Poster #5082

Cost-Effectiveness of Axicabtagene Ciloleucel Versus Mosunetuzumab in Relapsed or Refractory Follicular Lymphoma in the US

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Introduction

- Non-Hodgkin lymphoma (NHL) accounts for about 4% of all cancer cases in the US. [1]
- NHL can be categorized into two states based on rate of progression: indolent NHL (iNHL) or aggressive NHL. [2] Approximately one-third of all NHL cases are iNHL. [3] Among NHLs, follicular lymphoma (FL) makes up approximately 15-20% of all NHLs (within Western countries). Despite advancements in first-line treatments improving overall survival for iNHL, relapse and recurrent progression are common among FL patients, with 19% relapsing within two years of treatment. [4,5] Additionally, median overall survival (OS) and progression-free survival (PFS) decrease with each subsequent line of therapy; mOS and mPFS are 67.6 months and 11.0 months, respectively, for patients on 3rd line of therapy. [6]
- Novel therapies for 3L+ relapsed/refractory (r/r) follicular lymphoma (FL) have been approved recently by the US Food and Drug Administration including anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapies, such as axicabtagene ciloleucel (axi-cel), and CD20 × CD3 T-cell-engaging bispecific monoclonal antibodies, such as mosunetuzumab (mosun). [7-9]

Objectives

- The objective of this study was to assess the cost-effectiveness of axi-cel compared to mosun 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 three-state partitioned survival model was developed in Microsoft Excel 365 to estimate the cost-effectiveness of axi-cel compared to mosun in US adults (age ≥18) with r/r FL who are receiving their third or higher line of therapy (i.e., 3L+).
- Using 1-month cycles, the model structure includes three mutually exclusive, progressive health states: progression-free (PF) → progressed disease (PD) → death (Figure 1)
  - All patients initiate in the PF state and experience a probability of transitioning to either PD or death based on underlying survival data from ZUMA-5 [10] and GO29781 [11] for axi-cel or mosun, respectively. Patients can progress or remain in their current health state but can never go back to the PF state. Progressed disease is further divided into on- and off-treatment to capture the different health utilities associated with each sub-state. The lifetime time horizon requires that all patients eventually progress to death.
  - After failure of the initial 3L+ therapy, patients may begin subsequent lines of 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 comparator survival curves.
- The base case time used a lifetime horizon, and a 3% discount rate was applied to costs and outcomes according to US modeling guidelines [12]. Adverse event (AE) rates were obtained from clinical trial data.

Figure 1. Model Structure

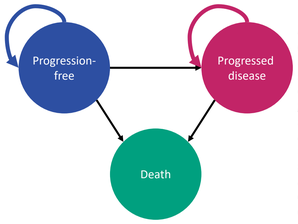


Figure 1. Cost-effectiveness model (CEM) structure. *The partitioned-survival model includes three health states: progression-free, progressed disease, and death. Progression-free survival (PFS) and overall survival (OS) curves for axi-cel and mosun arms were used to model the transitions between health 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

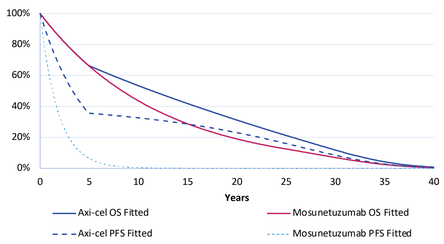
- ZUMA-5 is a multicenter, single-arm Phase 2 study of axi-cel patients with r/r iNHL (FL or MZL) who have been treated with two or more lines of therapy. [13] The 24-month ZUMA-5 FL patient-level data were the basis for the axi-cel survival analysis and were used to align with independent review committee assessment of outcomes with the mosun trial for matching-adjusted indirect comparison (MAIC) analysis. [14]

Methods (contd.)

Clinical Inputs (contd.)

- Parametric models were fit to the overall survival (OS) and progression-free survival (PFS) data to extrapolate outcomes over a lifetime time horizon (Figure 2). For the axi-cel survival curves exponential, Weibull, Gompertz, log-logistic, generalized gamma, gamma, and log-normal were all tested. 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 and Bayesian information criterion.
- A piecewise extrapolation was used for the axi-cel arm to model a proportion of the axi-cel population experiencing long-term survival. Exponential models for OS and for PFS were used for a 5-year time horizon. After 5 years, OS and PFS were calculated as a weighted average where 60% of the population continued to experience the base case survival extrapolations and 40% of the population experienced the general population survival after applying a standardize mortality ratio (SMR) adjustment of 1.09. [15] The 40% cure fraction is based on a reported 43% of FL patients who were progression-free at 5 years. [16]
- Mosun survival was modeled via hazard ratios (HRs) applied to axi-cel exponential survival curves. For PFS, the HR was estimated via a matching indirect comparison to adjust for differences between the trial populations. The PFS HR was estimated to be 0.38 for axi-cel versus mosun. [14]
- As a conservative assumption, a HR of 1.0 was used to model mosun OS due to lack of published results. The mosun arm did not include the cure assumption at 5 years because long-term remission is not expected with monoclonal antibodies in r/r FL.

Figure 2. Axi-cel and Mosun Fitted OS and PFS Curves



Adverse Events

- Grade ≥ 3 AEs from the ZUMA-5 and GO29781 trials were included in the model for costing purposes and to account for treatment-related disutilities.
- For axi-cel, it was assumed that all severe AEs related to axi-cel were treated during the initial inpatient admission per the ZUMA-5 trial protocol, except for hypogammaglobulinemia, which is a long-term AE. This approach prevents double-counting AE management costs, as the initial inpatient visit cost is captured as part of the overall axi-cel treatment cost and would be inclusive of AE management.
- For mosun, grade ≥ 3 AE rates were retrieved from the pivotal clinical trial [17]. Because there is no initial inpatient admission, AE costs are applied separately for mosun. AE costs were calculated by multiplying the rate of each AE by the mean unit hospital commercial costs obtained from the US Department of Health & Human Services, HCUPnet - Healthcare Cost and Utilization project. Costs were inflated to 2023 USD based on inflation estimates from the US Bureau of Labor Statistics (BLS). [18]

Resource Use and Costs

Treatment Costs in Progression-Free State (Table 1)

- Axi-cel treatment costs consisted of axi-cel acquisition and administration costs, conditioning chemotherapy, leukapheresis, and axi-cel hospitalization for monitoring and treatment of adverse events.
- Mosun is given in 21-day cycles, with the first cycle consisting of step-up doses of 1 mg, 2 mg, and 60 mg, followed by a second cycle of 60 mg, and 30 mg cycles thereafter, to a recommended treatment duration of eight 30 mg cycles.
- The total cost of mosun is adjusted by a relative dose intensity of 98.7%. [19] This cost is applied once for patients in the comparator arm in PFS at the first model cycle.

Treatment Costs in Progressed State (Table 2)

- Patients incur a one-time treatment cost for subsequent lines of therapy (LoT) given that each subsequent LoT is not explicitly modeled.

Methods (contd.)

Resource Use and Costs (contd.)

- ***Treatment Costs in Progressed State (Table 2) (contd.)***
  - To calculate the one-time PD treatment cost, a weighted average cost per course across the entire market basket was calculated based on a market basket of available FL chemotherapy regimens weighted by the market shares for each treatment. Next, this weighted average cost was multiplied by the proportion of patients transitioning to each subsequent LoT and the resulting cost was applied once when patients entered PD.
- ***Health State Costs (Table 2)***
  - Other health state costs [19] were considered for each arm, including inpatient visits, ED visits and physician office visits that may be incurred [19]. The rate of monitoring during treatment was the same for both axi-cel and mosun. [20,21]
- ***End of Life Costs (Table 2)***
  - End of life costs were included in the model and were based on published literature. The costing approach involved using the median length of stay (LOS) in hospice, the daily cost of palliative care, and the percentage of patients using hospice. The median LOS in hospice for patients with iNHL was 12 days. [22]
  - Daily cost of palliative care was calculated based on the 6 last months of life costs reported by Chastek et al. 2012 for US patients with lymphoma. [23]

Table 1. Treatment Costs in Progression-Free State

Cost	Value	Notes
Costs associated with axi-cel		
Leukapheresis	$1,363.16	Medicare unadjusted APC payment for CPT code 36511 [24]
Axi-cel acquisition cost	$424,000.00	Medispan PriceRx [25]
Conditioning chemotherapy	$2,707.48	Calculated value based on dosing regimen and schedule specified in Yescarta PI, [8] drug prices from Medispan PriceRx, [25] and administration unit costs from CMS fee schedules [19]
Axi-cel infusion - Administration (30 min IV)	$148.30	HCPCS 96413 from CMS Physician Fee Schedule [19]
Axi-cel infusion - Hospitalization LOS	13 days	Median LOS for initial hospitalization was 13 days [26]
Hospitalization unit cost (per day)	$3,461.43	HCUP Statistical Brief #125 from 2012 specifies a mean hospitalization cost per day due to NHL equal to $2,400 [27]
Costs associated with comparator arm		
Mosunetuzumab acquisition cost (30 mg/30 ml vial)	$17,821.78	Medispan PriceRx [25]

Table 2. Other Direct Medical Costs

Input	Value	Notes
Progressed disease treatment cost inputs		
Maximum number of subsequent LoT	7	SCHOLAR-5 Data on File [28]
Time between subsequent LoT (months)	10	
Median OS (months)	48	
Percentage of patients undergoing each subsequent LoT		
1st subsequent LoT	44.4%	SCHOLAR-5 Data on File [28]
2nd subsequent LoT	15.6%	
3rd subsequent LoT	11.1%	
4th subsequent LoT	11.1%	
Treatment cost at time to first progression	$121,335	Calculated
Other costs		
Health state costs (per month)	$292	Weighted monthly cost of inpatient visits, ED visits, and physician office visits
End of life cost	$1,616	Calculated

Health Utility Inputs

- Two sources were identified that reported health state utilities (pre- and post-progression) for iNHL, both of which published results from the same study. [29, 30] A PF utility of 0.805 from this study assumes complete response.
- The PD utility captured both on-treatment and off-treatment HRQoL, assuming patients received additional treatment after failure of 3L therapy and experienced different HRQoL compared to those not receiving any treatment. The PD on-treatment utility used in the model is 0.620 (i.e., combined health states of active disease), and the off-treatment utility is 0.736 (i.e., relapsed FL).

Scenario Analyses and Sensitivity Analyses

- A one-way sensitivity analysis was conducted in which key model parameters were varied by ± 20% of their base case values or using reported standard errors or confidence intervals if available, to test their impact on overall outcomes [incremental cost effectiveness ratio (ICER) and incremental costs].

Methods (contd.)

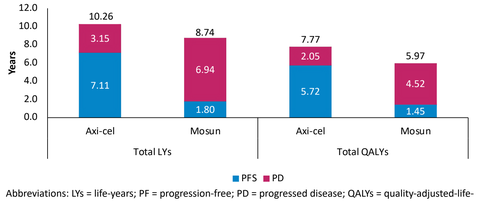
Scenario Analyses and Sensitivity Analyses (contd.)

- A probabilistic sensitivity analysis was also generated by running 1000 iterations. Parameters with known standard errors were used directly to capture the uncertainty around the default value, while assumptions were made for those without reported uncertainty (i.e., assumed 10% variation). All parameters were assigned a default distribution, including normal, beta, log-normal, or gamma distributions depending on the type of data.

Base Case Results

- The base case analysis estimated a 1.51 LY increase and a 1.80 QALY increase when comparing axi-cel to mosun in 3L+ r/r FL, axi-cel (Figure 3, Table 3). Both LY and QALY gains of axi-cel were attributed to the additional time spent in the PFS health state relative to mosun. It should be noted that the higher incremental QALY relative to LY is because the majority of LYs for mosun are in PD whereas the majority of LYs for axi-cel are in PF.
- Progression-free survival for axi-cel patients was 7.1 LY compared to 1.8 LY for mosun, which resulted in a PF state cost increase of $215,045 primarily driven by the one-time cost of axi-cel treatment.
- Axi-cel was also associated with small cost-offsets in progression (-$63,000) driven by reduced treatment costs due to patients spending less time with PD and had lower costs for subsequent treatment lines when compared to the mosun arm. Total incremental costs for axi-cel were $151,425, resulting in an ICER of $84,016/QALY gained.

Figure 3. Differential Effectiveness (LYs and QALYs)



Abbreviations: LYs = life-years; PF = progression-free; PD = progressed disease; QALYs = quality-adjusted-life-years

Table 3. Base Case Results

	Mosun	Axi-cel	Incremental results
Total costs	**$462,547**	**$613,973**	**$151,425**
Total PFS costs	**$282,469**	**$497,514**	**$215,045**
Treatment	$265,118	$471,995	$206,877
Administration	$2,916	$148	-$2,768
Monitoring resource	$2,029	$6,159	$4,130
Adverse events	$6,108	$99	-$6,009
Health state costs	$6,297	$19,113	$12,815
Total PD costs	**$178,882**	**$115,582**	**-$63,300**
Treatment	$131,922	$99,678	-$32,244
Administration	$1,537	$1,161	-$376
Monitoring resource	$7,830	$2,541	-$5,288
Health state costs	$37,593	$12,201	-$25,391
End-of-life costs	***$1,197***	***$877***	***-$320***
Incremental cost-effectiveness ratio (ICER; Δ$/ΔQALY)			**$84,016**

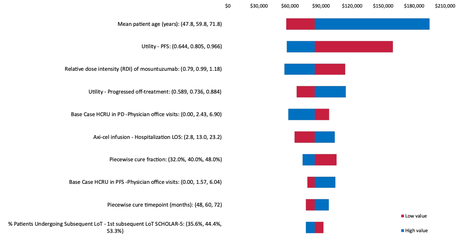
Abbreviations: PF = progression-free; PD = progressed disease; QALYs = quality-adjusted-life-years

Sensitivity Analyses

- In the probabilistic sensitivity analysis , axi-cel had an 71% probability of being cost-effective across 1,000 iterations using a $150,000 willingness-to-pay threshold (not shown).
- Across all parameters varied in the one-way sensitivity analysis (Figure 4), the ICER varied between $194,952 and $56,320; the ICER was most sensitive to mean patient age. This can be explained because as patients age, they accrue lower total LYs and QALYs (and therefore, impact incremental QALYs). The ICER was also sensitive to the relative dose intensity of mosun, PF and PD health state utilities, PD health care resource use, axi-cel hospital LOS, and the piecewise cure fraction.

Sensitivity Analyses

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



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 mosun, a matching-adjusted indirect comparison was necessary to derive the PFS and OS curves for the mosun arm. However, due to limited follow-up data, it was not possible to accurately estimate a hazard ratio for mosun OS curves.
- A market basket approach based on SCHOLAR-5 data was used to estimate treatment and administration, and AE costs for the subsequent treatments after axi-cel or mosun.
- Despite these limitations, this study provides an estimate of comparative effectiveness and cost-effectiveness of axi-cel for treatment in r/r FL patients who are 3L+ therapy.

Discussion and Conclusions

- A recent cost-effectiveness analysis of mosun for treatment of 3L+ r/r FL in the US used a similar three-state partitioned survival model, but found mosun dominant compared to axi-cel, and dominant or cost-effective against all comparator treatments except for rituximab + lenalidomide. [31] The extrapolation of data in this analysis does not align with the assumptions of our analysis, however. While the previous analysis assumed no cure effect for mosun, it likewise assumes no cure effect for CAR-T therapies, which fails to account for published evidence for treatments with this mechanism of action. [15] That analysis therefore underestimates the potential benefits of CAR-T. Additionally, their analysis did not assume a treatment waning effect for mosun, which does not align with the PFS differences nor their own ITC. [31]
- A recently published ITC of mosun vs. axi-cel which showed a PFS benefit for axi-cel, which is consistent with our study findings. [32]
- 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.

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