An Economic Model to Estimate Costs of Adverse Events in Patients Treated With Lisocabtagene Maraleucel, Axicabtagene Ciloleucel, or Tisagenlecleucel for Relapsed or Refractory Follicular Lymphoma

EE434

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Introduction

- Chimeric antigen receptor (CAR) T cell therapies have demonstrated clinically meaningful responses in patients with R/R follicular lymphoma (FL)
- Despite promising efficacy, CAR T cell therapies are associated with several AEs, including cytokine release syndrome (CRS), neurological events (NE), prolonged cytopenia, and infections (grade 3—4), with incident rates that vary across CAR T cell products for R/R FL
- Understanding economic implications of CAR T cell therapies and associated AEs is crucial for informed decision-making and to underscore key economic and safety differences across these therapies

Objectives

- To estimate the per-patient cost of managing CRS, NE, prolonged cytopenia, and infections (grade 3—4) among adult patients with R/R FL treated with lisocabtagene maraleucel (liso-cel), axicabtagene ciloleucel (axi-cel), and tisagenlecleucel (tisa-cel)
- To evaluate the opportunity cost of using axi-cel or tisa-cel instead of liso-cel in a hypothetical 100-patient scenario, by estimating the difference in the number of patients who could have been treated if liso-cel had been chosen while maintaining the same overall budget

Methods

- A decision tree economic model was developed to estimate the AE-related costs (by severity grade) across 3 FDA-approved CAR T cell therapies for R/R FL (**Figure 1**, **Table 1**)
- AE-related health care costs were derived from a microcosting analysis of the TRANSCEND FL clinical study data,[1] which estimated direct medical costs by severity grade of AE. These costs were then uniformly applied to each CAR T cell therapy using the AE incidence rates reported in the TRANSCEND FL (NCT04245839; liso-cel),[2] ELARA (NCT03568461; tisa-cel),[3] and ZUMA-5 (NCT03105336; axi-cel)[4] clinical studies for CRS and NE for all therapies, and prolonged cytopenia and infection (grade 3—4) for liso-cel
- Axi-cel and tisa-cel did not report rates of prolonged cytopenia or serious infection in their publications, so these rates were sourced from product prescribing information[5,6]
- Monte Carlo simulations were used to address uncertainty surrounding the model inputs, yielding a generalizable estimate of mean per-patient AE costs

Figure 1. Decision tree design

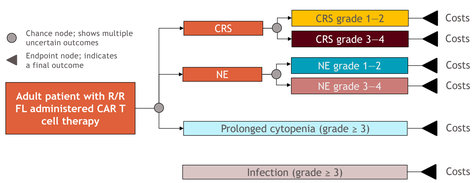


Table 1. Model overview

	Description
Model design	Decision tree model
Data sources	• AE rates were obtained from the TRANSCEND FL, ELARA, and ZUMA-5 studies, and product prescribing information • AE-related health care costs were estimated from a separate microcosting analysis of the TRANSCEND FL clinical study
Population	R/R FL
Perspective	Health care system perspective
Therapies included	• Liso-cel • Axi-cel • Tisa-cel
Clinical inputs	• CRS (grade 1—2 and grade 3—4) • NE (grade 1—2 and grade 3—4) • Prolonged cytopenia (grade ≥ 3) • Infection (grade ≥ 3)
Time horizon	CAR T cell therapy administration to AE resolution
Economic inputs	• Cost of AE management by grade and type • Cost of CAR T cell therapy
Outcomes	• Modeled per-patient weighted average cost per AE • Overall per-patient weighted average cost (for all AEs)

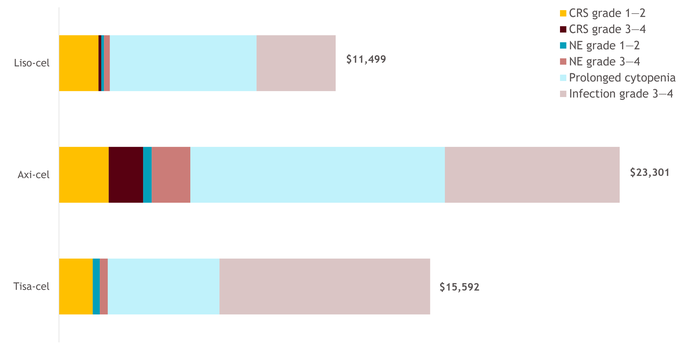
Liso-cel incurs the lowest AE costs with fewer severe complications compared with axi-cel and tisa-cel potentially enabling treatment of more patients with the same budget

Table 3. Modeled total and percent (%) differences in per-patient costs across therapies

	Mean	SD	Lower 95%	Upper 95%	%Δ to liso-cel	%Δ to axi-cel	%Δ to tisa-cel
CRS[a]							
Liso-cel	$1757	$508	$1725	$1788	—	−49.8%	11.9%
Axi-cel	$3497	$1148	$3426	$3568	99.1%	—	122.8%
Tisa-cel	$1570	$601	$1532	$1607	−10.6%	−55.1%	—
NE[a]							
Liso-cel	$358	$191	$346	$370	—	−81.8%	−42.4%
Axi-cel	$1964	$623	$1925	$2002	448.0%	—	215.4%
Tisa-cel	$623	$291	$605	$641	73.7%	−68.3%	—
Prolonged cytopenia[b]							
Liso-cel	$6097	$1823	$5983	$6210	—	−42.4%	31.3%
Axi-cel	$10,579	$2892	$10,400	$10,758	73.5%	—	127.8%
Tisa-cel	$4644	$1526	$4549	$4739	−23.8%	−56.1%	—
Infection (grade 3—4)							
Liso-cel	$3288	$1308	$3207	$3369	—	−54.7%	−62.4%
Axi-cel	$7262	$2337	$7117	$7407	120.9%	—	−17.1%
Tisa-cel	$8756	$2933	$8574	$8938	166.3%	20.6%	—
Overall[c,d]							
Liso-cel	$11,499	$3831	$11,262	$11,737	—	−50.6%	−26.2%
Axi-cel	$23,301	$7000	$22,867	$23,736	102.6%	—	49.4%
Tisa-cel	$15,592	$5351	$15,260	$15,924	35.6%	−33.1%	—

[a]CRS/NE total costs are combined from grade 1—2 and grade 3—4 costs; [b]Prolonged cytopenia was defined in TRANSCEND FL as grade ≥ 3 cytopenia based on laboratory values at day 29, and in ZUMA-5 as grade ≥ 3 cytopenia present on or after day 30 after infusion.[2,4] In ELARA, prolonged cytopenia was reported as individual types of AE events (ie, neutropenia, thrombocytopenia, leukopenia) lasting ≥ 28 days.[3] [c]Overall costs are CRS, NE, prolonged cytopenia, and infection (grade 3—4) costs combined. [d]All cost reported in USD. SD, standard deviation.

Figure 3. Per-patient costs by AE and therapy



Model inputs

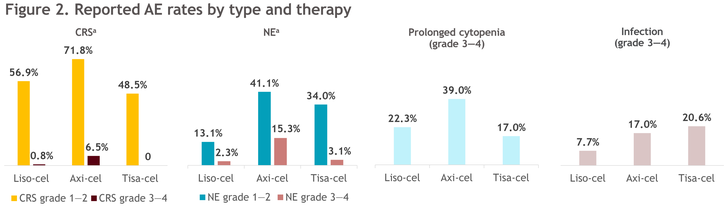
- NEs in TRANSCEND FL were defined as investigator-identified AEs related to liso-cel and graded per the NCI CTCAE, version 5.0, whereas those in ZUMA-5 and ELARA used "MedDRA high-level group terms" search queries. Prolonged cytopenia was defined in TRANSCEND FL as grade ≥ 3 cytopenia based on laboratory values at day 29, and in ZUMA-5 as grade ≥ 3 cytopenia present on or after day 30 after infusion.[2,4] In ELARA, prolonged cytopenia was reported as individual types of AE events (ie, neutropenia, thrombocytopenia, leukopenia) lasting ≥ 28 days.[3] All 3 studies used similar definitions for CRS and serious infections. AE rates from the 24-month TRANSCEND FL study and 24-month follow-up data from ELARA and ZUMA-5 were used for comparison[2—4]
- Patient-level data from the TRANSCEND FL clinical study were used to quantify key health care resource utilization (HCRU) incurred during each AE (eg, medications, procedures, hospitalizations). Unit costs were applied to each of these HCRU events and aggregated to generate a direct cost estimate for each AE
- Costs for CRS and NE were aggregated across grade 1—2 and grade 3—4 events to provide severity-specific cost estimates for inclusion in the model. Costs for prolonged cytopenia and infection (grade 3—4) were restricted to grade 3—4 events (**Table 2**)
- These AE-specific costs were applied uniformly across therapies (liso-cel, axi-cel, tisa-cel) using the rates reported in their respective FL clinical studies or product prescribing information (**Figure 2**) to ultimately estimate the net AE-related costs distributed across 100 hypothetical patients who were administered each product (liso-cel, axi-cel, tisa-cel), including both those who did and did not experience the AEs (**Table 3**)

Table 2. TRANSCEND FL study AE costs applied to the model[a]

	Median total	Mean total
CRS		
Grade 1—2	$1097	$2872
Grade 3—4	$22,191	$22,191
NE		
Grade 1—2	$129	$867
Grade 3—4	$6126	$10,505
Prolonged cytopenia		
Grade 3—4	$1543	$27,125
Infection		
Grade 3—4	$42,205	$42,205

[a]Cost reported in USD.

Figure 2. Reported AE rates by type and therapy



[a]Liso-cel reported only grade 3 events for CRS and NE.

Results

Primary objective: To estimate the modeled per-patient cost of managing CRS, modeled NE, prolonged cytopenia, and infection (grade 3—4) among adult patients with R/R FL treated with liso-cel, axi-cel, and tisa-cel

- Across therapies, mean per-patient costs were $1570—$3497 for CRS, $358—$1964 for NE, $4644—$10,579 for prolonged cytopenia, and $3288—$8756 for infection (grade 3—4) (**Table 3**). Breakdowns by AE grade are also shown (**Table4**)
- Overall AE-related costs (aggregated across CRS, NE, prolonged cytopenia, and infection [grade 3—4]) were lowest for liso-cel at $11,499 ($11,262—$11,737) versus $15,592 ($15,260—$15,924) for tisa-cel and $23,301 ($22,867—$23,736) for axi-cel (**Figure 3**)

Table 4. Modeled per-patient costs by grade across therapies[a,b]

	Liso-cel		Axi-cel		Tisa-cel	
	Median	Mean	Median	Mean	Median	Mean
CRS						
Grade 1—2	$1611	$1641	$2043	$2066	$1354	$1403
Grade 3—4	$118	$115	$1329	$1431	$89	$166[c]
NE						
Grade 1—2	$108	$113	$344	$357	$288	$295
Grade 3—4	$216	$245	$1553	$1607	$283	$327
Prolonged cytopenia	$5890	$6097	$10,444	$10,579	$4469	$4644
Infection, grade 3—4	$3071	$3288	$7027	$7262	$8340	$8756

[a]AE incidence was assumed to follow a beta distribution (0—1) in the Monte Carlo simulation. Costs were assumed to follow a gamma distribution to account for skewed cost data. [b]Cost reported in USD. [c]Given that there were no CRS grade 3—4 events for tisa-cel in the base case to which no alpha and beta parameters could be estimated for the Monte Carlo simulations, the alpha and beta values for tisa-cel grade 3—4 CRS were assumed to be the same as those generated for grade 3—4 CRS of liso-cel, which was associated with a similarly low rate of grade ≥ 3 CRS (1.0%)

Secondary objective: To evaluate the opportunity cost of using axi-cel or tisa-cel instead of liso-cel in a hypothetical 100-patient scenario, by estimating the difference in the number of patients who could be treated with liso-cel for the same overall budget

- Due to the lower costs of managing AEs, liso-cel has the potential to treat 2.4 and 0.8 additional patients per 100 patients treated over axi-cel and tisa-cel, respectively

Assumptions

- AE-related costs, which are based on data obtained from the TRANSCEND FL clinical study, are assumed to reflect general AE management for each CAR T cell therapy (and thus are applied uniformly across all comparators)
- It is assumed that grade 1—2 events do not require inpatient admissions, while grade 3—4 events will require admission and incur related costs
- For the Monte Carlo simulations, it is assumed that AE rates followed a beta distribution and AE management costs followed a gamma distribution
- Given that there were no CRS grade 3—4 events for tisa-cel in the base case to which no alpha and beta parameters could be estimated for the Monte Carlo simulations, the alpha and beta values for tisa-cel grade 3—4 CRS were assumed to be the same as those generated for grade 3—4 CRS of liso-cel, which was associated with a similarly low rate of grade ≥ 3 CRS (1.0%)
- It was assumed that management of AEs is similar across CAR T cell therapies

Limitations

- The AE costs reflect the setting of CAR T cell administration in the liso-cel clinical study, which is primarily inpatient. Such estimates may not reflect real-world costs, as liso-cel may have greater outpatient use and thus CRS and NE management costs may differ
- Differences in CRS- and NE-reported definitions across the clinical studies may cause additional bias
- Estimated costs in this analysis were distributed across the entire study population (those with and without CRS and NE) and should not be confused with cost per event
- Follow-up times across the CAR T cell therapies were not equal due to differences in reporting AEs, which may lead to an under or overestimation of AE rates in comparison to each other

Conclusions

- The simulated total costs of managing AEs (aggregated across CRS, NE, prolonged cytopenia, and infection [grade 3—4]) were estimated to be 26%—51% **lower among patients treated with liso-cel** relative to tisa-cel and axi-cel, respectively
- These cost differences were mostly attributable to the **lower rates of prolonged cytopenia** observed for liso-cel (22.3%) compared with axi-cel (39.0%) and **lower rates of infection (grade 3—4) observed for liso-cel** (7.7%) compared with axi-cel and tisa-cel (17.0% and 20.6%, respectively)
- For the same budget, **the lower costs associated with liso-cel therapy** could hypothetically be used to provide lifesaving treatment to an additional ~1—2 patients per 100 patients treated compared with tisa-cel and axi-cel
- These results highlight the economic importance of differentiated safety profiles between CAR T cell therapies for the treatment of R/R FL

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