Poster EE355

THE IMPACT OF DYNAMIC MORTALITY ON THE COST-EFFECTIVENESS OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE AS SECOND-LINE THERAPY IN PATIENTS WITH LARGE B-CELL LYMPHOMA IN FRANCE

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BACKGROUND

- Axi-cel, an anti-CD19 autologous chimeric antigen receptor (CAR) T-cell therapy, was previously approved for treatment of patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after ≥2 prior systemic therapies.
- The phase 3 ZUMA-7 trial (NCT03391466) was designed to compare axi-cel with second-line (2L) standard-care therapy (SoC) in patients with early relapsed or primary refractory LBCL.
- At a median follow-up of 45.8 months, the superiority of axi-cel was demonstrated on the primary outcome, with a 58% improvement in event-free survival (EFS) (HR= 0.42 ; 95%IC [0.33 ; 0.55]) and the second endpoint with a 27% improvement in overall survival (OS) (HR= 0.73 ; 95%IC [0.54 ; 0.98]).
- In the case of a cost-effectiveness model, substantial long-term survival benefits can be expected, leading to long-term remission with patients approaching a mortality risk similar to the general population. This necessitates additional thought on how best to incorporate background mortality into mixture cure models within cost-effectiveness analyses.
- This may imply moving from the conventional static background mortality modelling approach to a dynamic one, allowing future health improvements to be considered over time[1].

OBJECTIVE

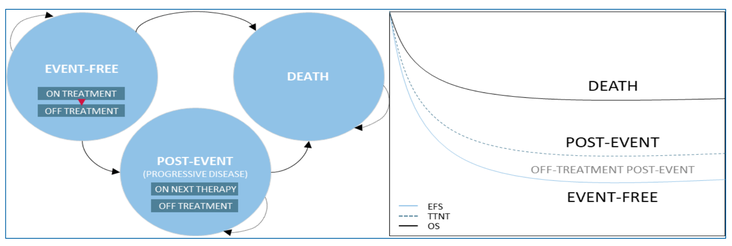
- The objective was to compare the cost-effectiveness of axi-cel versus SoC in 2L LBCL from a French perspective when using either a static or dynamic approach to modelling background mortality.

METHODS

Model structure

- A three-state partitioned survival model comprising the health states 'event-free', 'post-event', and 'death' was developed (**Figure 1**). Costs and health outcomes were projected over a 50-year lifetime horizon and discounted at 2.5% per year.

Figure 1. CE model structure



The panel on the right shows the implementation method of the partitioned survival model, whilst the panel on the left demonstrates the underlying transitions in the model. The post-event state may be disaggregated using the TTNT curve to estimate delays in initiation of third line therapy with respect to the timing of disease progression. The on/off treatment is used to determine costing of acquisition or administration of treatments based on mean durations of treatment obtained from ZUMA-7 or the literature.
Abbreviations: EFS, event-free survival; OS: overall survival; TTNT, time to next treatment

Model inputs

- Efficacy and safety data were derived from ZUMA-7 trial (cut off January 25th, 2023).
- Grades 3+ adverse events (AE) with an incidence ≥ 5% and special interest AEs were considered, with an impact on costs and utilities.
- French value set weighted EQ-5D-5L data derived from the ZUMA-7 and ZUMA-1 trials were used to estimate utilities for the event-free and post-event health states respectively (**Table 1**).

Table 1. Main model inputs

	Inputs	Source
Patients' characteristics		
Median age	59 years-old	ZUMA-7
% of male	79%	ZUMA-7
Health state utilities		
Event-free	0.892	ZUMA-7
Post-event	0.874	ZUMA-1
AE disutilities	-0.026	ZUMA-7

Abbreviations: AE, adverse event

- Only direct medical costs (in €2022) were considered, including treatment acquisition and administration, transportation, follow-up, adverse events, subsequent treatments and end-of-life care costs.

Efficacy extrapolation

- EFS, TTNT and OS were fitted independently and extrapolated using mixture cure models (MCMs), simulating a proportion of patients in long-term remission with the same mortality as in the general population. For uncured patients, a parametric extrapolation has been performed. This approach was applied to both treatment arms (**Figure 2A and 2B**).

METHODS *(CONTINUED)*

Figure 2A. Axi-cel survival plots

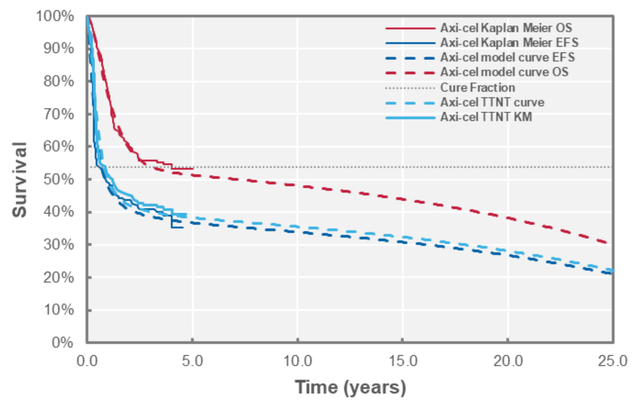
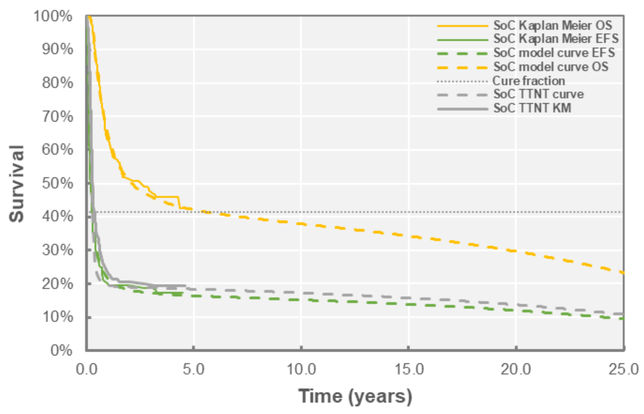


Figure 2B. SoC survival plots

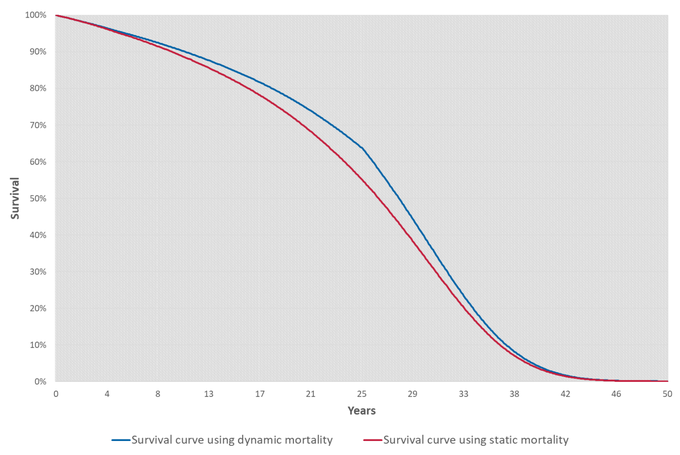


Abbreviations: EFS, event-free survival; KM, Kaplan Meier; OS, overall survival; SoC, standard of care; TTNT, time to next treatment

Mortality

- French general population mortality from INSEE was simulated in two ways:
  - A static approach using the latest observed age- and sex-specific mortality data of year 2020.
  - A dynamic approach using age-, sex-, and year-specific projected mortality for the years 2021 to 2070.
- A scenario analysis using 2019 mortality data rates for the static approach and projecting from 2020 for the dynamic approach was conducted to overcome possible bias given excess mortality observed during the Covid-19 period.
- Background mortality was modeled from the median age retrieved from ZUMA-7 trial, of 59 years-old and over the simulation, adjusted with a standardized mortality ratio of 1.09.
- Dynamic background mortality is important to consider given future life expectancy is likely to improve over time due to various drivers (economic growth, investment and policy drivers within healthcare, healthcare advancements…[1]). This is in contrast to static background mortality that will remain the same as that observed in 2020 (**Figure 3**).

Figure 3. French general population survival evolution over the time horizon



RESULTS

Cost-effectiveness results applying the static mortality approach

- Over a lifetime horizon, the model demonstrated that axi-cel was associated with an incremental QALY gain of 1.49 and an incremental cost of €124,950 compared to the SoC, resulting in an incremental cost-effectiveness ratio (ICER) of €84,020/QALY when using the conventional static mortality modelling approach (**Table 2**).

Sensitivity analysis

- The scenario analysis using 2019 mortality data rates led to an ICER reduction of 2% (€82,486/QALY).
- With a willingness-to-pay (WTP) threshold up to €170,250/QALY, axi-cel has at least

RESULTS *(CONTINUED)*

Table 2. Cost-effectiveness results applying the static mortality method

	Axi-cel	SoC	Incremental results
Health outcomes			
Total life-years (LYs)			
LYs in PFS	7.14	3.29	3.84
LYs in PD	2.98	4.91	- 1.92
Total	**10.12**	**8.20**	**1.92**
Total QALYs			
QALYs in PFS	5.76	2.67	3.09
QALYs in PD	2.46	4.06	- 1.60
Total	**8.22**	**6.73**	**1.49**
Cost outcomes			
2L treatment	€317,944	€31,736	€286,208
Subsequent treatment	€16,833	€174,761	- €157,929
Other	€18,633	€21,962	- €3,329
Total	**€353,409**	**€228,459**	**€124,950**
Cost-effectiveness			
Cost per LY gained			**€65,124**
Cost per QALY gained			**€84,020**

Abbreviations: 2L, second line; LY, life years; PD, progression disease; PFS, progression-free survival; QALY, quality-adjusted life-years

Cost-effectiveness results applying the dynamic mortality approach

- The dynamic mortality modelling approach led to a 11.7% increase in predicted median OS for axi-cel and a 6.4% increase in incremental QALY gained, resulting in a reduction in the ICER, estimated at €78,979/QALY (**Table 3**).
- The scenario analysis projecting from 2020 mortality data rates led to an ICER reduction of 0.3% (€78,761/QALY).

Table 3. Cost-effectiveness results applying the dynamic mortality method

	Axi-cel	SoC	Incremental results	Variation vs static mortality approach
Health and costs outcomes				
Total LYs	10.61	8.58	2.03	+ 5.7%
Total QALYs	8.65	7.07	1.58	+ 6.4%
Total costs	€353,345	€228,339	€125,006	+ 0.04%
Cost-effectiveness				
Cost per LY gained			**€61,663**	**- 5.3%**
Cost per QALY gained			**€78,979**	**- 6.0%**

Abbreviations: LY, life years; QALY, quality-adjusted life-years

- Axi-cel acquisition cost is one of the main drivers of the ICER. Axi-cel price is expected to be renegotiated, impacting the ICER (**Table 4**).

Table 4. ICER level variation depending on Axi-cel price

	ICER level (in €/QALY)	Variation
Axi-cel price		
€333,867 (2019)[2]	€96,886	+15.3%
€299,500 (2024)[3] – **basecase**	€84,020	-
€272,000 (2024)[4] (expected)	€73,912	-12.0%

Abbreviations: QALY, quality-adjusted life-years

KEY FINDINGS

- **A French cost-effectiveness analysis of axicabtagene ciloleucel (axi-cel) demonstrated incremental gains in QALYs and costs** versus standard of care in 2L R/R LBCL, leading to an ICER of **€84,020/QALY**. This analysis was estimated using the **most recent published negotiated price** and applied a **static mortality approach** when modelling background mortality within mixture cure models for survival outcomes.
- Given a proportion of patients are considered **long-term survivors** when using mixture cure models, the mortality risk applied to these patients should **capture improvements in general population mortality** over time.
- Applying a **dynamic approach to modelling background mortality** allows for expected future health improvements to be considered in survival extrapolations1. This results in **substantial decreases in ICERs** as it **avoids the overestimation of long-term mortality rates**, which can be particularly important when a substantial proportion of the modelled cohort **experiences long-term survival**.

CONCLUSIONS

- Model-based analysis suggests that **axi-cel is a cost-effective strategy in 2L R/R LBCL**, improving life expectancy, QALYs, decreasing progression and reducing subsequent treatment costs.
- Static mortality fails to account for improving survival of the general population over time, leading to **an overestimation of long-term mortality rates.**
- The application of a **dynamic mortality approach** that considers future improvements in health, had a **meaningful impact on the ICER estimated at €78,979/QALY (-6% *versus* the static approach)** and should be considered an **appropriate modelling approach in future French HTA submissions.**

References
1. Lee D, McNamara S. Value in Health. 2023
2. Journal Officiel. Axi-cel price. 2019
3. Journal Officiel. Axi-cel price. 2024
4. New list price of Axi-cel, effective from November 15, 2024

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