PCN108

An Economic Model to Estimate the Cost of Cytokine Release Syndrome (CRS) and Neurological Events (NEs) Observed in Chimeric Antigen Receptor (CAR) T Cell Therapies Administered to Patients With Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL)

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Introduction

- Chimeric antigen receptor (CAR) T cell therapies have demonstrated responses in difficult-to-treat patient populations[1-3]
- Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel are 2 CAR T cell therapies currently available for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (LBCL) in the United States and Europe
- Lisocabtagene maraleucel (liso-cel) is an investigational, CD19-directed, defined composition, 4-1BB CAR T cell product administered at equal target doses of CD8+ and CD4+ CAR+ T cells and is being tested in clinical trials for patients with R/R LBCL
- Cytokine release syndrome (CRS) and neurological events (NEs) are known adverse events (AEs) associated with CAR T cell therapy[4]
  - Clinical trials have found varying CRS and NE rates across CAR T cell therapies[5-7]

Objectives

Primary Objective

- To estimate the mean patient cost of CRS and NEs for a population of patients with LBCL treated with a CAR T cell therapy (liso-cel, axi-cel, or tisagenlecleucel) based on clinical trial rates

Secondary Objective

- To estimate the opportunity cost of using liso-cel versus other CAR T cell therapies, as well as the potential value of that opportunity cost for use in treating additional patients with liso-cel

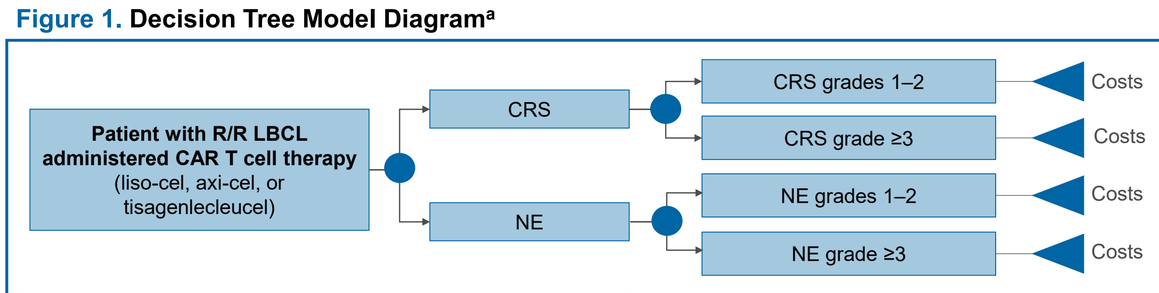
Methods

Table 1. Model Overview

Overview	Description
Model design	Decision tree model
Data source	Peer-reviewed evidence and prescribing information served as the main data sources for AE rates and cost of AE management
Population	Patients with R/R LBCL administered CAR T cell therapy
Perspective	Costs to the health care system[a]
Scenarios to evaluate	Three CAR T cell therapies: liso-cel, axi-cel, and tisagenlecleucel
Approach	Costs of management by AE type and grade are applied to publicly available AE rates to obtain a weighted average cost
Time horizon	Day 0 (CAR T cell therapy administration day) to AE resolution
Clinical inputs	CRS rates by grade (1/2 and ≥3) NE rates by grade (1/2 and ≥3) Time to AE resolution (variable)
Economic inputs	Cost of AE management by grade and type Cost of CAR T cell therapy (hypothetical)
Outcome	Weighted average cost for the treated patient

[a]The health care system cost perspective reflects true costs to all providers across sites of care who may treat and manage AEs.
AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; NE, neurological event; R/R, relapsed/refractory.

Figure 1. Decision Tree Model Diagram[a]



Circle node = chance node; shows multiple uncertain outcomes. Triangle node = end point node; indicates a final outcome.
[a]CRS and NEs may have occurred in the same patients but were modeled separately for this analysis.
CAR, chimeric antigen receptor; CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; NE, neurological event; R/R, relapsed/refractory.

- A decision tree economic model was developed using clinical trial and real-world evidence to estimate an average weighted cost per patient with R/R LBCL undergoing CAR T cell therapy administration from the health care system perspective by CAR T cell therapy
- Due to the data limitations for granular rates by each severity grade (1–4) and the limited evidence on the cost of CRS and NEs by grade, the following conceptual framework was developed that most robustly utilized the available data[5-7]

Table 2. Key Clinical Inputs

	Liso-cel	Axi-cel	Tisagenlecleucel
Source	**Abramson et al 2019[5]**	**YESCARTA PI 2017[6]**	**KYMRIAH PI 2018[7]**
n	268	101	106
CRS overall	42%	94%	74%
CRS grade ≥3	2%	13%	23%
CRS grades 1–2[a]	40%	81%	51%
NEs[b] overall	30%	87%	58%
NEs[b] grade ≥3	10%	31%	18%
NEs[b] grades 1–2[a]	20%	56%	40%

Note: Grading criteria differ across trials, with liso-cel and axi-cel using the Lee criteria[9] and tisagenlecleucel using the Penn criteria.[10] The differences in grading may cause overlap between grades 2 and 3. Scenario analysis will be conducted to assess the impact of such overlap and uncertainty in the AE economic differences observed across the CAR T cell therapies. NEs were graded according to NCI CTCAE v4.03.
[a]The source clinical evidence was broken into 2 categories using the overall rates and the grade ≥3 rates (**Table 3**). To estimate the categories, the grade ≥3 AE rates were subtracted from the overall rates to estimate the grade 1–2 AE rates; [b]Definitions for NEs differed for the 3 CAR T cell therapies.
AE, adverse event; CRS, cytokine release syndrome; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, neurological event; PI, prescribing information.

Table 3. Key Economic Inputs[a]

	Facility	Drugs	Diagnostics
CRS			
Grades 1–2	$14,357	$272	$138
Grade ≥3	$80,044	$3876	$1413
NEs			
Grades 1–2	$18,038	$305	$411
Grade ≥3	$76,223	$845	$1390

[a]Costs reflect 2019 US dollars.
CRS, cytokine release syndrome; NE, neurological event.

- The model incorporated the 2 AEs of interest to CAR T cell therapy, CRS and NEs, using publicly available rates from different clinical trials
- Three CAR T cell therapies were included in the analysis: liso-cel, axi-cel, and tisagenlecleucel
  - The rates of CRS and NEs were based on the prescribing information or most recently presented evidence
- The cost inputs for management of CRS and NEs were obtained from peer-reviewed literature[8]
  - The costs reflected management of CRS and NEs per the TRANSCEND NHL 001 clinical trial management protocol
  - The analysis was based on unit costing from a health care system perspective with the costs of CRS and NEs by severity grade
- Weighted average costs (weighted based on sample size) were calculated from the source data to estimate a cost for the model AE categories:
  - Grades 1–2 CRS and NE cost inputs were a weighted average cost from grades 1-2 median costs from the source data
  - The CRS grade ≥3 cost input was the weighted average of CRS or NEs occurring at the same time (concurrent) or not at the same time (non-concurrent)
  - The cost of grade 3 NEs from the source data was used as the grade ≥3 NE cost input
- Base case cost inputs were broken down into 3 AE management categories: facility, drugs, and diagnostics

Table 4. Model Parameters and Distribution of Variance

Parameters	Base Case Input	Distribution of Variance
Liso-cel		**Beta Distribution:** The beta distribution is 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.
CRS grades 1–2	40.0%	
CRS grade ≥3	2.0%	
NE grades 1–2	19.8%	
NE grade ≥3	10.1%	
Axi-cel		
CRS grades 1–2	81.0%	
CRS grade ≥3	13.0%	
NE grades 1–2	56.0%	
NE grade ≥3	31.0%	
Tisagenlecleucel		
CRS grades 1–2	51.0%	
CRS grade ≥3	23.0%	
NE grades 1–2	40.0%	
NE grade ≥3	18.0%	
CRS grades 1–2		**Gamma Distribution:** Cost data, specifically using small sample sizes, are 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 a few outliers that impact the mean cost.
Facility	$14,357	
Drugs	$272	
Diagnostics	$138	
CRS grade ≥3		
Facility	$80,044	
Drugs	$3876	
Diagnostics	$1413	
NE grades 1–2		
Facility	$18,038	
Drugs	$305	
Diagnostics	$411	
NE grade ≥3		
Facility	$76,223	
Drugs	$845	
Diagnostics	$1390	

CRS, cytokine release syndrome; NE, neurological event.

- Due to uncertainty surrounding AE rates and AE costs, a Monte Carlo simulation modeling approach was used
- Model inputs and assumed distribution for the economic decision tree model were assessed
- A beta distribution was used for AE rate variance, and a gamma distribution was used for cost variance
- The Monte Carlo simulation ran 1000 iterations to calculate an expected cost of the average treated patient

Statistical Analyses and Model Outcomes

- Descriptive statistical analyses were performed on the expected cost of the average treated patient for each CAR T cell therapy, including mean, median, min–max, standard deviation, and 95% confidence interval
  - Secondary analyses were performed on model outcomes and broken down by AE and AE severity

Scenario Analyses

Alternative AE Rates

- A scenario analysis was conducted to assess outcomes with alternative AE profiles, taken from real-world data for axi-cel and peer-reviewed literature for tisagenlecleucel[11,12]
  - The rates used were investigator-identified cases (whereas the base case analysis used AE rates as determined by the US Food and Drug Administration reviewer)

Consensus CRS Grading

- A scenario analysis was conducted to assess differences using a consistent CRS grading scale
- Due to the use of the Penn grading scale in the tisagenlecleucel clinical trial,[10] some patients may have been assigned higher grades than those in the studies that used the Lee grading criteria[9]
- The rates used in this scenario analysis assume that 25% of all grade 3–4 events were grades 1–2 in the tisagenlecleucel cohort

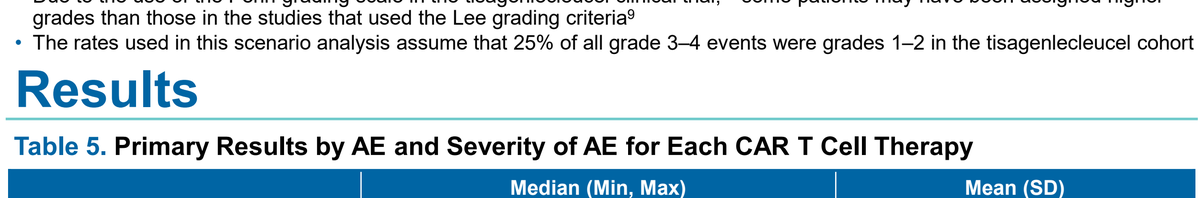
Results

Table 5. Primary Results by AE and Severity of AE for Each CAR T Cell Therapy

	Median (Min, Max)	Mean (SD)
Liso-cel		
CRS grades 1–2	$5627 ($2526, $11,708)	$5720 ($1477)
CRS grade ≥3	$1601 ($258, $7158)	$1758 ($889)
NE grades 1–2	$3587 ($1201, $8204)	$3707 ($1021)
NE grade ≥3	$7568 ($2597, $18,399)	$7919 ($2454)
Axi-cel		
CRS grades 1–2	$11,328 ($4942, $22,883)	$11,546 ($2860)
CRS grade ≥3	$10,620 ($3321, $30,264)	$11,256 ($4137)
NE grades 1–2	$10,228 ($3773, $22,143)	$10,434 ($2682)
NE grade ≥3	$23,343 ($9006, $54,831)	$24,315 ($7142)
Tisagenlecleucel		
CRS grades 1–2	$7064 ($3108, $14,170)	$7285 ($1917)
CRS grade ≥3	$19,276 ($6909, $44,822)	$20,029 ($5988)
NE grades 1–2	$7317 ($2444, $16,326)	$7496 ($1981)
NE grade ≥3	$13,503 ($3631, $34,815)	$14,163 ($4498)

AE, adverse event; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NE, neurological event; SD, standard deviation.

Figure 2. Primary Results: Total Per Patient Cost

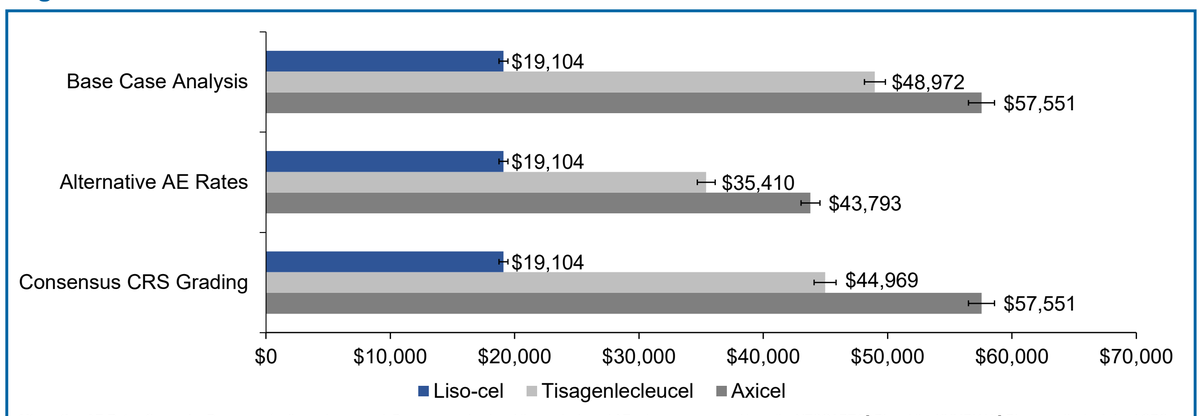


	Liso-cel	Axi-cel	Tisagenlecleucel
CRS[a]	$7478	$22,802	$27,314
NE[a]	$11,626	$34,749	$21,658
Overall[b]	**$19,104**	**$57,551**	**$48,972**
SD	$5841	$16,820	$14,384
Lower 95% CI	$18,742	$56,507	$48,080
Upper 95% CI	$19,467	$58,595	$49,865

[a]CRS and NE total costs are combined from grades 1–2 and grade ≥3 costs (**Table 5**).
[b]Overall costs are combined CRS and NE costs.
CI, confidence interval; CRS, cytokine release syndrome; NE, neurological event; SD, standard deviation.

- The overall weighted average costs per treated patient for liso-cel, axi-cel, and tisagenlecleucel were $19,104, $57,551, and $48,972, respectively
  - The weighted average costs for CRS management per treated patient for liso-cel, axi-cel, and tisagenlecleucel were $7478, $22,802, and $27,314, respectively
  - The weighted average costs for NE management per treated patient for liso-cel, axi-cel, and tisagenlecleucel were $11,626, $34,749, and $21,658, respectively
- The economic model found that treatment with liso-cel resulted in the lowest mean CRS and NE management costs across all severity categories compared with axi-cel and tisagenlecleucel

Figure 3. Results Overview



Alternative AE Rates Scenario: Base case for liso-cel was used. Base case axi-cel and tisagenlecleucel AE rates were sourced from the YESCARTA® PI and the KYMRIAH ® PI, respectively. Axi-cel CRS rates for the scenario analysis were sourced from Pasquini MC, et al. 2019.[11] The proportion of NE grades 3–4 AEs from the base case was applied to the overall NE rate (61%) from Pasquini MC, et al.[11] as breakdown by grade is unavailable. Tisagenlecleucel CRS rates for the scenario analysis were sourced from Schuster SJ, et al.[12] NE rates were sourced from Schuster SJ, et al.[13]
Consensus CRS Grading Scenario: Base case AE rates for liso-cel and axi-cel were used. Tisagenlecleucel base case NE rates were used. It was assumed that 25% of tisagenlecleucel CRS grade 3-4 events (from the PI) were assumed to be grade 1-2 for this scenario analysis (Schuster SJ, et al. 2018[12] determined that 5 of 24 CRS grade ≥3 events [21%] were grades 1–2 when regraded using Lee criteria).[9]
AE, adverse event; CRS, cytokine release syndrome; NE, neurological event; PI, prescribing information.

Exploratory Analysis—Opportunity Cost

- Using the mean cost difference between liso-cel and axi-cel and liso-cel and tisagenlecleucel, and an assumed hypothetical sample of 100 treated patients, the total cost differences for the 100 treated patients are divided by a potential, hypothetical liso-cel acquisition cost of $373,000
  - Based on this analysis, the resulting opportunity costs from treating 100 patients with liso-cel instead of axi-cel would allow for the treatment of an additional 10.3 patients
  - Additionally, the resulting opportunity costs from treating 100 patients with liso-cel instead of tisagenlecleucel would allow for the treatment of an additional 8.0 patients

Limitations

- The model assumed that managing CRS or NEs would not differ across CAR T cell therapies
  - The analysis was based on a singular cost source derived from the liso-cel clinical trial[8]
- The base case inputs were varied using assumed distribution
  - The standard deviation of costs was estimated assuming a normal distribution, as the true distribution was unavailable
- The base case analysis used CRS incidence rates that reflected different grading definitions
  - The consensus CRS grading scenario analysis found that the grading criteria had a limited impact on the overall costs of CRS and NE management
- Differences in NE-reported definitions may have caused additional bias
- Costs of managing CRS and NE may overlap, which may result in overestimations
- Costs represented national averages and may not be generalizable to specific institutions; costs may also vary from provider to provider
- Costs in this analysis were distributed across the entire trial population (those with and without CRS and NE) and should not be confused with cost per event (cost per event has been detailed in Abramson, et al.[3])
- Prophylactic measures and management in the real world are improving, and trial guidelines may not reflect real-world clinical practice

Conclusions

- The potential cost offsets for liso-cel due to lower CRS and NE rates were $38,447 and $29,868 when compared with axi-cel and tisagenlecleucel, respectively
- Treatment with liso-cel resulted in cost savings compared with axi-cel and tisagenlecleucel in all tested scenarios
- The cost savings from treatment with liso-cel may be an important factor in clinical decision-making
- These findings highlight the economic importance of differences in the safety profiles among CAR T cell therapies

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Disclosures

- AN is an employee of BluePath Solutions, received consulting fees from Bristol-Myers Squibb Company during the conduct of the study, and receives consulting fees from Bristol-Myers Squibb Company outside the submitted work; JG is an employee of Juno Therapeutics, a Bristol-Myers Squibb Company, and may own stock in Bristol Myers-Squibb Company; MG is the Managing Director of BluePath Solutions, received consulting fees from Juno Therapeutics, a Bristol-Myers Squibb Company, during the conduct of the study, and receives consulting fees from Bristol-Myers Squibb Company outside the submitted work; MPJ is an employee of Bristol-Myers Squibb Company, and may own stock in Bristol-Myers Squibb Company
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