The assumptions and modeling choices are presented in Table 3.

Table 3. Summary of the approach to clinical data integration

Health status	Assumptions and modeling choices
First five years in the event-free state	• The event-free survival curve of the TRANSFORM study was extrapolated
First five years in the post-event state	• Post-event survival was modelled from the: • DESCAR-T registry if patient received a CAR-T in event-free (overall survival 2, e.g., after a first progression) or in post-event states (overall survival)[12] • SCHOLAR-1 study's if patient had received no CAR-T (overall survival)[13]
More than 5 years without an event in event-free or post-event health states	• A hypothesis of cure was retained • Age- and sex-adjusted mortality of the general French population was considered, increased with a standardized mortality ratio (2.2)[14]

CAR-T: chimeric antigen receptor-T

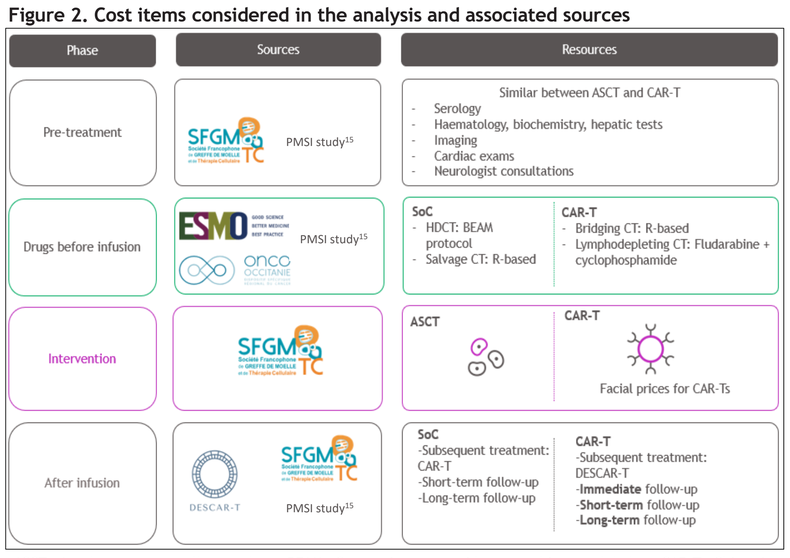
- Adverse events were selected according to their occurrence in the TRANSFORM trial and were applied only in the EF health state.

Methods (continued)

Costs

- Costs considered were identified from French and European recommendations on the care pathway of patients treated with CAR-T in 3L+ and from a real-world study carried out using data from the medicalization program of information systems (PMSI) and were expressed in euro 2023 (Figure 2).[15]
- Prices were the public facial prices, without accounting for any confidential prices/discounts (liso-cel: €345,000 excluding taxes).

Figure 2. Cost items considered in the analysis and associated sources



ASCT: Autologous stem cell transplant; BEAM: Carmustine, etoposide, cytarabine, melphalan; CAR-T: Chimeric antigen receptor-T; CAR-T REAL study: see reference #15 CT: Chemotherapy; DESCAR-T: French Registry of CAR-T Cell Therapies[12]; ESMO: European Society of Medical Oncology[3]; HDCT: High-dose chemotherapy; PMSI: *Programme de médicalisation des systèmes d'information;* R: Rituximab; SFGM-TC: Francophone Society of Marrow Transplant and Cell Therapy[16]; SoC: Standard of care

Outcomes

- Life years (LYs) gained and costs, both total and by health state, were assessed.
- The incremental cost-effectiveness ratio (ICER) of liso-cel vs. SoC was calculated.

Sensitivity analyses

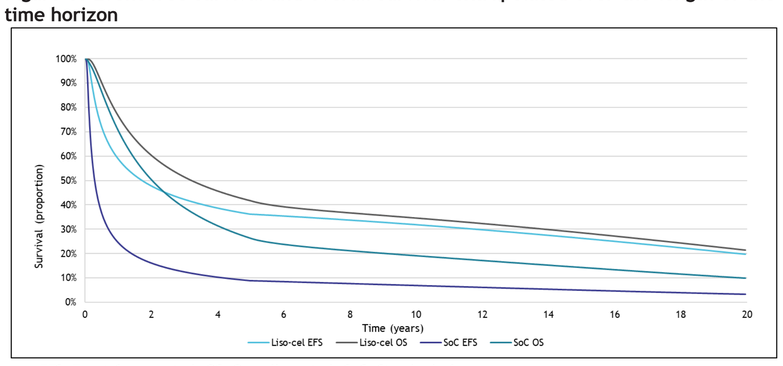
- Univariate sensitivity analyses were performed, with variables varied within 95% confidence interval, or ±20%.[11]
- Probabilistic senstivity analyses (multivariate analyses) were conducted through 1,000 simulations according to a 2nd order Monte Carlo process.[11]

Results

Health outcomes

- By the end of the time horizon, approximately 20% of patients treated with liso-cel are alive and event-free, versus around 5% among those treated with SoC (Figure 3). Overall survival rate was almost doubled for patients treated with liso-cel vs. SoC at the end of the time horizon (Figure 3).

Figure 3. Event-free survival and overall survival extrapolated over the length of the time horizon



EFS: Event-free survival; OS: Overall survival; SoC: Standard of care

- In terms of life years, liso-cel generated 6.4 LYs versus 5.1 for SoC. Most of LYs generated by liso-cel were in the EF (5.6, 88%) versus PE for SoC (3.2, 63%) (Table 4).

Table 4. Survival results over a 20-year time horizon

Intervention	Total LYs	LYs spent in the event-free state	LYs spent in the post-event state
SoC	5.1	1.9	3.2
Liso-cel	6.4	5.6	0.8

LY: Life years ; SoC: standard of care

Costs

- The total management cost with liso-cel was estimated at €381,775 over 20 years. Eighty-nine percent were related to the acquisition of drugs (liso-cel and rituximab) in the EF state (Table 5).
- The total management cost in the SoC arm was estimated at €256,932 over 20 years. Eighty-three percent were related to the acquisition of CAR-T as subsequent therapies in the PE state (Table 5).

Table 5. Costs item for liso-cel and SoC arms, over a 20-year time horizon

Cost Item	Liso-cel arm	SoC arm
Event-free		
Pre-treatment phase	€6,099	€9,820
Treatment	€349,631	€13,350
Acquisition	€339,930	€0
Administration	€9,701	€0
HDCT+ASCT	€0	€13,350
Adverse events	€10,236	€7,424
Short-term follow-up	€1,603	€563
Long-term follow-up	€2,856	€4,163
Post-event		
Costs related to subsequent treatments	€6,727	€213,358
Short- and long-term follow-up	€282	€3,516
End-of-life costs	€4,341	€4,740
Total	**€381,775**	**€256,932**

ASCT: Autologous stem cell transplant; HDCT: High-dose chemotherapy; SoC: standard of care

Results (continued)

Cost-effectiveness results

- Liso-cel provided more LYs (+1.3) and was more costly (+€124,843) than SoC, resulting in an ICER of €91,531/LY gained over a 20-year time horizon (Table 6).

Table 6. Results of the cost-effectiveness analysis of liso-cel compared to the standard of care - base case analysis

Intervention	Total Costs	LYs gained	ICER (€/LYs gained)
SoC	€256,932	5.1	-
Liso-cel	€381,775	6.4	€91,531/LY

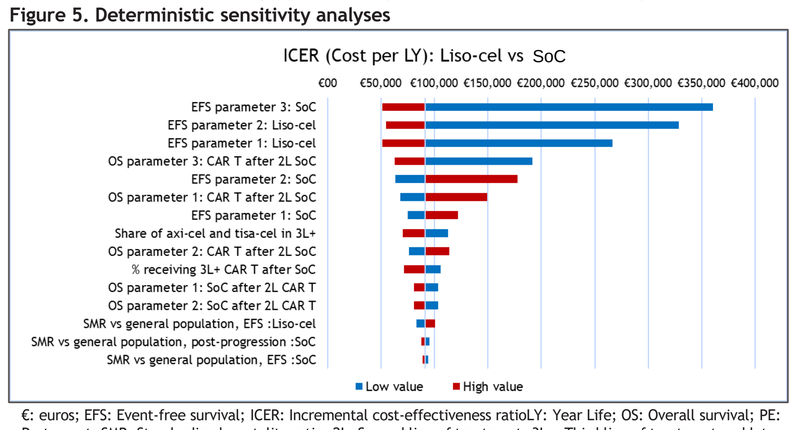
LY: Life year; SoC: standard of care

Sensitivity analyses

Deterministic sensitivity analyses

- The variables with the greatest impact on the ICER were those defining the distribution used to extrapolate EFS (regardless of the treatment)(Figure 5).

Figure 5. Deterministic sensitivity analyses



€: euros; EFS: Event-free survival; ICER: Incremental cost-effectiveness ratioLY: Year Life; OS: Overall survival; PE: Post-event; SMR: Standardized mortality ratio; 2L: Second line of treatment; 3L+: Third line of treatment and later
Parameters 1, 2 and 3 represent the parameters which are defining the distributions used to extrapolate survival

Probabilistic sensitivity analyses

- In the probabilistic sensitivity analyses, ICER of liso-cel versus SoC was €99,886/LY gained over a 20-year time horizon (Table 7). Difference with deterministic ICER was essentially due to uncertainty related to incremental LYs rather than incremental costs.
- Liso-cel was more costly and more effective than SoC in 92% of the simulations and had an 80% probability of being cost-effective for a propensity to pay of €200,000/LY gained.

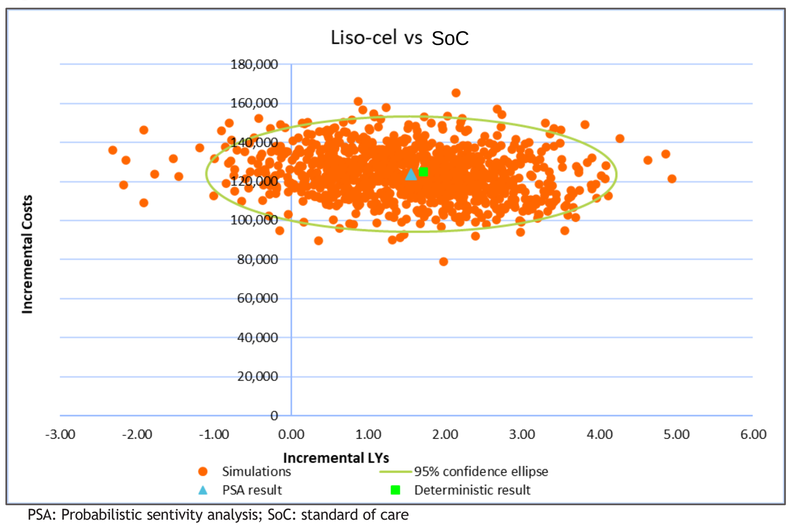
Table 7. Probabilistic sensitivity analysis results

Intervention	Total Costs	LYs gained	ICER (€/LY gained)
SoC	€255,569	5.1	-
Liso-cel	€379,355	6.3	€99,886/LY

ICER: Increment cost-effectiveness ratio; LY: Life year

- Most of the simulations fell in the north-eastern quadrant of the cost- effectiveness plan (Figure 6).

Figure 6. Cost-effectiveness plan - Incremental costs and outcomes of liso-cel versus SoC



PSA: Probabilistic sentivity analysis; SoC: standard of care

Conclusion

- This cost-effectiveness analysis conducted in accordance with French recommendations estimated the number of years of life gained with liso-cel compared to SoC in patients with LBCL RR≤12 in France.
- Over a 20-year time horizon, the ICER of liso-cel compared to SoC is estimated at €91,531/LY. Despite no cost-effectiveness threshold currently in use in France, €120,000/LY could be considered as a reasonable one.[17] Under this assumption, liso-cel is cost-effective versus SoC to treat patients with LBCL RR≤12 in France.
- The distribution of LYs gained and costs by health state for liso-cel and SoC reflects the use of CAR-T in 2nd and 3rd line of treatment, respectively.
- The structure of the model allowed for the use of data from the DESCAR-T registry and to incorporate long-term data into the model, despite estimated OS might be underestimated considering latest clinical trial data published[18].
- One limitation of this cost-effectiveness analysis is the absence of axi-cel as a comparator of liso-cel. This choice was made in the lack of robust comparative data in the literature.
- The generation of real-world data could confirm the long-term modelled outcomes, the cost-effectiveness of liso-cel, and document the uncertainty surrounding it.

References

1. Klink A et al. Journal of Clinical Pathways 2020
2. Crump M et al. Blood. 2017 Oct 19; 130(16):1800-8.
3. Tilly H et al. Annals of Oncology. 2015 Sep 1; 26:v116-25.
4. Onco-Occitanie. Regional Repository 'Treatment of Adult Lymphomas' - Updated January 2023
5. NCCN Guidelines Version 5.2023 Diffuse Large B-Cell Lymphoma.
6. Haute Autorité de la Santé. Breyanzi. September 2022.
7. Kamdar M et al. Lancet. 2022 Jun 18; 399(10343):2294-308.
8. Bommier C et al. Hematol Oncol. 2022 Apr 18.
9. Kambhampati S et al. Blood. 2022 Aug 1; blood.2022016747.
10. NICE. DSU 19. 2020.
11. Haute Autorité de la santé. Methodological guide of cost-effectiveness analysis. 2020.
12. Di Blasi R, et al. Blood 140:2584-2593.
13. Crump M, et al. Blood 130:1800-1808.
14. Assouline S et al. 2020. Blood Advances 4:2011-2017.
15. Thieblemont C et al. Value in Health 26, S295-S296 (2023).
16. Farge D, et al. La Revue de Médecine Interne 45:79-99. (2024)
17. Téhard B, et al. Value in Health 23:985-993. (2020)
18. Kamdar M, et al. J Clin Oncol. 42(suppl 16). (2024)

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- All authors contributed, reviewed, and approved this poster.

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