Poster 4681

Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma in the United States

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BACKGROUND

- Non-Hodgkin lymphoma (NHL) accounts for about 4% of all cancer cases in the US. [1]
- Indolent NHL (iNHL) comprises approximately one-third of NHL cases, of which follicular lymphoma (FL) is ~15-20% of all NHLs in Western countries.[2] Although FL is typically diagnosed at an advanced stage due to its asymptomatic nature in earlier stages,[3] advancements in first-line treatments have substantially increased overall survival for iNHL, with multiple cycles of treatment typically controlling disease prior to relapse.[4] However, relapse and recurrent progression are common among FL patients, with 19% of patients relapsing within two years of treatment.[5,6]
- There is no standard guidance on treatment for patients with relapsed/refractory (r/r) FL who have failed more than two lines of therapy, and FL patients are commonly re-treated with conventional therapies. Currently, FL patients in the third line of treatment face a median progression-free survival (PFS) of 11 months, demonstrating the need for treatment options that lead to long-term remission.
- Axicabtagene ciloleucel (axi-cel) was granted accelerated US Food and Drug Administration (FDA) approval in early 2021 for the treatment of adults with r/r FL after 2 or more lines of systemic treatment.

OBJECTIVE

- The objective of this study was to assess the cost-effectiveness of axi-cel under a range of model assumptions compared to standard of care (SOC) treatments in r/r FL patients who have had at least two lines of prior therapy from a US third-party payer perspective.

METHODS

Model Approach

- A partitioned survival model was developed in Microsoft Excel to estimate the cost-effectiveness of axi-cel compared to a basket of SOC treatments in US adults with r/r FL who have received at least two prior systemic therapies (3L+). The model structure includes three mutually exclusive health states, progression-free (PF) (starting state), progressive disease (PD), and death. **(Figure 1)**
  - The modeled patient cohort starts in the PF state and at the start of each model cycle either transition to PD or death state based on underlying survival data from ZUMA-5 and the model comparator. Patients who progress can remain in PD or transition to death, but can never go back to PF. All patients eventually enter the death state (an absorbing health state).
  - The model allowed patients to receive subsequent lines of treatment after progression from initial 3L treatment. The model assumed that there was no differential survival between the intervention and comparator attributed to subsequent lines of treatment; survival differences were only driven by the main treatment comparison survival curves.
- The base case used a lifetime time horizon, with a 3% discount rate applied to costs and outcomes according to US modeling guidelines.[8] Adverse event rates were obtained from clinical trial data and product prescribing information.

Figure 1. Model Structure

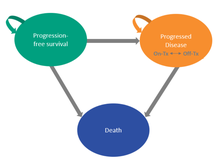


Figure 1. Cost-effectiveness model (CEM) structure. The partitioned-survival model includes three health states: progression-free, progressed disease, and dead. Progressed disease is further divided into on- and off-treatment to capture the different health utilities associated with each sub-state. Progression-free survival (PFS) and overall survival (OS) curves for the intervention and SOC arms were used to model the transitions between health states. The time spent in each health state is used to estimate cumulative total costs and health outcomes over the time horizon for a cohort of patients receiving each intervention.

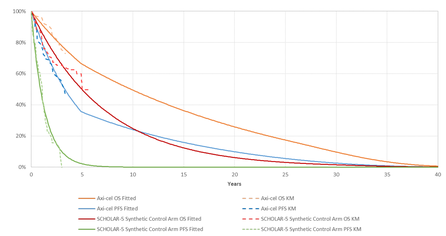
Clinical Inputs

- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel patients with r/r iNHL (FL or MZL) who have been treated with two or more lines of therapy.[9] The 36-month ZUMA-5 patient-level data for patients with r/r iNHL, specifically follicular B-cell non-Hodgkin lymphoma [FL], were the basis for the axi-cel survival analysis. Parametric models were fit to the overall survival (OS) and progression-free survival (PFS) data to extrapolate outcomes over a lifetime time horizon. The following parametric models were tested: exponential, Weibull, Gompertz, log-logistic, generalized gamma, gamma, and log-normal. Model fit was evaluated by clinical review, visual inspection (assessing fit to data and clinical plausibility of long-term extrapolation), and by considering both the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Exponential and Weibull were the best fitting distributions for OS and PFS, respectively.
- A real-world study (SCHOLAR-5) was used to generate a synthetic control arm, which served as the primary comparator, for 3L+ population in the single-arm ZUMA-5 trial. Patient level data from SCHOLAR-5 was adjusted using a matched-adjusted indirect comparisons (MAICs) approach.

METHODS (CONTINUED)

- For this analysis, a piecewise extrapolation was used for the axi-cel arm to model a proportion of the axi-cel population experiencing long-term remission. The base case exponential model for OS and base case Weibull model for PFS were used for a 5-year time horizon. After 5 years, OS and PFS were calculated as a weighted average where 75% of the population continued to experience the base case survival extrapolations, and based on clinical opinion, 25% of the population experienced the general population survival after applying a standardized mortality ratio (SMR) adjustment of 1.09.[10] **(Figure 2)**
- A systematic literature review was conducted to gather evidence on existing iNHL cost-utility and cost and resource use studies, health-related quality of life (HRQoL) studies, and clinical trials.[11]

Figure 2. SCHOLAR-5 and Axi-cel OS and PFS Kaplan Meier Curves



Adverse Events

- Adverse events (AEs) with grades of ≥ 3 and incidence rates of ≥ 10% from the ZUMA-5 trial were included in the model for costing purposes. Four more clinically meaningful AEs (i.e., CAR-T Cytokine release syndrome, pneumonia, diarrhea, and infusion reaction) were also included. However, in the base case analysis it was assumed that all severe AEs related to axi-cel were treated during the initial inpatient admission per the ZUMA-5 trial protocol, with the exception of hypogammaglobulinemia, which is a long-term AE. This approach prevents double-counting AE costs, as the initial inpatient visit cost is captured as part of the overall axi-cel treatment cost.
- For the model comparator, AE rates for each treatment in the market basket were retrieved from product prescribing information (PI) or pivotal clinical trials. The overall AE rates for the comparator arm were calculated as a weighted average of all treatments, using the market shares for each treatment as the weights.

Resource Use and Costs

Treatment Costs in Progression-Free State (Table 1)

- Axi-cel treatment costs include leukapheresis, axi-cel acquisition and administration costs, conditioning chemotherapy and axi-cel hospitalization for monitoring and treatment of side effects
- Treatment costs for the comparator, estimated using a weighted market basket of available FL chemotherapy regimens, were applied in the first model cycle for PFS.

Treatment Costs in Progressed State

- A one-time treatment cost for subsequent lines of therapy (LoT) is applied upon progression, because each subsequent LoT is not explicitly modeled
- The one-time PD comparator treatment cost the weighted average cost per course across the entire market basket.

Table 1. Treatment Costs in Progression-Free State

Cost	Details	Value
Costs associated with axi-cel		
Leukapheresis	April 2021 Medicare Unadjusted APC Payment for CPT code 36511[15]	$1,363.16
Axi-cel acquisition cost	2022 value reported by Medi-Span Price Rx[16]	$424,000
Conditioning chemotherapy	Calculated value based on dosing regimen and schedule specified in Yescarta PI,[17] drug prices from Medi-Span Price Rx,[16] and administration unit costs from CMS fee schedules[18]	$2,707.48
Axi-cel infusion - Administration (30 min IV)	HCPCS 96413 from CMS Physician Fee Schedule[18]	$148.30
Axi-cel infusion - Hospitalization LOS	Median LOS for initial hospitalization was 13 days[19]	13 days
Hospitalization unit cost (per day)	HCUP Statistical Brief #125 from 2012 specifies a mean hospitalization cost per day due to NHL equal to $2,400.[20] The cost was indexed to 2021.	$3,461.43
Costs associated with comparator arm		
Weighted treatment cost	Treatment costs consider recommended dose per product PIs, treatment duration, and market share weights.	$151,003

Health State Costs

- Other health state costs in each model arm include inpatient visits, ED visits and physician office visits that may be incurred.

End of Life Costs

- End of life costs were calculated using the median length of stay (LOS) in hospice (12 days for iNHL), the daily cost of palliative care,[13] and the percentage of patients using hospice.

Health Utility Inputs

- The PF utility of 0.805 assumes complete response and is based on results from a published study.[21, 22]
- The PD utility captured both on-treatment (0.62; combined active disease health states) and off-treatment (0.736; relapsed FL) HRQoL, assuming patient experience differs by current treatment status.

Scenario Analyses and Sensitivity Analyses

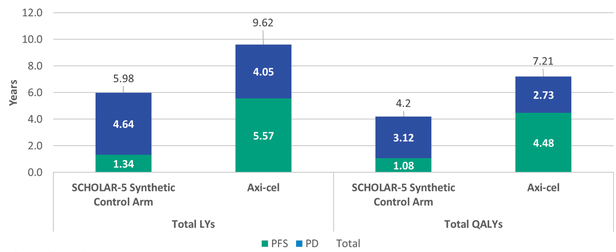
- In one-way sensitivity analysis (OWSA), key model parameters were varied by ± 20% of their base case values or reported standard errors or confidence intervals, if available, to test impact on overall outcomes.
- Probabilistic sensitivity analysis (PSA) with 1,000 iterations used known standard deviations to capture uncertainty around default values; 10% variation was assumed for those without reported uncertainty.
- Scenario analyses were conducted to test sensitivity to long-term remission values, ranging from 0% to 40%.

RESULTS

Table 2. Base Case Results

	SCHOLAR-5 Synthetic Control Arm	Axi-cel	Incremental Results
Total costs	**$316,933**	**$629,916**	**$312,982**
Total progression-free (PFS) costs	$166,830	$499,295	$332,465
Total treatment costs	$151,003	$473,273	$322,270
Administration	$3,374	$148	-$3,226
Monitoring resource	$1,513	$6,282	$4,768
Adverse events	$6,243	$99	-$6,144
Health state costs	$4,696	$19,493	$14,796
Total progressive disease (PD) costs	**$148,773**	**$129,467**	**-$19,306**
Treatment	$116,528	$101,319	-$15,210
Administration	$1,891	$1,644	-$247
Monitoring resource	$5,232	$4,569	-$664
Health state costs	$25,121	$21,935	-$3,186
End-of-life costs	$1,330	$1,154	-$176
Incremental cost-effectiveness ratio (ICER; ΔS/ΔQALY)			**$104,078**

Figure 3. Differential Effectiveness (LYs and QALYs)



Base Case Results

- In the base case scenario comparing axi-cel to the SCHOLAR-5 comparator in 3L+ r/r FL, axi-cel was associated with a 3.64 LY increase and a 3.01 QALY increase **(Figure 3, Table 2)**. The LY and QALY gains of axi-cel were attributed to the longer PFS relative to the comparator.
- When comparing the detailed cost breakdown between axi-cel and the comparator, the increased time spent in the PF state for axi-cel resulted in a PF state cost increase of $332,465. The majority of these increased PF costs were treatment costs (97.0%).
- Axi-cel was also associated with small cost-offsets in progression (-$19,306) driven by reduced treatment costs due to a smaller proportion of patients progressing prior to death when compared to the SCHOLAR-5 arm. The incremental costs associated with axi-cel were $312,982, resulting in a base case ICER of $104,078 per QALY gained.

One-way Sensitivity Analysis and Probabilistic Sensitivity Analysis

- Across all parameters varied in the OWSA **(Figure 4)**, the ICER varied between $84,867 and $143,882; the ICER was most sensitive to mean patient age. This is largely due to the treatment costs being accrued in the initial cycles of the PFS and PD health state and as patients age, they accrue incrementally lower total LYs and QALYs (and therefore, impact incremental QALYs). The model was also sensitive to the PF health state utility, axi-cel hospital LOS, and the proportion of patients that achieved long-term remission.
- In the PSA, axi-cel had an 89% probability of being cost-effective across 1,000 iterations using a $150,000 willingness-to-pay threshold (WTP) threshold.

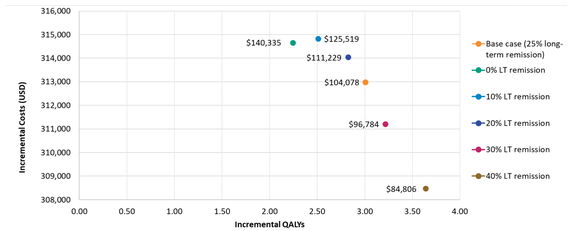
RESULTS (CONTINUED)

Figure 4. One-Way Sensitivity Analysis – Tornado Diagram of ICER

Scenario Analyses

- In scenario analyses testing different proportions of long-term remission ranging from 0% to 40%, the ICER varied from $84,806 to $140,335 per QALY gained. **(Figure 5)**
- Scenario analysis results remained well below a commonly-cited $150,000 per QALY gained willingness-to-pay US threshold.

Figure 5. Cost-Effectiveness Plane Varying Axi-cel Long-term Remission



Limitations

- As is the case with most cost-effectiveness analyses based on clinical trial data, limited sample sizes may lead to increased uncertainty around model inputs and may not always be generalizable to a real-world setting.
- In addition, due to the lack of a head-to-head comparison of axi-cel and other FL treatments, an indirect comparison was necessary to derive the PFS and OS curves for the SCHOLAR-5 arm. A market basket approach was used to estimate treatment, administration, and AE costs for the SCHOLAR-5 and SLR comparators, where market shares were either obtained from treatment patterns in the SCHOLAR-5 clinical study or Kite market research data. Treatment pattern data were not obtained from the same population as the survival data.
- Despite these limitations, this study provides a reasonable estimate, informed by best available evidence, of the comparative effectiveness and cost-effectiveness of axi-cel for treatment in r/r FL patients who have had a least two prior lines of systemic therapy.

CONCLUSIONS

- Under a range of long-term remission assumptions, including long-term remission proportions up to 40%, using axi-cel as treatment in r/r FL patients who have had a least two lines of prior systemic therapy would be considered cost-effective compared to SOC using the commonly cited $150,000 US WTP threshold.
- In addition to extending life-years gained, time spent in the progression free health state was an important contributor to the over all QALY gain from Axi-cel.
- Cost-effectiveness results were robust across a range of sensitivity analyses accounting for parameter uncertainty.
- Long-term follow-up is necessary to reduce uncertainties about the proportion of patients receiving axi-cel who experience long-term remission.
- Additionally, given there are several new and potentially effective FL therapies in trials and pending FDA approval that were not incorporated into SCHOLAR-5, future studies should evaluate the cost-effectiveness of axi-cel against a comparator arm that includes these new treatments, once they have been approved.

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