

An economic model to estimate costs of cytokine release syndrome and neurological events among patients treated with lisocabtagene maraleucel or axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma

Jack Badaracco,¹ Brian Ung,² Matthew Gitlin,¹ Scott J. Keating²

¹BluePath Solutions, Los Angeles, CA, USA; ²Bristol Myers Squibb, Princeton, NJ, USA

Introduction

- Chimeric antigen receptor (CAR) T cell therapies have demonstrated responses in difficult-to-treat patients with high-risk, transplant-intended relapsed/refractory (R/R) large B-cell lymphomas (LBCL)^{1–3}
- Despite promising efficacy, CAR T cell therapies are associated with potentially severe adverse events (AE), including cytokine release syndrome (CRS) and neurological events (NE)^{4,5}
- These events range in severity from mild to severe^{4,5} and are associated with different clinical and economic consequences
- The rates of CRS and NE have been shown to differ among CAR T cell therapies^{4,5}

Objective

- The objective of this analysis was to estimate the total weighted patient cost of CRS and NEs in transplant-intended R/R aggressive B-cell non-Hodgkin lymphomas treated with lisocabtagene maraleucel (liso-cel) or axicabtagene ciloleucel (axi-cel) as second-line (2L) therapy based on rates reported in the TRANSFORM (NCT03575351) and ZUMA-7 (NCT03391466) trials

Methods

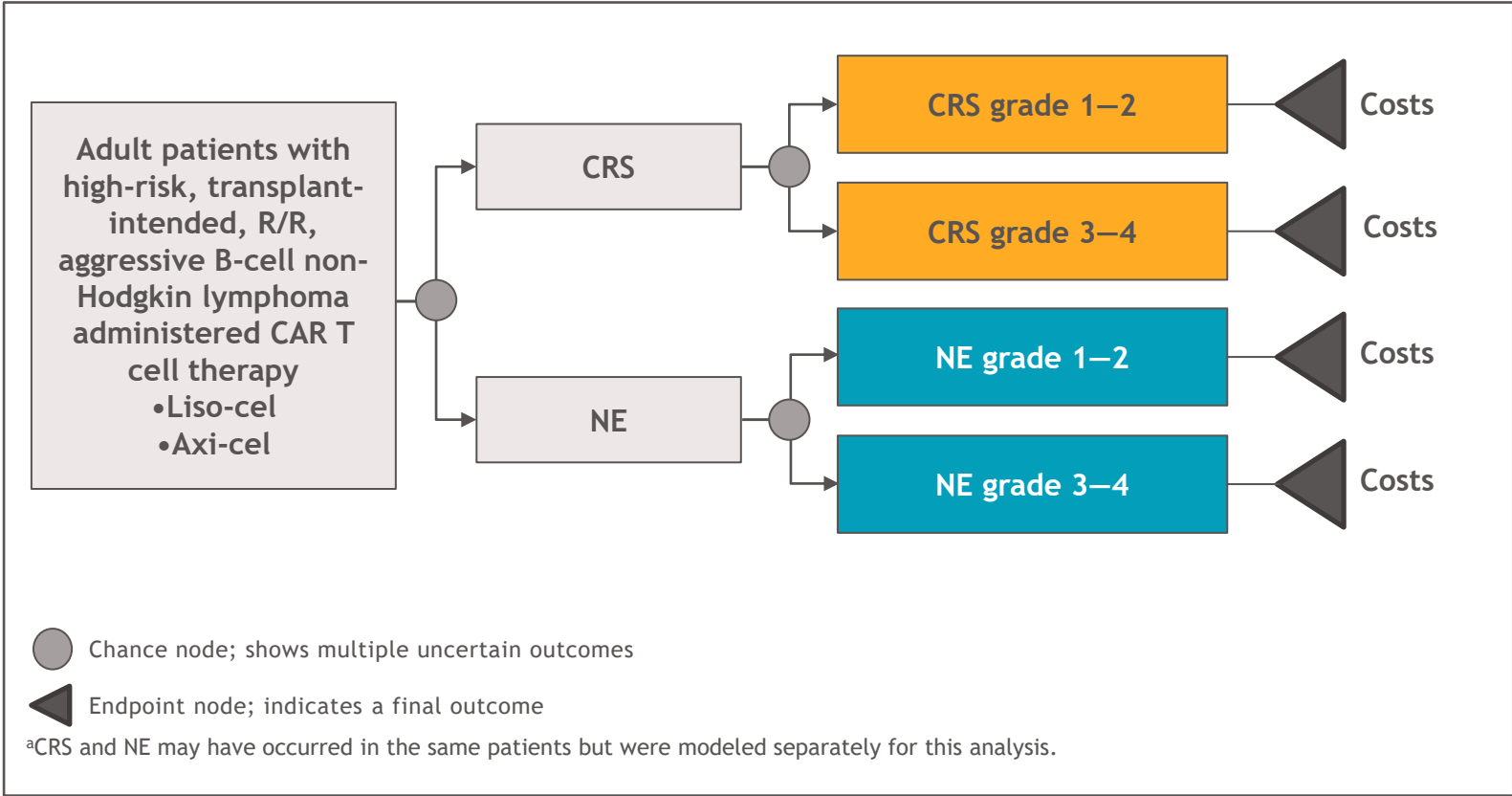
- A decision tree economic model was developed using CRS and NE rates from the TRANSFORM and ZUMA-7 trials to estimate per-patient CRS and NE management costs from a health care system perspective in 2021 United States dollars (USD; **Table 1** and **Figure 1**)
- CRS and NE cost estimate inputs were based on a microcosting analysis of TRANSFORM, and the model assumed that cost inputs of CRS or NE management would not differ across therapies
- A probabilistic sensitivity analysis was conducted using Monte Carlo simulation methods to address uncertainty surrounding the costs of key inputs
- A scenario analysis was conducted to assess CRS and NE costs for each CAR T cell therapy from a commercial payer perspective

Table 1. Model overview

Overview	Description
Model design	Economic decision tree model
Population	Patients with high-risk, transplant-intended, R/R, aggressive B-cell non-Hodgkin lymphoma who received CAR T cell therapy
Perspective	<ul style="list-style-type: none">Health care system (base case)^aCommercial payer perspective (scenario analysis)
Comparators	<ul style="list-style-type: none">Liso-celAxi-cel
Approach	Costs of management by AE type and grade were applied to AE rates to obtain a weighted average cost per treated patient
Time horizon	Day 0 (CAR T cell therapy administration day) to AE resolution
Clinical inputs	<ul style="list-style-type: none">CRS rates by grade (1–2 and 3–4)NE rates by grade (1–2 and 3–4)
Economic inputs	Cost of CRS or NE AE management by grade
Outcome	Weighted average cost for the treated patient

^aReflects true costs to all providers across sites of care who may treat and manage AEs.

Figure 1. Decision tree model diagram^a



Clinical inputs

- The model incorporated 2 AEs most often associated with CAR T cell therapy, CRS and NE, using rates from the TRANSFORM³ and ZUMA-7 trials,² for liso-cel and axi-cel, respectively (**Table 2**)

Table 2. CRS and NE rates

	Liso-cel	Axi-cel
Source ^a	TRANSFORM clinical trial ³	ZUMA-7 clinical trial ²
CRS (any grade)	48.9%	92.4%
Grade 1–2	47.8%	85.9%
Grade 3–4	1.1%	6.5%
NE (any grade)	12.0%	60.0%
Grade 1–2	7.6%	38.8%
Grade 3–4	4.3%	21.2%

^aThe source clinical evidence was stratified into 2 categories using the overall rates and grade ≥ 3 rates. To estimate grade 1–2 and grade 3–4 categories, the source grade ≥ 3 AE rates were subtracted from the overall rates to estimate the grade 1–2 AE rates. No grade 5 events were reported in either trial.

Costs of CRS and NE events

- The cost of CRS and NE was obtained from the TRANSFORM microcosting analysis⁶ that used individual patient-level data from the TRANSFORM clinical trial³
 - The TRANSFORM trial is one of few available sources where actual resource use specific to CRS and NE by grade was obtained. The costs reflect AE management per the guidelines of the clinical trial
- Because of the limited granularity of the evidence for both CAR T cell therapies evaluated, CRS and NE rates by grade were categorized as grade 1–2 and grade 3–4
 - No grade 4 or 5 events were reported in TRANSFORM³; no grade 5 events were reported in ZUMA-7²
- All costs were adjusted to 2021 USD using the medical component of the Consumer Price Index⁷ (**Table 3**)
- Owing to the minimal difference between the median and mean values of the microcosting study, only the mean values were used
- CRS and NE cost estimates were generated based on mean cost values and weighted based on sample size from the microcosting analysis, as shown below
 - CRS grade 1–2:** The method to estimate CRS grade 1–2 was to use a weighted average of CRS grade 1 and grade 2 events. Therefore, the CRS grade 1–2 cost estimation is the weighted average of CRS grade 1 only and CRS grade 2 only
 - CRS grade 3–4:** The method to estimate CRS grade 3–4 was to use a weighted average of CRS grade 3 and grade 4 events. Therefore, the CRS grade 3–4 cost estimation is the weighted average of CRS grade 3 only, CRS grade 4 only, nonconcurrent grade ≥ 3 CRS or NE, nonconcurrent grade ≥ 3 CRS and NE, concurrent grade ≥ 3 CRS or NE, and concurrent grade ≥ 3 CRS and NE
 - NE grade 1–2:** The method to estimate NE grade 1–2 was to use a weighted average of NE grade 1 and grade 2 events. Therefore, the NE grade 1–2 cost estimation is the weighted average of NE grade 1 only and NE grade 2 only
 - NE grade 3–4:** The method to estimate NE grade 3–4 was to use a weighted average of NE grade 2 and grade 3 events. Therefore, the NE grade 3–4 cost estimation is the weighted average of NE grade 3 only, NE grade 4 only, nonconcurrent grade ≥ 3 CRS or NE, nonconcurrent grade ≥ 3 CRS and NE, concurrent grade ≥ 3 CRS or NE, and concurrent grade ≥ 3 CRS and NE
- Although the health care resource utilization and cost estimates for AE management come from the TRANSFORM trial, the model assumed that managing CRS or NEs did not differ across CAR T cell therapies and time to resolution of events was consistent

Table 3. CRS and NE costs: base-case inputs, in 2021 USD

Severity	Mean total costs ^a
CRS	
Grade 1–2	\$3827
Grade 3–4	\$46,362
NE	
Grade 1–2	\$3401
Grade 3–4	\$56,920

^aAll costs were adjusted to 2021 USD using the medical component of the Consumer Price Index.⁷

Statistical analyses

- A probabilistic sensitivity analysis was conducted using Monte Carlo simulation methods to address uncertainty surrounding the costs of key inputs
- Monte Carlo simulation with 1000 iterations was performed to provide 95% confidence interval (CI) for the total cost of each AE stratified by CAR T cell therapy

- Model inputs and assumed distribution for the decision tree model were assessed in the simulation
 - A beta distribution was used for AE rate variance
 - The beta distribution was applied to model the behavior of random variables limited to finite length. Given the estimates cannot be < 0 , the beta distribution was selected. The beta distribution is a suitable model for the random behavior of percentages and proportions
 - A gamma distribution was used for cost variance
 - Cost data, specifically using small sample sizes is often not normally distributed (mean and median are not similar), thus cost studies often use a gamma distribution to address the skewness of cost data that are subject to wide variance and likely wide range, with few outliers that impact the mean cost
- Descriptive statistical analyses were estimated from the simulation for each CAR T cell therapy including mean, median, minimum (min) to maximum (max), standard deviation (SD), and 95% CI
- The model outputs were analyzed and presented by CAR T cell therapy, overall costs, and costs by AE and AE severity
- Secondary analyses were performed, and the cost differences were estimated and reported as absolute and percentage differences for liso-cel versus axi-cel

Scenario analysis

- A scenario analysis was conducted to assess CRS and NE costs for each CAR T cell therapy from a commercial payer perspective
- Probabilistic payment to cost ratios were used from the American Hospital Association Trend Watch Chartbook 2020⁸ (**Table 4**)
 - The commercial payment to cost ratio of 144.8% was used

Table 4. Commercial payer scenario analysis clinical and economic outputs

	Mean total costs ^a	Scenario analysis incidence inputs	
		Liso-cel ³	Axi-cel ²
CRS ^b			
Grade 1–2	\$5541	47.8%	85.9%
Grade 3–4	\$67,132	1.1%	6.5%
NE			
Grade 1–2	\$4925	7.6%	38.8%
Grade 3–4	\$82,419	4.3%	21.2%

^aAll costs were adjusted to 2021 USD using the medical component of the Consumer Price Index.⁷ ^bCRS was graded per the Lee 2014 criteria.⁹

Results

- The overall per-patient weighted average mean cost for CRS and NEs was \$4997 (liso-cel) and \$19,454 (axi-cel) (**Table 5**; **Figure 2**)
- Per-patient weighted average mean cost per CRS event was \$2297 (liso-cel) and \$6227 (axi-cel). Per-patient weighted average cost per NE was \$2700 (liso-cel) and \$13,227 (axi-cel) (**Table 6**; **Figure 2**)
- In the commercial payer perspective scenario analysis, the overall per-patient weighted average mean cost was \$7310 (liso-cel) and \$28,212 (axi-cel) (**Table 7**; **Figure 3**)

Table 5. Monte Carlo simulation results: total per treated patient costs stratified by AE and severity grade^a

	Mean total costs ^b	Median total costs	Min	Max	SD
Liso-cel					
CRS					
Grade 1–2	\$1790	\$1739	\$739	\$3986	\$506
Grade 3–4	\$507	\$323	\$0	\$4590	\$549
NE					
Grade 1–2	\$263	\$238	\$41	\$1106	\$126
Grade 3–4	\$2437	\$2124	\$240	\$9875	\$1406
Axi-cel					
CRS					
Grade 1–2	\$3212	\$3159	\$1376	\$6227	\$823
Grade 3–4	\$3015	\$2795	\$737	\$8339	\$1238
NE					
Grade 1–2	\$1326	\$1283	\$529	\$2994	\$367
Grade 3–4	\$11,900	\$11,454	\$3600	\$28,111	\$3474

^aUsing AE rates multiplied by AE costs, the results represent the weighted average per treated patient; ^bAll costs were adjusted to 2021 USD using the medical component of the Consumer Price Index.⁷

Table 6. Total costs per treated patient: base case, in 2021 USD

	Mean total costs	SD	Lower 95%	Upper 95%
CRS ^a				
Liso-cel	\$2297	\$1055	\$2231	\$2362
Axi-cel	\$6227	\$2062	\$6099	\$6355
NE ^a				
Liso-cel	\$2700	\$1532	\$2605	\$2795
Axi-cel	\$13,227	\$3840	\$12,988	\$13,465
Overall ^b				
Liso-cel	\$4997	\$2587	\$4836	\$5307
Axi-cel	\$19,454	\$5902	\$19,088	\$20,661

^aCRS/NE total costs are combined from grade 1–2 and grade 3–4 costs; ^bOverall costs are CRS and NE costs combined.

Figure 2. Mean total costs per treated patient: base case, in 2021 USD

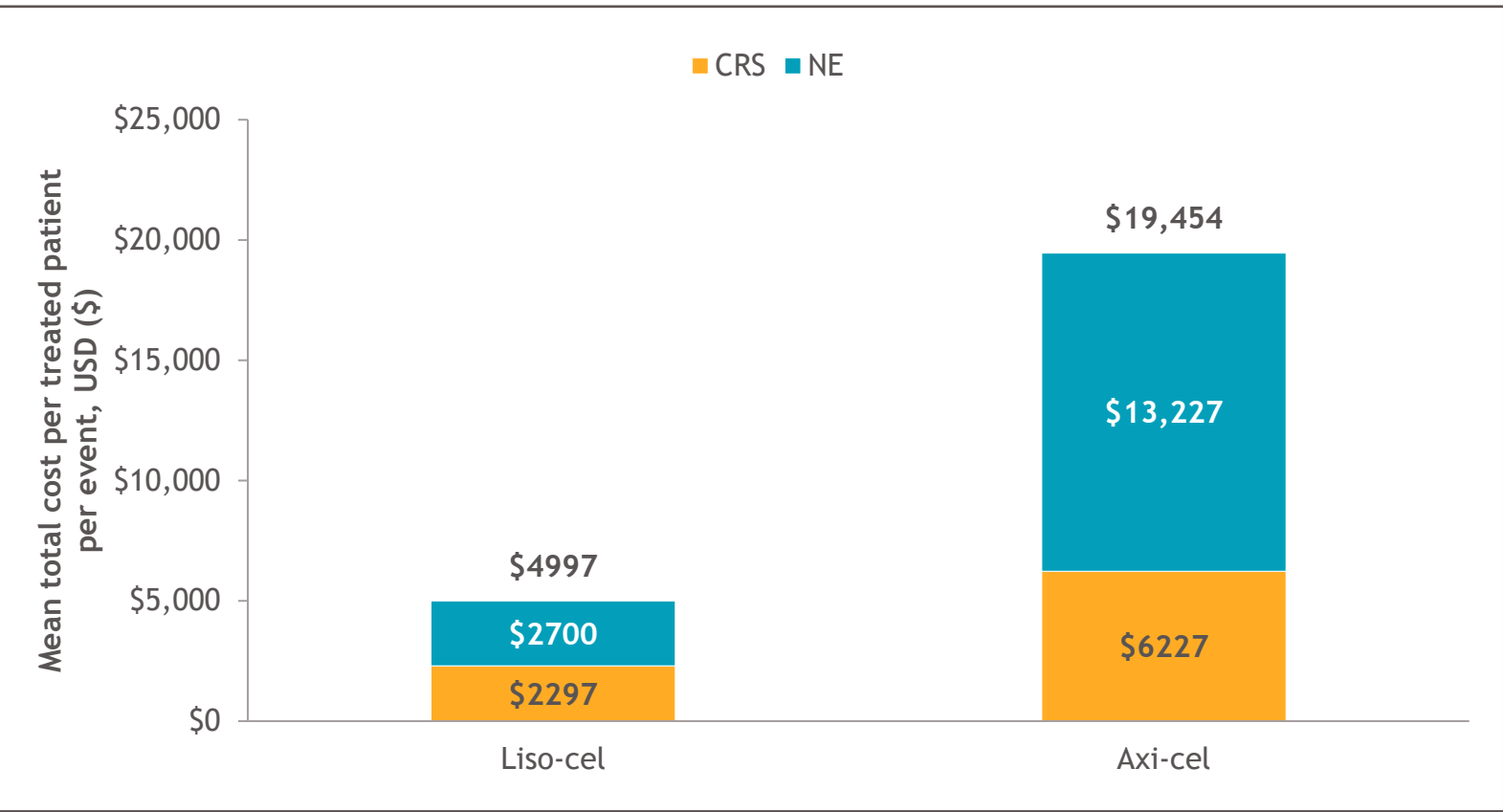


Table 7. Total costs per treated patient: commercial payer perspective, in 2021 USD

	Mean total costs	SD	Lower 95%	Upper 95%
CRS ^a				
Liso-cel	\$3364	\$1497	\$3271	\$3457
Axi-cel	\$9177	\$2970	\$8992	\$9361
NE ^a				
Liso-cel	\$3946	\$2181	\$3811	\$4081
Axi-cel	\$19,035	\$5497	\$18,694	\$19,376
Overall ^b				
Liso-cel	\$7310	\$3678	\$7082	\$7764
Axi-cel	\$28,212	\$8467	\$27,687	\$29,963

^aCRS/NE total costs are combined from grade 1–2 and grade 3–4 costs; ^bOverall costs are CRS and NE costs combined.

Figure 3. Mean total costs per treated patient: commercial payer perspective, in 2021 USD

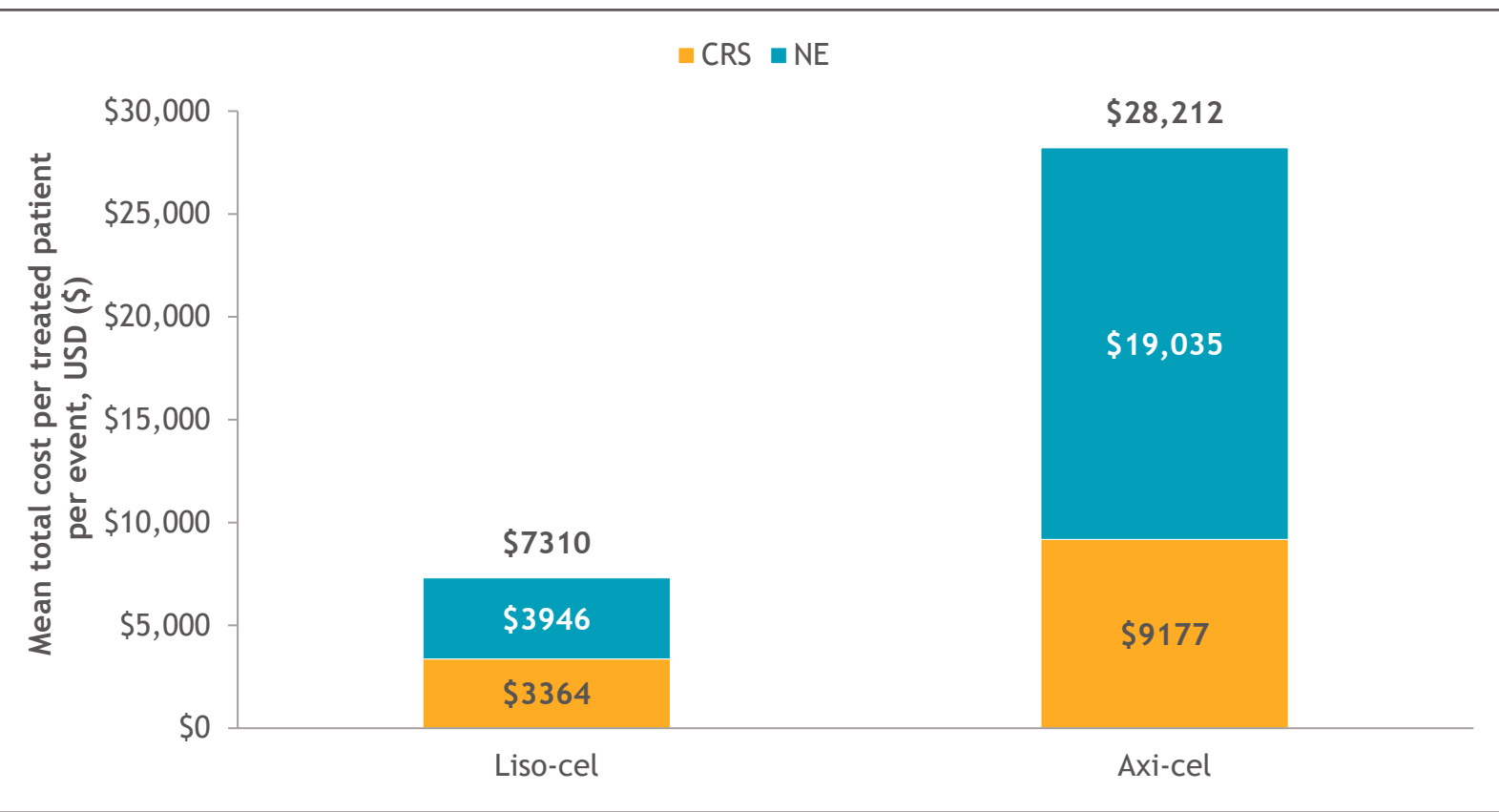
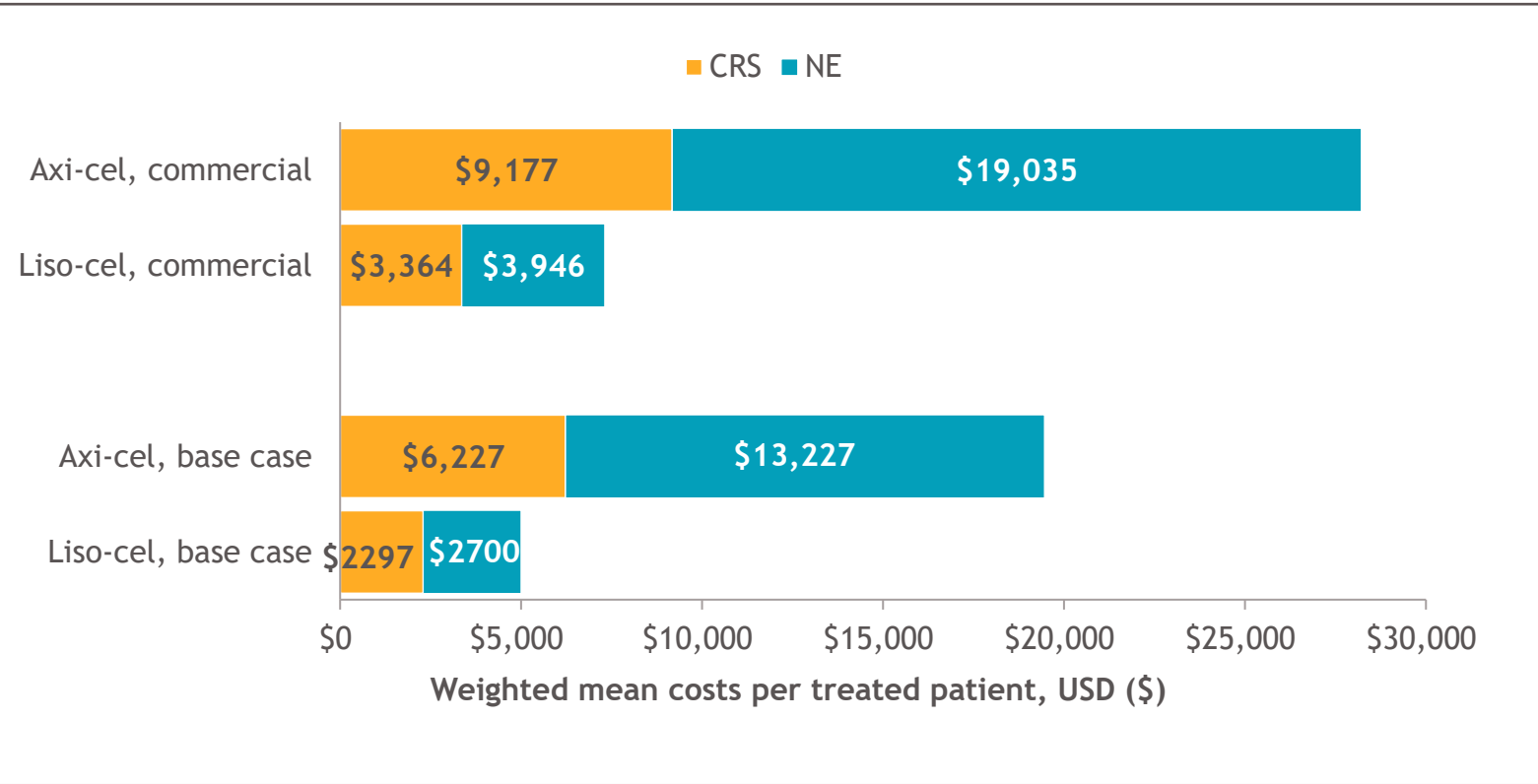


Figure 4. Base-case and scenario analysis results overview, in 2021 USD



- Overall mean cost savings for liso-cel compared with axi-cel were \$14,457 for the base case and \$20,902 for a commercial payer perspective. In both scenarios, costs were 74% lower with liso-cel (**Figure 4**)
- Differences in estimated mean costs per treated patient for liso-cel compared with axi-cel by AE type were \$3930 for CRS (–63.1%) and \$10,527 for NE (–79.6%) in the base-case scenario and \$5813 (–63.3%) and \$15,089 (–79.3%), for CRS and NE respectively, in the scenario analysis

Limitations

- The analyses used published AE rates for CRS and NEs. Because of the limited granularity of the evidence for both CAR T cell therapies evaluated, CRS and NE rates by grade were categorized into grade 1–2 and grade 3–4
- The model assumed that cost inputs of CRS or NE management would not differ across therapies
- As costs may be estimated or represent national averages, they may not reflect true cost and may not be generalizable to specific institutions
- Costs were limited to those observed within the clinical trial setting and may not have captured all potential costs that might be incurred in a real-world setting. Additionally, the TRANSFORM and ZUMA-7 trials had differing protocols, such as the use of bridging therapies, that may have led to confounding factors in the patient populations. Thus, findings may not be generalizable to other CAR T cell therapies or to settings outside of a clinical trial
- The AE costs reflect current CAR T cell site of administration that was observed in TRANSFORM, which was primarily inpatient. Such estimates may not be reflective of real-world costs as liso-cel may result in greater outpatient use and, thus, CRS and NE management costs may differ

Conclusions

- Reductions in estimated per-patient average cost for CRS and NEs with liso-cel compared with axi-cel, due to lower CRS and NE rates, were \$3930 and \$10,527, respectively, per the base-case economic model
- Total estimated difference in average cost was \$14,457 (74% lower with liso-cel) using base-case analysis
- In the commercial payer perspective scenario analysis, liso-cel had a lower weighted average cost per treated patient compared with axi-cel
- These lower estimated average costs highlight the economic importance of differentiated safety profiles between CAR T cell therapies, which may lead to significant differences for the cost of care in the real-world setting
- Estimated CRS and NE management costs are approximately equal among liso-cel–treated patients, while NE management costs make up roughly two-thirds of axi-cel CRS and NE management costs

References

- Nastoupil LJ, et al. *J Clin Oncol* 2020;38:3119–3128.
- Locke FL, et al. *N Engl J Med* 2022;386(7):640–654.
- Kamdar M, et al. *Blood* 2021;138(suppl 1):91.
- BREYANZI® (lisocabtagene maraleucel) [package insert]. Bothell, WA: Juno Therapeutics, Inc, a Bristol-Myers Squibb Company; February 2021.
- YESCART® (axicabtagene ciloleucel) [package insert]. Santa Monica, CA: Kite Pharma, Inc; January 2022.
- McGarvey M, et al. *J Manag Care Spec Pharm* 2022;28(3-a suppl):S22.
- Consumer Price Indexes (CPI) for medical care 2021. Bureau of Labor Statistics website. <https://data.bls.gov/cgi-bin/surveymost?cu>. Accessed August 1, 2021.
- Trendwatch chartbook 2020. Supplementary data tables, trends in overall health care market. American Hospital Association website. www.aha.org/system/files/media/file/2020/10/TrendwatchChartbook-2020-Appendix.pdf. Accessed March 30, 2022.
- Lee DW, et al. *J Clin Oncol* 2014;32(2):188–195.

Acknowledgments

- This study was funded by Bristol Myers Squibb
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Tony Sica, PharmD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb