Cost-effectiveness analysis of axicabtagene ciloleucel *vs* tisagenlecleucel for the management of diffuse large B-cell lymphoma in Spain

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BACKGROUND

- Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL). In Europe, its incidence is 3.8 per 100,000 new cases every year[1], and approximately 30% of these patients will relapse or become refractory (R/R) DLBCL[2], presenting a significant burden to healthcare systems and patients alike.
- Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are CAR T-cell therapies that have gained approval by the European Medicines Agency for the treatment of R/R DLBCL after ≥2 lines of therapy based on their pivotal trials: ZUMA-1 and JULIET, respectively[4,5]. Both treatments showed exceptional survival gains versus standard of care.
- In order to enable the comparison of survival outcomes between axi-cel and tisa-cel, a matching-adjusted indirect comparison (MAIC) was developed, where patient-level data from ZUMA-1 study and aggregate-level data of JULIET study were used to adjust the ZUMA-1 patient characteristics in order to create a more balanced comparison[6].

OBJECTIVE

- The aim of this study was to evaluate the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) of axi-cel in comparison to tisa-cel in adults with R/R DLBCL after ≥2 lines of systemic therapy, from the Spanish National Health System (NHS) perspective.

METHODS

- A partitioned survival mixture-cure model (PS-MCM) was used to model a cohort of patients in terms of their lifetime costs and health outcomes. These were used to estimate total costs, life years gained (LYG) and quality-adjusted life years (QALYs) in the intervention and comparator arms.
- The model included the following health states: pre-progression, post-progression and death. Patients could transition between health states based on progression-free survival (PFS) and overall survival (OS) data from the ZUMA-1 and JULIET trials[4,5]. The ZUMA-1 data was adjusted by a MAIC approach which used a logistic regression based on the propensity score, whose details have been previously published elsewhere[6].
- PFS curves for axi-cel and tisa-cel were extrapolated using a Log-logistic distribution, whereas a Gamma distribution was used for axi-cel OS curve and a Log-normal distribution for tisa-cel OS curve.
- The analysis was performed from the Spanish NHS perspective.
- QALYs were estimated using utility values derived from ZUMA-1[7,8] (Table 1).

Table 1. Utilities

Health state	Utility value
Pre-progression: CAR-T on treatment (1st month)	0.740
Pre-progression: off-treatment ≤12 months	0.782
Pre-progression: off-treatment >12 months	0.820
Post-progression	0.390

CAR-T, chimeric antigen receptor T-cell; Source: Lin 2018[7], Chen 2018[8].

- Adverse events (AEs) rates and proportion of patients undergoing stem cell transplant (SCT) were derived from indirect comparison[6] and clinical trials[4,5], respectively.
- Healthcare resource consumption was defined by clinical experts in the haemato-oncology field.
- The total costs (€, 2020) included CAR-T acquisition, leukapheresis, lymphodepleting chemotherapy, cell infusion and monitoring costs, health state medical resource, SCT, end of life care and AEs management costs (Table 2).
- Drug costs were estimated based on ex-factory prices[9] with national mandatory deduction applied[10].
- Unit costs were derived from local cost databases[9,11].
- A lifetime horizon was considered and an annual discount rate of 3% was applied for costs and outcomes[12]. The cycle length was one month.
- One-way sensitivity analyses (OWSA), scenario analysis (SA) and probabilistic sensitivity analyses (PSA) were performed to confirm the robustness of the model.

METHODS

Table 2. Drug and healthcare resource costs (€,2020)

	Cost, €
Drug acquisition: axi-cel	313,920.00*
Drug acquisition: tisa-cel	307,200.00*
Leukapheresis	1,064.79
Lymphodepleting chemotherapy: axi-cel	174.84
Lymphodepleting chemotherapy: tisa-cel	138.18
CAR-T administration and monitoring	8,767.73
ICU hospitalisation (per day)	1,338.45
Non-ICU hospitalisation (per day)	722.89
Allo-SCT	70,559.14
Auto-SCT	48,591.37
Pre-progression management costs	704.89
Post-progression management costs	1,153.43
End of life care	3,132.52
AE management cost: Cytokine release syndrome	1,073.59
AE management cost: Neurological event	713.09

* Axi-cel and tisa-cel costs were based on list price[9] with a 4% of mandatory deduction applied[10].
AE, adverse event; axi-cel, axicabtagene ciloleucel; Allo-SCT, allogenic stem cell transplant; Auto-SCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell; ICU, intensive care unit; tisa-cel, tisagenlecleucel; Source: Expert panel, Bot Plus 2.0[9], RDL 8/2010[10], eSalud[11].

RESULTS

- In the base case, axi-cel yielded 2.74 incremental LYG per patient and 2.31 incremental QALYs per patient compared to tisa-cel (Table 3).
- Over a lifetime horizon, axi-cel incurred an additional €30,135 per patient compared to tisa-cel, mainly due to patients spending more time in the pre-progression state which led to higher disease management costs (Table 3).
- The ICER and ICUR of axi-cel vs tisa-cel resulted in €10,999/LYG and €13,049/QALY gained, respectively (Table 3).
- Sensitivity analyses confirmed the model's robustness (Figure 1, Figure 2). Utility and costs in the pre-progression state were the parameters with the highest impact in the OWSA. Within the SA, PS-MCM without MAIC also showed substantial influence (Figure 1).
- In the PSA, axi-cel was cost-effective vs tisa-cel in 92.3% of the 1,000 simulations at a threshold of €22,000/QALY and 99.2% at a threshold of €60,000/QALY (Figure 2)[13,14].

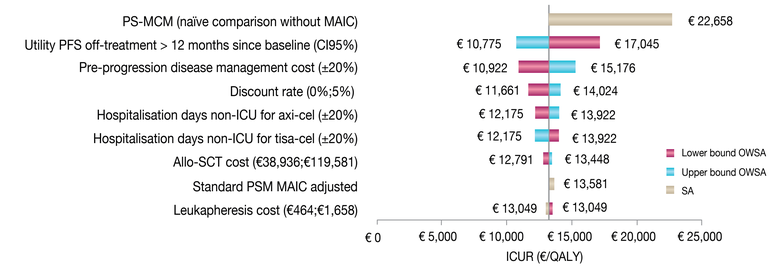
Table 3. Base case results

	Axi-cel	Tisa-cel	Incremental
TOTAL LYG	**9.45**	**6.71**	**2.74**
LYG in pre-progression state	8.87	5.97	2.90
LYG in post-progression state	0.58	0.75	-0.16
TOTAL QALYs	**7.47**	**5.16**	**2.31**
QALYs in pre-progression state	7.25	4.87	2.37
QALYs in post-progression state	0.23	0.29	-0.06
TOTAL COSTS PER PATIENT	**€430,747**	**€400,612**	**€30,135**
ICER (axi-cel vs tisa-cel)		**€10,999/LYG**	
ICUR (axi-cel vs tisa-cel)		**€13,049/QALY**	

Axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; LYG, life years gained; QALY, quality-adjusted life year; tisa-cel, tisagenlecleucel

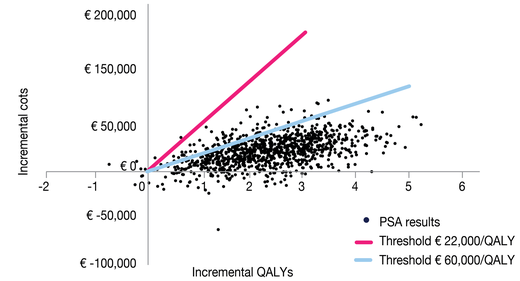
RESULTS

Figure 1. One-way and scenario sensitivity analyses Tornado diagram



Allo-SCT, allogenic stem cell transplant; Axi-cel, axicabtagene ciloleucel; CI, confidence interval; ICU, intensive care unit; ICUR, incremental cost-utility ratio; MAIC, matching adjusted indirect comparison; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSM, partitioned survival model; PS-MCM, partitioned survival mixture cure model; PSM, partitioned survival model; QALY, quality-adjusted life year; SA, scenario analysis; tisa-cel, tisagenlecleucel

Figure 2. Probabilistic sensitivity analysis results



PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

CONCLUSIONS

- Patients treated with axi-cel experienced better survival outcomes in terms of LYG and QALYs compared to those treated with tisa-cel.
- The results of this analysis indicate axi-cel is a cost-effective therapy compared to tisa-cel for the treatment of R/R DLBCL after two or more lines of systemic therapy, when considering the frequently-used €22,000/QALY and €60,000/QALY gained willingness-to-pay thresholds in Spain[13,14].

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DISCLOSURES

Mariana Bastos-Oreiro has received conference and consulting fees from BMS, Celgene, Kite Pharma, Novartis, Roche and Takeda. Anna Sureda has received conference and consulting fees from BMS, Celgene, Gilead, Janssen, MSD, Novartis, Roche, Sanofi and Takeda. Mariana Bastos-Oreiro and Anna Sureda have received honoraria from Gilead for advocacy tasks related to this project. María Presa, Ana de las Heras and Miguel Ángel Casado are employees of Pharmacoeconomics & Outcomes Research Iberia, a consultant company specialised in economic evaluation of health technologies which has received unrestricted funding for development of the analysis. Carlos Pardo and Victoria Martín-Escudero are employees of Gilead Sciences Spain.